The Encyclopedia of MOVEMENT DISORDERS

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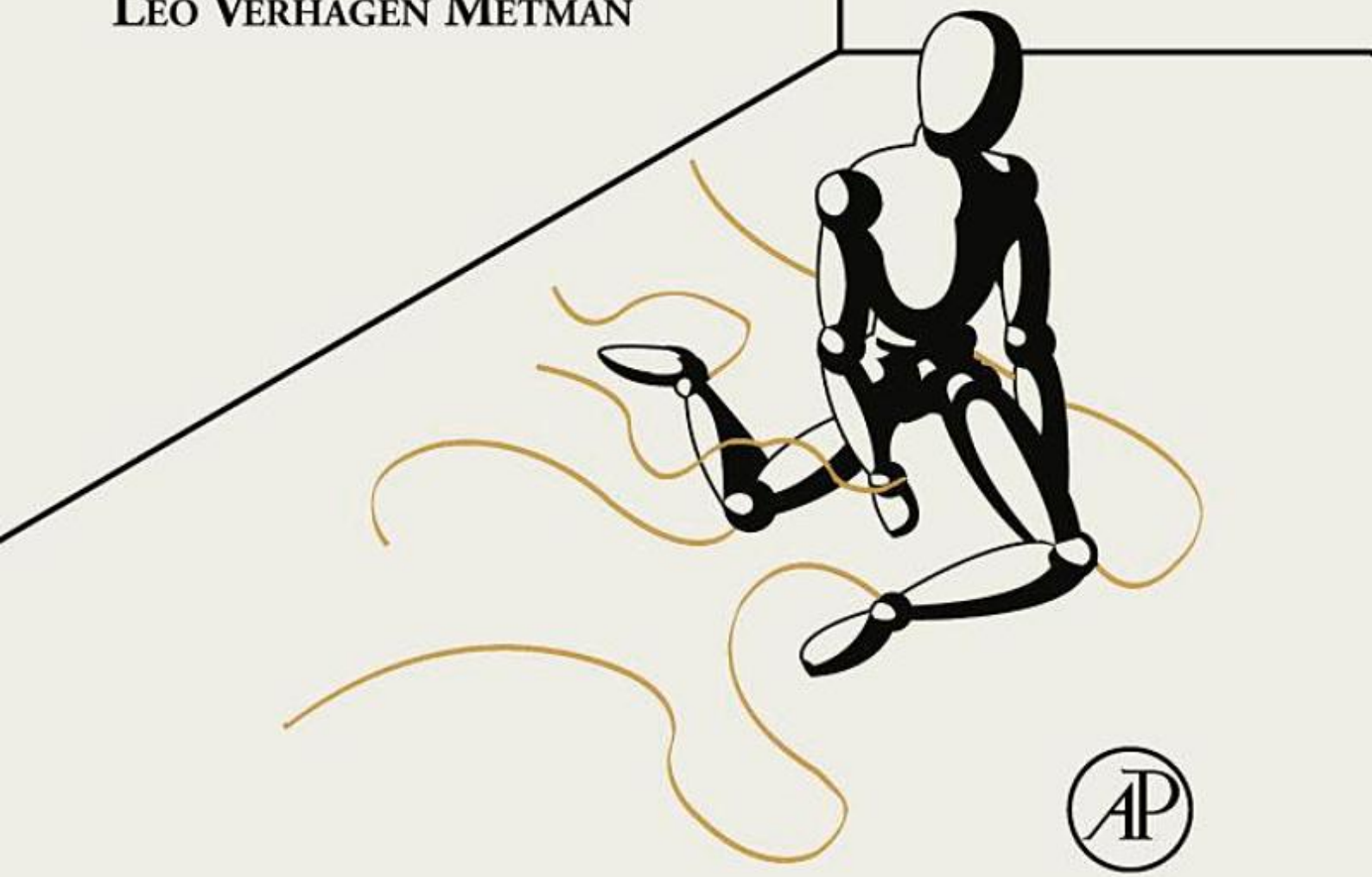

ENCYCLOPEDIA OF MOVEMENT DISORDERS

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PREFACE

When we were first approached by Elsevier to develop this *Encyclopedia of Movement Disorders,* it was not immediately evident to us how an encyclopedia would be different from existing textbooks on the same topic. Exploring the concept, we consulted the omnipresent mother of all modern encyclopedias, Wikipedia, where we found the following explanation of the origin of the word: encyclopaedia comes from the Greek ἐγκύκλιος παιδεία, transliterated 'enkyklios paideia'; 'enkyklios' meaning 'cyclical, periodic, or ordinary', and 'paideia' meaning 'education'. Together, the phrase literally translates as a '[well-] rounded education'. In Latin, the two words were unified into 'encyclopaedia', which subsequently became part of the English vocabulary. This etymologic detail, while interesting, did not provide us with a clearer vision of the project at hand, so we gathered existing encyclopedias and compared them to standard textbooks. This comparison revealed immediately that textbooks have tables of contents, and the content is separated into chapters and sections. The hierarchical format of a textbook pre-defines an order that is the core of a unified narrative that builds from page to page. In contrast, an encyclopedia is harnessed by an alphabetical order with cross referencing to related topics. This type of structure has not been previously presented for a work focusing on movement disorders and the printed and digital format options proposed by the publisher for this work convinced us that this project would be a novel and useful addition to the international literature.

Organization, structure, and digital innovations, however, are not enough to differentiate a textbook from an encyclopedia. We have developed this encyclopedia with the primary mission of providing up to date and easily accessible information. We have not developed the encyclopedia to infringe on the primary goal of a textbook as a teaching tool. Whereas a textbook is anchored as a progressive teaching program with its step-by-step development of chapters and prescribed order of presentation to instruct readers, our mission is the efficient delivery of information.

As a result, the *Encylopedia of Movement Disorders* is organized in alphabetical manner and contains 402 entries encompassing clinical and basic science topics relating to movement disorders, including anatomy, physiology, molecular biology, pharmacology, toxicology, genetics, pathology, epidemiology, behavioral neurology, neuro-ophthalmology, imaging, surgery, and psychiatry. Most entries are relatively brief and highly focused to allow the reader to hone in on the topic without needing to wade through introductory information. The cross references in the printed version and the search engine in the electronic version allow the reader rapid access to additional information in either a more general or a more specific format. This particular feature makes the encyclopedia accessible to anyone regardless of background knowledge, including students, general physicians, basic scientists, and movement disorder specialists. Each entry contains a 'further reading list' that will steer the reader to the most essential published works on the subject. In addition, cross references are offered throughout the work, to facilitate the reader's navigation between entries, zooming out from the more focused to the more general article, and zooming back in to related focused entries.

The discipline of Movement Disorders relies heavily on recognition of phenomenology. Therefore no Movement Disorder reference work is complete without video clips. Numerous authors have complemented their written work with visual testimonies that will greatly enhance the reader's learning experience. We are grateful for the authors' extra effort to make this possible and to their patients who consented to be videographed.

The remarkable pace of discovery in neurosciences and the scope of this work defy any attempt at being absolutely comprehensive. However, the dynamic nature of our on-line version allows for timely updates and makes this reference work conceptually and practically an ongoing work-in-progress.

We feel privileged to have worked with the authors, most of them world renowned, some at earlier stages of their careers, but all experts in their designated topics. We thoroughly enjoyed the opportunity to review their latest work and to communicate our editorial comments. When we started out, the freshly introduced electronic manuscript submission website (EMSS) may have caused initial hardship for some, but overall the ability to communicate through this website and to have a paper trail of different manuscript versions, figures, videos, and communications among author, associate editors, Elsevier, and us was an invaluable asset and we thank all participants for their persistence. We are indebted to our

Associate Editors who were instrumental in recruiting expert authors, and in the review and editing of the manuscripts in their respective areas of expertise. At the publisher, Elsevier, many people are responsible for the ultimate product currently resting in your hands, but we want to single out Developmental Editor Jason Mitchell whose optimism and professionalism never failed us.

Co-editing this work was greatly facilitated if not enabled by our close professional and personal relationship. At the occasional juncture on the long and windy road where one of us became discouraged, there was always the other to take the helm and bring the energy and determination to re-ignite the spark. The mutuality of that process has happily brought the *Encyclopedia of Movement Disorders* to its timely completion.

EDITOR'S BIO

Leonard Verhagen Metman earned his medical degree from the University of Leiden in the Netherlands in 1983. He moved to the United States in 1985 to work in the Artificial Heart Program at the University of Utah with Dr. Willem J. Kolff (1985–1987). He first pursued his interest in the Neurosciences by joining the Division of Restorative Neurology and Human Neurobiology at Baylor College of Medicine in Houston, Texas with Dr. Milan R. Dimitrijevic (1987–1988). Following an internship at Waterbury Hospital Health Center in Connecticut (1988–1989), he completed his Neurology residency at Thomas Jefferson University Hospital in Philadelphia, Pennsylvania under Robert J. Schwartzman (1989–1992). He then accepted a fellowship at the National Institutes of Health, in the Experimental Therapeutics Branch of the National Institute of Neurological Disorders and Stroke in Bethesda, Maryland under Thomas N. Chase (1992–1994). Upon completion he remained at the NIH as Visiting Associate and later as Visiting Scientist until 1999 when he joined the Movement Disorder Section of the Department of Neurological Sciences at Rush University Medical Center in Chicago, Illinois, directed by Dr. Christopher G. Goetz. In 2002 Dr. Verhagen received his Ph.D. from the University of Leiden based on his studies of motor response complications in Parkinson's disease. Over the past 10 years at Rush, Dr. Verhagen has served as Assistant Professor (1999–2000) and Associate Professor (2001-current) of Neurological Sciences. In addition, he established the Rush Movement Disorder Surgery Program and serves as its Medical Director. His clinical research interests include the development of new medical and surgical therapies for patients with advanced movement disorders. Dr. Verhagen is board certified in psychiatry and neurology (1994-present) and is a member of the American Academy of Neurology, the American Neurological Association and the Movement Disorder Society.

Dr. Kompoliti was born in Greece and completed her early education there, including Medical School. She graduated from the University of Patras, college of Medicine in 1988. She came to the United States in 1989, where she completed the rest of her medical education. She first trained in internal medicine (1990–1992) at St Francis Hospital, Evanston, IL. Following that she pursued her interest in neuroscience by completing a residency in Neurology at Northwestern University, Chicago, IL (1992–1995). After the completion of her residency she held a fellowship in Movement Disorders at Rush University Medical Center, Chicago, IL (1995–1997). She became Assistant Professor of Neurology in 1998 and Associate Professor in 2004. She is board certified in Neurology (1997-present) and is a member of the American Academy of Neurology, the American Neurological Association and the Movement Disorders Society. The author and coauthor of numerous publications, her clinical interests as a principal investigator have focused on several therapeutic areas of on-going research including studies to evaluate the safety and efficacy of new compounds to treat Parkinson's disease, Tourette syndrome, and Psychogenic Movement Disorders. Special interests of Dr. Kompoliti's include the gender differences in Parkinson's disease and other movement disorders, studies to define the effect of neuroleptics on weight, risk for diabetes and dyslipidemia in patients with Tourette syndrome, and define the current status of use of Complementatry and Alternative Medicine in patients with Tourette syndrome. Finally, Dr. Kompoliti has been conducting studies to assess therapeutic interventions for patients with functional movement disorders. Dr. Kompoliti is a member of the National Medical Advisory Board of the Tourette Syndrome Association and has given numerous lectures and Grand rounds around the country to increase public awareness in Tourette Syndrome.

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3-Nitropropionic Acid

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Glossary

SDH (succinate dehydrogenase) – An enzyme that catalyzes the transformation of succinate into fumarate.
Succinate – A tricarboxylic acid that is an intermediate metabolite in the so-called tricarboxylic acid cycle (TCA cycle or Kreb's cycle).
TCA – Transforms and uses the energy that is 'stored' in the covalent bonds between carbon atoms through a number of reactions (including decarboxylation and dehydrogenation).

Definition and History

The neurotoxin 3-nitropropionic acid (3NP), a metabolite of 3-nitropropanol, was identified many decades ago in western United States of America as a toxic agent responsible for livestock poisoning. Animals intoxicated with leguminous plants (e.g., *Indigofera* or *Astragalus*) presented motor abnormalities consisting of general weakness and incoordination of the hindlimbs that evolved to paralysis. More recently, it was reported that accidental ingestion of sugar cane, contaminated with the fungus *Arthrinium* that produced 3NP was also the causal agent responsible for the development of acute encephalopathy in man. Most patients fall into a comatose state that can last several days. After coma, a large proportion of patients recovered completely without neurological alterations. However, a substantial number of subjects displayed a persistent neurological impairment characterized by delayed onset dystonia, torsion spasm, facial grimacing, and jerk-like movements. In these cases, computerized tomography (CT) and magnetic resonance imaging (MRI) examination usually indicate the presence of basal ganglia lesions mainly implicating the putamen, and less commonly, the caudate nucleus.

Pathogenesis/Pathophysiology

The dose-dependency of 3NP toxicity in man is unknown. Indeed, contamination of sugar cane is likely highly variable. The first controlled studies in mice and rats were performed in the early 1980s, suggesting that striatal degeneration was produced for acute doses in the range of 15–180 mg kg^{-1}. In nonhuman primates, the acute toxic dose is in the range of 20–30 mg kg^{-1} day^{-1}.

Biochemical studies have established that 3NP is a suicide inhibitor of succinate dehydrogenase (SDH), an enzyme located in the mitochondrial inner membrane and responsible for the oxidation of succinate to fumarate. The toxin irreversibly binds to the substrate site. This blocks the tricarboxylic acid (TCA) cycle (oxidative use of carbohydrates) and hampers the flow of electrons in the respiratory chain, reducing the capacity of mitochondria to produce ATP through namely 'oxidative phosphorylation.' Thus, the basic mechanism of 3NP is to produce impairment of energy metabolism.

How does 3NP trigger striatal neurodegeneration? Mitochondrial dysfunction produced by 3NP triggers oxidative stress and dysregulation of Ca^{2+} homeostasis. The increase in concentrations of Ca^{2+} in the cytosol and mitochondria activates a number of enzymes and intracellular signaling pathways that produce cell death resembling necrosis.

Certain mechanisms have been suggested to play an important role in the particular vulnerability of the striatum to 3NP toxicity. Some neurotransmitters and their receptors have been identified to play a key role, including glutamate and dopamine.

The links between brain lesion and symptoms can be underlined from in vivo imaging studies using CT scan and MRI in poisoned patients and from the observations in laboratory animal studies. General energy failure likely causes noninflammatory encephalopathy associated with coma, a phase that likely occurs in the absence of detectable tissue damage. After the period of coma, degeneration

of the putamen and the globus pallidus, two important structures of the basal ganglia, likely underlies most of motor symptoms. Postmortem studies of the brain of intoxicated patients have never been reported. From animal studies, it is known that the striatum is preferentially damaged. Neuropathological evaluation showed that medium-size spiny neurons are highly vulnerable. The globus pallidum, and sometimes, the hippocampus and substantia nigra pars reticula and substantia nigra pars compacta can also be found affected in acute intoxication.

Epidemiology/Risk Factors

In man, acute intoxication has been only reported in North China. Nearly 1000 cases of intoxication were reported between 1972 and 1989. The cause of intoxication is related to the fact that sugar cane is stored in humid and warm places where fungus proliferates very rapidly to produce high amounts of 3NP. The sugar cane was sold informally as sweets during the Chinese New Year celebration. Thus, the presence of the fungus in molded sugar cane could not be anticipated before the occurrence of overt intoxications.

Apart from environmental factors (food habits, warm climate, sugar cane storage), no other risk factors have been clearly identified. However, the Chinese neurologists who reported the cases of 3NP poisoning in man point to the fact that children are more commonly affected than adults. It is possible that children eat more contaminated sugar cane than adults do. Indeed studies in laboratory animals showed that adult animals (mice, rats, and monkeys) are in fact more vulnerable compared with young adolescents.

Differential Diagnosis

The striatum and the globus pallidus are known for their peculiar vulnerability to mitochondrial toxins (e.g., cyanide), hypoxia, and carbon monoxide intoxication. In the case of cyanide poisoning (suicidal ingestion), the poison can be detected. In the case of hypoxia, loss of consciousness occurs rapidly in the absence of major gastrointestinal signs. Carbon monoxide as 3NP might cause nausea, vomiting, headache, and drowsiness before coma. In the acute phase of 3NP poisoning, detection of normal levels of carboxyhemoglobin in venous arterial blood permits to rule out carbon monoxide intoxication.

Long-lasting neurological symptoms (in particular dystonia) can be found in many disorders associated with striatal degeneration. Certain aspects of Huntington's disease (HD), including choreiform involuntary abnormal movements and frontal-type cognitive symptoms and the selective pattern of cell death in the striatum, can be replicated in nonhuman primates, using chronic treatment with 3NP. Disorders associated with genetic mitochondrial defects can also lead to striatal degeneration and dystonia. However, absence of inheritance, absence of symptoms progression, record of an episode of gastrointestinal signs of acute intoxication followed by a period of coma, and suspicion of sugar cane ingestion can help to diagnose long-term neurological effects of 3NP poisoning and rule out genetic diseases.

Diagnostic Work-up/Tests

The first signs of intoxication are gastrointestinal signs (e.g., vomiting) and general weakness. The first signs of intoxication occur few hours after the ingestion of sugar cane. Gastrointestinal signs in the absence of fever might help to exclude viral origin. The absence of signs of brain inflammation (temperature change, nuchal rigidity, normal CSF) and gastrointestinal symptoms might help to diagnose poisoning. The neurological manifestations in children in the acute stage of 3NP poisoning indicate both diffuse and focal brain impairment. Chinese neurologists who reported these cases in children underline that the presence of convulsive attacks, coma, and bilateral extensor plantar responses suggest diffuse encephalopathy. They also report forced upward gaze, with deviation of the eyes and (horizontal or vertical) nystagmus. All these acute symptoms are reversible suggesting a general widespread brain dysfunction. When coma occurs, it lasts several days. Some of the comatose patients recovered completely without neurological alterations. In patients with delayed neurological manifestations, CT scan or MRI indicate the presence of basal ganglia lesions mainly implicating the putamen, and less commonly, the caudate nucleus.

The detection of *Arthrinium* in contaminated sugar cane should likely be the best proof of 3NP poisoning. Methods to detect 3NP in urine in animals have been reported but are not very sensitive and have to be set up and validated for helping diagnosis. Elevated nitrate levels in blood might also be indicative of 3NP poisoning. Improvement should be done to detect traces of 3NP in blood (for instance using mass spectroscopy).

Management

There is no particular management reported. During the initial phase of intoxication (at onset of gastrointestinal signs), hospitalization with an intensive health care follow-up is recommended. From animal studies showing

rapid elimination of 3NP in urine, it can be inferred that stomach washout and physiological serum venous perfusion to increase elimination immediately after 3NP ingestion should improve the prognosis.

There is no known antidote against 3NP in man. 3NP is rapidly eliminated through the urine as shown in animal studies. Apart from factors related to elimination, various pharmacological agents might be protective if given simultaneously or shortly after 3NP ingestion. Among these agents, for example, arginine, free radical scavengers, dopamine D2 receptor antagonists, and several agents reducing the entry of Ca^{2+} into neurons can prevent 3NP toxicity in cellular and animal models. Whether these findings could be extrapolated to the human condition is unknown. After the phase of acute encephalopathy and coma, when the presence of striatal lesions has been diagnosed using imaging, no treatment has been tested to reduce the severity of neurological symptoms. Since the lesions are stable and do not evolve toward aggravation, a partial recovery linked to neuronal plasticity can be expected. However no report of rehabilitation trial has been reported. Experimental results in nonhuman primates suggest that grafting of embryonic striatal neurons could have beneficial effects to improve symptoms. Clinical trials have not been carried out.

Prognosis

Approximately 10% of the intoxicated persons died from 3NP poisoning. Among the patients recovering from coma, ~10–15% displayed a persistent neurological impairment, while the others had no persistent symptoms. Neurological symptoms appearing after coma remain essentially stable thereafter.

See also: Chorea; Choreiform Disorders; Dystonia: Animal Models; Dystonia, Secondary; Huntington's Disease.

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6-OH Dopamine Rat Model

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Glossary

Dopamine – Dopamine is a neurotransmitter occurring in a wide variety of animals, including both vertebrates and invertebrates. In the brain, it can activate five types of dopamine receptors: D1, D2, D3, D4, and D5, and their variants. Dopamine is produced in several areas of the brain, but the largest aggregates of dopamine-producing neurons are found in two midbrain nuclei named 'substantia nigra' and 'ventral tegmental area.' Dopamine is also a neurohormone released by the hypothalamus. Its main function as a hormone is to inhibit the release of prolactin from the anterior lobe of the pituitary. Severe dopamine deficiency in the striatum is the prime cause of the motor symptoms typical of PD (in particular, slowness of movement, poverty of movement, difficulty in movement initiation, resting tremor, rigidity).

L-dopa (or levodopa) – L-dopa (3,4-dihydroxyphenyl-L-alanine) is a medication that is used to increase the amount of dopamine in the brains of patients with PD and other disorders (in particular, dopa-responsive dystonia). Dopamine as such cannot be administered systemically because it does not cross the blood–brain barrier, whereas the dopamine precursor, L-dopa is transported across the blood–brain barrier by an endothelial carrier system.

Motor complications – This term refers to motor fluctuations (i.e., rapid transitions between poor mobility and good motor function) and dyskinesia (i.e., abnormal involuntary movements) that usually occur after a few years of L-dopa therapy in patients with PD.

Nigrostriatal projection – Axon fibers that originate from neurons in the substantia nigra pars compacta

and reach the striatum. This projection uses dopamine as its primary transmitter.

Oxidative stress – Oxidative stress is caused by an imbalance between the production of reactive oxygen and a biological system's ability to readily detoxify the reactive intermediates or repair the resulting damage. The ensuing toxic effects are mediated by peroxides and free radicals that damage all components of the cell, including proteins, lipids, and DNA. Oxidative stress is believed to contribute to the death of nigral dopamine neurons in PD.

Striatum – The corpus striatum (commonly referred to as 'striatum') is a subcortical structure (i.e., located inside the telencephalon/cerebrum) consisting of two main components: the caudate nucleus and the putamen. These nuclei are the major input station of the basal ganglia system, and receive dense axonal projections from the entire cerebral cortex. The striatum plays a very important role in the selection and control of actions and movements. A ventral extension of the putamen, called nucleus accumbens, is now commonly referred to as 'ventral striatum.' This structure is part of the brain reward systems.

6-Hydroxydopamine (6-OHDA) is a naturally occurring, endogenous autooxidation product of dopamine that has been widely used as a catecholamine neurotoxin. When injected systemically, the toxin only affects sympathetic nerve terminals in the peripheral nervous system. When injected intracerebrally, 6-OHDA causes degeneration of central monoamine neurons with a pattern that depends on the dose, the route (intraventricular or intraparenchymal), and the coordinates of toxin injection. 6-Hydroxydopamine is efficiently taken up and accumulated by neurons that have a membrane transport mechanism for catecholamines (dopamine or noradrenaline), which accounts for the specificity of its action. High concentrations of the toxin, however, can produce nonspecific neuronal damage, as seen in close proximity to intraparenchymal injection sites. The neurodegenerative process induced by 6-OHDA is rapid, and mainly depends on the production of reactive oxygen species and oxidative stress. The toxin is indeed susceptible to nonenzymatic autooxidation associated with the formation of a number of reactive and potentially cytotoxic products. In addition, 6-OHDA inhibits mitochondrial complex I activity. Axon terminals are more sensitive than cell bodies to the cytotoxic action of 6-OHDA. The most common application of 6-OHDA in the scientific literature is related to Parkinson's disease (PD) research.

Rodent 6-OHDA Models in Studies of PD-like Neurodegeneration

Intracerebral injections of 6-OHDA can be used to study the mechanisms and consequences of catecholamine neuron degeneration. Rodents with 6-OHDA lesions remain the model of choice to address the biochemical and molecular consequences of the severe dopamine depletion typical of PD. In this sort of studies, injections of 6-OHDA in the nigrostriatal axon bundle are most commonly used because they cause acute death of nigral dopamine neurons and denervation-induced adaptations in striatal neurons that are complete within a few days. On the other hand, injections of 6-OHDA in the striatum are most commonly used to study mechanisms of nigral cell death and the effects of potential neuroprotective treatments. Intrastriatal 6-OHDA injections have been reported to produce a rapid loss of striatal dopaminergic terminals, and a biphasic pattern of dopamine cell death in the substantia nigra, where a first rapid phase of cell loss (1–2 days) is followed by atrophy and progressive loss of dopamine neurons continuing over 8–16 weeks. Programmed cell death with the morphology of apoptosis has been shown to occur in this model.

Rodent 6-OHDA Lesion Models in Behavioral-Pharmacological Research

Based on the observation that unilateral electrolytic lesions of the substantia nigra produce an asymmetric posture in the rat, with the head and tail deviating towards the side of the lesion, Ungerstedt and Arbuthnott developed a unilateral 6-OHDA lesion model where amphetamine administration is used to produce vigorous rotation towards the side of the lesion, and this behavior is quantified using automated 'rotometer' bowls. In the same animal model, dopamine receptor agonists induce rotation towards the side contralateral to the lesion. Since these seminal observations, drug-induced contralateral rotation in rats with unilateral 6-OHDA lesions has been the most commonly used animal model for screening drugs with antiparkinsonian potential. The success of the model greatly depends on its ease of execution and quantification, and on the well-documented relationship between the extent of drug-induced rotation and the severity of dopamine denervation in the nigrostriatal system. More recently, the specificity and predictive validity of contralateral rotation has been questioned because the effects of dopaminergic drugs on rotation do not correlate well with their capacity to improve spontaneous motor behaviors, and because some aspects of rotational behavior may predict motor complications rather than reversal of parkinsonism. Rats with unilateral 6-OHDA lesions have been

shown to exhibit qualitative and quantitative impairments in the limbs contralateral to the lesion during walking, climbing, reaching-and-grasping, postural adjustments, and other behaviors. Simple tests have been developed to measure these deficits, which can be applied in the preclinical assessment of PD treatments. A relatively novel application of unilaterally 6-OHDA lesioned rats is that related to L-dopa-induced dyskinesia. When treated with L-dopa, these animals exhibit abnormal involuntary movements that affect the limbs contralateral to the lesion, the trunk, and the orofacial musculature. These movements have the same time course as peak-dose dyskinesia in PD, and, like the human disorder, they disrupt physiological motor activities. Rating scales have been developed and validated to quantify treatment-induced abnormal involuntary movements in both rats and mice with unilateral 6-OHDA lesions. Rats subjected to bilateral 6-OHDA lesions of the nigrostriatal pathway display a bilateral parkinsonian-like syndrome including akinesia, gait abnormalities, hunched posture and other postural deficits, increased muscle resistance to passive stimuli, and tremulous jaw movements. The bilateral lesion procedure has been used parsimoniously in preclinical PD research mainly because animals subjected to this lesion require intensive postoperative care.

See also: Basal Ganglia; Climbing Behavior; Complex I Deficiency; Cylinder Test (Paw Reach Test); Dopamine Receptors; Dyskinesias; Levodopa; Rotation, Drug-induced; Staircase (Skilled Reaching) Test; Stepping (Forelimb Akinesia) Test; Substantia Nigra; Tail-pinch Stimulus.

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A

Abetalipoproteinemia (ABL)

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Glossary

Acanthocyte – Erythrocyte of thorn like-protrusion ('acantha' from Greek for thorn). Seen in patients with advanced liver disease, neuroacanthocytosis syndromes, postsplenectomy state.
Acanthocytosis – The presence of acanthocytes in the blood.
Apolipoprotein B-100 – A major transporter of lipids in plasma, it is secreted from liver, the full length is comprised of 4536 amino acids, and is the main constituent protein of VLDL and LDL.
Apolipoprotein B-48 – Apolipoprotein B-48 is secreted from the enterocytes. Apo B-48 is identical to 48% of the amino-terminal portion of apo B-100, and is the translational product of apo B-100 mRNA edited at amino acid position 2152 to form a termination codon. The editing enzyme is a cytidine deaminase that converts cytidine to uridine.
Microsomal triglyceride transfer protein (MTP) – A protein located in the lumen of endoplasmic reticulum, and acts as a chaperone that facilitates the transfer of lipid onto apoB. Failure of lipidation of apo B results in degradation of apoB, accumulation of partially assembled lipoproteins in the endoplasmic reticulum of enterocytes and hepatocytes, and subsequent deficiency of apo B containing lipoproteins 'LDL and VLDL' in plasma.
Retinitis pigmentosa – A type of inflammation of the retina. Characterized by; progressive loss of retinal responses, retinal atrophy, and clumping of the pigment.

Abetalipoproteinemia (ABL)

Definition and History

The syndrome comprising fat malabsorption, ancanthocytosis, Friedreich-like ataxia, and atypical retinitis pigmentosa was originally given the eponym 'Bassen–Kornzweig syndrome' in the 1950s. This syndrome was later linked to low plasma lipoproteins, leading to the redesignation as 'abetalipoproteinemia' in 1960. Improvements in analysis of plasma lipoproteins during the 1970s narrowed the fundamental defect in ABL to the inability to synthesize lipoprotein particles containing apolipoprotein (apo) B, namely chylomicrons, very low density lipoprotein (VLDL), and low density lipoprotein (LDL).

Pathogenesis and Pathophysiology

ABL has an autosomal recessive mode of transmission. Typically, obligate heterozygotes have normal plasma lipid levels. Disease frequency is <1 in 100 000. ABL is caused by mutations in the gene encoding the microsomal triglyceride transfer protein (MTP; MIM 157147) on chromosome 4q22–24. MTP is required for normal assembly and secretion of apo B-containing lipoproteins. MTP is a heterodimer composed of the multifunctional enzyme protein disulfide isomerase (PDI), and a unique 97-kDa subunit. PDI appears to be necessary to maintain the structural integrity of MTP, however, no mutations in PDI have been reported. In the absence of MTP, apo B cannot be properly lapidated, and undergoes rapid presecretory degradation.

Clinical and Pathological Features

At birth, infants with ABL are asymptomatic. Gastrointestinal symptoms typically develop shortly after birth. The initial presentation resembles celiac disease with diarrhea, vomiting, and abdominal swelling. Subsequently, the gastrointestinal signs subside in part because the patients learn to avoid fatty foods. Chronic malabsorption of lipids also leads to fat-soluble vitamin deficiency because the plasma transport and delivery of these vitamins to tissues depend almost exclusively (for vitamin E and β-carotene) or in part (for vitamins A, D, and K) on intact synthesis and secretion of apo B-containing lipoproteins.

Without intervention, the vitamin deficiencies result in neuro-opthalmologic complications by the third decade of life, which dominate the clinical picture, and determine the morbidity of ABL. However, there is heterogeneity in disease presentation. Almost all reported ABL patients >20 years of age who had not received vitamin E supplementation developed neuro-retinal complications. Some were blind and bedridden. In ~25% of reported cases, the diagnosis was made after the age of 20. This clinical heterogeneity is unexplained, although there may be some correlation with the severity of the molecular defect.

With a normo-lipidemic diet, steatorrhea is invariably present. This symptom reflects lipid malabsorption, and is attenuated or fully relieved after the introduction of a low-fat diet. Lipid malabsorption affects growth and may lead to secondary malabsorption of other nutrients. Endoscopic examination of the intestine reveals a 'gelee blanche' or white frosting appearance, which reflects infiltration of the mucosa by lipids. The fat engorgement of intestinal cells provided an early clue that the metabolic defect in ABL prevented the normal secretion of dietary fat from enterocytes into the plasma through the intestinal lymphatics.

As with the intestine, the liver in ABL subjects can show marked lipid accumulation. This hepatic steatosis is occasionally associated with elevation of transaminases either with or without hepatomegaly. Rarely, evolution to fibrosis occasionally progresses to cirrhosis, requiring transplantation.

The initial neurological sign is often diminution then loss of deep tendon reflexes followed by a progressive loss of position and vibration sensation, a spinocerebellar syndrome, and muscular weakness. Also, slowed intellectual development is present in up to one-third of the patients. Neuropathology reveals axonal degeneration of the spinocerebellar tracts and demyelination of the fasciculus cuneatus and gracilis. Vitamin E deficiency was first recognized in ABL patients in 1965, and is now considered to be the cause of the spinocerebellar degeneration. The myopathy results from both neural degeneration and an intrinsic myositis. Although the clinical course is variable without treatment, it leads progressively to impaired mobility, and some patients become wheelchair-bound or even bedridden. The severe effects on the central nervous system are the ultimate cause of death in most patients with ABL, which (before the introduction of high-dose vitamin E therapy) often occurred by the fifth decade. However, early administration of vitamin E has been shown to cause objective arrest of the usually progressive neuropathy and myopathy.

Initially, ABL patients complain of decreased night and color vision, followed by a decrease in visual acuity. The visual field shows a concentric contraction. If left untreated, virtual blindness occurs by the fourth decade. Fundoscopy shows atypical pigmentation of the retina. Pathologically, the retina shows reduced numbers of photoreceptor cells and accumulation of lipofuscin. In some cases, angioid streaks, opthalmoplegia, ptosis, and anisocoria have also been described.

Acanthocytes are speculated to result from membrane deformation stemming from decreased membrane fluidity caused by changes in lipid composition. In addition to acanthocytosis, patients with ABL may have a moderate to severe anemia that results from hemolysis and shortening of the erythrocyte half-life. Abnormalities in coagulation (elevated prothrombin time) caused by deficiency in vitamin K-dependent coagulation factors may also be seen in ABL patients. This may be symptomatic, leading to bruising or hemorrhage.

Management

Early diagnosis and treatment are essential to prevent growth retardation and neuro-opthalmological complications in ABL secondary to chronic lipid malabsorption and deficiency in fat-soluble vitamins.

The steatorrhea and vomiting caused by the lipid malabsorption lead to secondary deficiencies in carbohydrates and proteins. A low-fat diet allows for normal absorption of carbohydrates and proteins. To provide an adequate amount of total calories, the proportion of protein and carbohydrate in the diet must be increased to allow resumption of growth in height and weight. The lipid-poor diet should provide the daily requirements in essential fatty acids in the form of vegetable oils. Oral medium-chain triglycerides provide dietary fatty acids for absorption through the portal circulation, thus bypassing the defective MTP-mediated assembly of apo B-containing lipoproteins in ABL. However, this treatment has been suggested to induce hepatic fibrosis in rare cases.

Vitamin E is thought to prevent lipid peroxidation. Therefore, its deficiency in ABL leads to an increase in the peroxidation of polyunsaturated fatty acids in photoreceptor cells, myelin, and cell membranes in general. ABL subjects require lifetime therapy with vitamin E in large oral doses of 100–300 mg per kilogram per day to prevent this complication. Such high doses of vitamin E are absorbed through the hepatic portal vein. Plasma levels of vitamin E rarely exceed 10% of normal even after long-term therapy. Nevertheless, levels in fat, liver, and erythrocytes almost always increase with large doses of vitamin E.

Vitamin A is thought to stabilize photoreceptor membranes in epithelial cells of the retina. In ABL patients, vitamin A deficiency is easily corrected by oral supplementation because after intestinal absorption and transport to the liver, vitamin A has a lipoprotein-independent own transport system, unlike vitamin E. Daily doses up to four-fold increase over recommended doses are required to normalize the levels of vitamin A or its surrogate analyte, β-carotene.

Vitamin K administration whether orally or parenterally rapidly corrects the coagulation abnormalities in ABL. The deficit in vitamin K is exacerbated when large doses of vitamin E are absorbed, and therefore, it is important to administer vitamin K prophylactically when beginning vitamin E therapy.

Vitamin D deficiency is not classically described in ABL because the metabolism of vitamin D does not depend much on apo B-containing lipoproteins, since there is partial absorption via the portal path and specific vitamin D transport proteins. However, the development of rickets and osteomalacia has been reported, and therefore, prophylaxis should be instituted in infants during growth.

Prognosis

Thus, early treatment with Vitamin E and vitamin A appears to prevent the onset of neuroretinal complications of ABL. However, vitamin therapy does not typically reverse clinical features if it is initiated too late, and neurological and opthalmological signs have already become established.

Familial Hypobetalipoproteinemia (FHBL)

Homozygous FHBL displays most of the clinical attributes of ABL, with the main distinguishing feature being half-normal plasma concentrations of plasma apo B-containing lipoproteins in heterozygote parents, contrasted with normal levels in parents of ABL subjects. Homozygous FHBL is rare, occurring in less than 1 in 100 000 persons. As in ABL, homozygotes may be ascertained at a young age because of fat malabsorption and reduced plasma cholesterol levels. Fat malabsorption results from an inability to form chylomicrons in the intestine and a subsequent failure to absorb fats and fat-soluble vitamins. The failure to form chylomicrons is directly due to the absence of apoB. Cholesterol absorption is also impaired, since a transgenic mouse that lacks intestinal apoB expression and chylomicron formation. Fat malabsorption may lead to a progressive neurologic degenerative disease resulting from vitamin E deficiency. It may also cause retinitis pigmentosa and acanthocytosis. Despite the low plasma cholesterol levels, steroidogenesis appears to be normal except when demands are quite high. Homozygotes that produce enough of a truncated isoform of apoB to facilitate some fat absorption may have a milder phenotype.

FHBL segregates as an autosomal codominant trait. Homozygotes have clinical and biochemical findings similar to ABL, with virtual absence of LDL cholesterol. Heterozygotes have LDL cholesterol below the tenth percentile for age and sex. Apart from hypocholesterolemia, FHBL heterozygotes are healthy and usually have no difficulty absorbing fat. Genetic linkage analyses in the 1980s indicated that the defect in some cases of FHBL was within the *APOB* gene on chromosome 2p24, which was distinct from the ABL locus. The *APOB* gene defects were mostly truncation-producing mutations of apo B of the nonsense or frameshift variety, although there are some missense mutations in this gene also.

The treatment of homozygous FHBL is similar to that of ABL. No specific treatment is indicated for heterozygotes, but dietary supplementation with fat-soluble vitamins is reasonable. Heterozygotes should be informed that if their spouses also have a very low plasma cholesterol level, the possibility exists that offspring could have homozygous or compound heterozygous FHBL; in this situation, subjects should be referred to a lipid clinic for genetic counseling.

Summary

Homozygosity for a defect either in apo B or MTP cripples this process, and results in failure to secrete apo B-containing lipoproteins into the plasma leading to deficiencies of fat-soluble vitamins, with vitamin E deficiency underlying the characteristic neuropathy in ABL and FHBL. Early diagnosis and high-dose oral supplementation with fat-soluble vitamins has helped normalize life expectancy and quality of life in patients with these rare metabolic conditions.

See also: Chorea; Chorea–acanthocytosis; McLeod Syndrome.

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Accelerometry

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Glossary

Accelerometer – A motion transducer that is sensitive to the acceleration of motion and earth's gravity.
Gravitational artifact – The portion of an accelerometer output signal that is produced by earth's gravity.
Gyroscopic transducer – A motion transducer that is sensitive to the velocity of the rotation of a body (i.e., angular velocity).
Rotational motion – Motion of a body that produces a change in orientation in space (i.e., spinning or rotation).
Translational motion – Motion of a body without any change in its orientation in space (i.e., without any spinning or rotation).

Accelerometers are small motion transducers that are based on Newton's law of mass acceleration (Force = mass × acceleration) and Hooke's law of spring action (Force = spring constant × change in length of a spring). Piezoresistive, piezoelectric, and capacitance devices are the three types of accelerometers used in human applications. All three types contain a small mass attached to an elastic element, and the elastic element is stretched or compressed in proportion to the acceleration. Very small transducers are produced using microelectromechanical systems (MEMS) technology.

Accelerometers are made for many industrial applications such as the measurement of machine vibrations and vehicle crashes. Consequently, accelerometers are available in many sizes, shapes, sensitivities, and accuracies. Users should consult with a technician to make sure that an accelerometer is suitable for the desired biological application. Some accelerometers are capable of measuring accelerations of $< 0.01g$ ($1\,g = 9.807\,\mathrm{m\,s^{-2}}$, the static acceleration of gravity), and therefore, these devices are capable of measuring very small accelerations such as physiologic tremor. Other accelerometers are less sensitive and are capable of measuring pathologic tremor but not physiologic tremor (e.g., Kinesia™, www.clevemed.com/pdfs/products/Kinesia.pdf and Tremorwatch®, www.salusa.se/Filer/Produktinfo/Aktivitet/tremorwatch.pdf). Insensitivity to physiologic tremor is an advantage when physiologic tremor is of no interest or might confound the measurement of pathologic tremor.

Motion of a body part usually consists of translational motion and rotation in three-dimensional space. Postural tremor in the horizontally extended hand is predominantly rotational motion about the wrist. Most accelerometers are linear accelerometers with one to three orthogonal axes of recording. A linear accelerometer measures translational movement, and it records rotational movement only to the extent that it is mounted some distance away from the axis of rotation (**Figure 1**). For example, if a linear accelerometer is mounted precisely on the axis of rotation of the hand (i.e., the wrist), it will detect only translational wrist motion and gravitational artifact. It will not measure the variable of interest: angular acceleration of the hand.

Gravitational artifact is an important confounder in accelerometry. Many investigators assume incorrectly that gravitational artifact is constant and can be removed simply by numerical subtraction or AC coupling. To the contrary, gravitational artifact occurs at all frequencies of body rotation, except when the accelerometer's axis of sensitivity rotates solely in the horizontal plane. For example, in **Figure 1**, the vertical Z axis of the accelerometer contains gravitational artifact equal to $g \cos(\theta)$ where θ is the angle between the Z axis and the gravity vector. For small angles of rotation ($<25°$), the Z axis and the gravity vector are approximately parallel, resulting in a gravitational artifact that is nearly constant ($\approx 1g$). Thus, true inertial acceleration is approximately equal to the accelerometer signal minus $1g$. However, for large angles

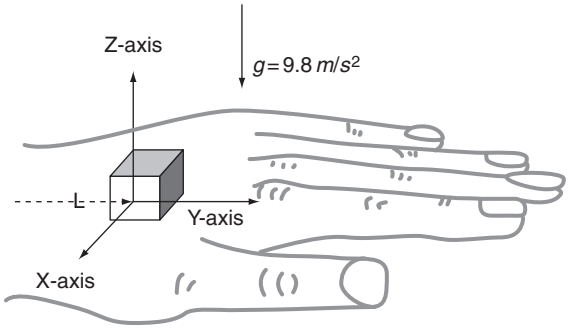

Figure 1 A triaxial accelerometer mounted on the dorsum of the hand will detect motion in the direction of its three axes of sensitivity. The accelerometer will detect translational motion and tilt with respect to gravity (g). The rotational acceleration is detected only when the accelerometer is located some distance L from the axis of rotation (e.g., the wrist). When $L = 0$, the accelerometer will simply spin in space, relative to gravity, making the output of the accelerometer pure gravitational artifact. Gravitational artifact can be as large as $\pm 1g$ at all frequencies of rotation.

of rotation, the gravitational artifact can vary as much as $\pm 1g$, at any frequency of rotation. This gravitational acceleration will, to some extent, obscure the inertial acceleration, which is the measurement of interest.

Except when an accelerometer simply moves up and down, more or less vertically, the task of separating the gravitational and inertial components of acceleration is impossible unless multiple accelerometers are used. Gravitational artifact will contaminate an accelerometer signal at all frequencies of rotational motion and in all planes of rotation except the horizontal plane. Biaxial and triaxial accelerometers are not a solution, because each axis of the accelerometer will contain gravitational artifact to the extent the accelerometer rotates or tilts with respect to gravity. At least six one-dimensional linear accelerometers must be strategically mounted on a body part to record translational and rotational movement of a body segment in three-dimensional space, and more than six accelerometers are needed in most instances.

Gyroscopic transducers (e.g., Kinesia™ and Motus® at www.motusbioengineering.com/index.htm) are not sensitive to gravity, and these devices are preferable to accelerometers when motion is predominantly rotational. Gyroscopic transducers are also constructed with MEMS technology, which makes them sufficiently small and lightweight for human applications. Gyroscopic transducers measure angular velocity, from which angular rotation and acceleration can be computed by numerical integration and differentiation respectively. Angular accelerometers are also commercially available (www.endevco.com/product/prodpdf/7302BM4.pdf). The technology of these devices is driven by industrial applications, but the manufacturers of these devices are increasingly in tune with biomedical applications (e.g., Xsens www.xsens.com/en/home.php).

Accelerometers and gyroscopic transducers require electrical filtering and amplification. Modern electronics enable these functions to be integrated with the transducer, forming a wireless portable device (Kinesia™, Tremorwatch®). Consequently, quantitative electrophysiologic study of movement disorders (e.g., tremor) is no longer restricted to a laboratory.

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Acetylcholine

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Glossary

Acetylcholinesterase inhibitors – Drugs that inhibit the break down of acetylcholine.
G protein – Cell membrane protein involved in the cellular signal transduction pathway.
Hydrophilic – Having strong affinity for water.
Lewy bodies – Abnormal aggregates of protein deposits in neurons.
Metabotropic receptors – G-protein coupled receptors.
Neuromuscular junction – A synaptic junction between a nerve and muscle cell.
Transmembrane receptors – Integral membrane proteins spanning the entire thickness of the membrane.

Introduction

Acetylcholine (Ach) is a neurotransmitter that is synthesized from choline and acetyl CoA by choline transferase enzyme and has a significant role in both the peripheral and central nervous systems. Acetylcholine is released at all preganglionic neurons, all parasympathetic postganglionic neurons, sympathetic postganglionic terminals of sweat glands, and neuromuscular junctions. Acetylcholine receptors are transmembrane (TM) receptors and are divided into two major groups: the metabotropic muscarinic receptors and the ionotropic nicotinic receptors.

Nicotinic Acetylcholine Receptors

The nicotinic acetylcholine (nACh) receptors are fast ionotropic receptors that are composed of distinct

subunits, α, β, δ, ε, and γ, and are arranged in different pentameric combinations around a ligand-gated excitatory ion channel permeable to Na^+, K^+, and Ca^{2+} ions.

All nACh receptor subunits have a large extracellular NH_2 terminal domain, three TM domains, a cytoplasmic loop in variable size and amino acid sequence, and a fourth TM domain with a short and variable extracellular COOH terminal. These subunits are further identified as α (alpha) or non-α (non-alpha) subunits based on the presence of a Cys–Cys pair near the TM1 entrance, which is required for the binding of the agonist. The nACh receptors are also subdivided according to whether their main site of distribution is muscle or nerve. Muscle nACh receptors consist of one α and four non-α (β, δ, ε, and γ) subunits. Neuronal subunits are formed in various combinations of α (α_2–α_{10}) and β subunits (β_2–β_4).

These subunits are widely distributed. For example, the mRNA of α_4 subunit is expressed in the thalamus, cerebral cortex, ventral tegmental area, and substantia nigra. Peripherally, these α_4 subunits are expressed in the trigeminal ganglion. The presence of α_6 subunits in striatum indicates their importance in locomotor activity. In addition to their presence in both the central and peripheral nervous systems, evidence exists that the neuronal subunits are also expressed by many nonneuronal cells, including cells of the digestive, pulmonary, and immune systems.

The binding site of ligands, such as nicotine, is in a hydrophobic pocket that is formed at the interface of adjacent subunits. The front side (positive site) of the binding site is formed by one of the following α subunits (α_1, α_2, α_3, α_4, α_6, α_7, α_9) with the Cys–Cys pair present, while the back site (negative site) of this binding site is formed by one of the following adjacent subunits (α_{10}, β_2, β_4, δ, ε, and γ). When a ligand binds the nACh receptor, it creates significant structural rearrangements throughout the receptor, which results in repositioning of the TM2 segment of each subunit, opening the ion channel in microseconds. The rotation of the TM2 segments plays a crucial role in supporting ion flow by temporarily replacing the hydrophilic barrier with hydrophilic residues and increasing the diameter of the channel.

Activation of nACh receptors by nicotine results in Na^+ influx, membrane depolarization, and activation of voltage-gated Ca^{2+} channels. Subsequently, stimulation of Ca^{2+} dependent kinases, including protein kinase C (PKC), protein kinase A (PKA), calmodulin-dependent protein kinase II, and extracellular signal-regulated kinases, occurs.

The activity of nACh receptors can be increased by nicotinic allosteric potentiating ligands (APLs) binding to the receptor at a site close to but distinct from the ACh binding site. For example, galantamine, an acetylcholinesterase inhibitor, improves synaptic transmission primarily by acting as an APL.

Muscarinic Acetylcholine Receptors

Muscarinic acetylcholine (mACh) receptors belong to the family of G-protein coupled receptors and consist of five different subtypes: M1, M2, M3, M4, and M5 receptors. These receptors are subdivided into two groups, based on their G-protein coupling properties. M1, M3, and M5 receptors couple to $G_{q/11}$ proteins, increasing formation of inositol-1,4,5-triphosphate, activating phospholipase C, mobilizing intracellular calcium, and increasing cAMP. On the other hand, M2 and M4 receptors exert their effects by binding primarily to $G_{i/o}$ proteins, inhibiting the activity of adenylyl cyclase and decreasing cAMP formation. The orthosteric binding site of these receptors is highly conserved and is located between TM helices 3, 5, 6, and 7.

M1 mACh receptors are highly expressed in the cerebral cortex, hippocampus, and striatum. This is consistent with their role in learning and memory. M2 mACh receptors are mainly located in the brainstem and thalamus; they are also found in the cortex, hippocampus, and striatum. Peripherally, these receptors play an important role in smooth muscle contractions. Compared with other muscarinic subtypes, there is less expression of M3 receptors in the CNS. Nonetheless, M3 receptors are highly expressed in the hypothalamus and have also been found in cerebral cortex and hippocampus. In the peripheral system, there is four times higher expression of M3 receptors in smooth muscle tissues compared with M2 receptors. Studies indicate a synergistic relationship between M2 and M3 receptors in contractions of smooth muscles. M4 receptors are found in the cortex, hippocampus, and on striatal projecting neurons. M4 agonists have shown to inhibit mesolimbic dopaminergic activity, suggesting antipsychotic properties. M5 receptors have been found in substantia nigra and ventral tegmental areas of the brain, indicating a probable role for these receptors in dopamine transmission. In the periphery, they are expressed at low levels in iris-ciliary muscle and salivary gland.

Physiological Properties

Cognition

Reduced function or expression of nACh receptors may play a significant role in the pathophysiology of the dementia seen in Alzheimer's disease (AD) or schizophrenia. The expression of $\alpha_4\beta_2$ nACh receptors is significantly decreased in AD. Different animal studies have also shown a decreased hippocampal expression of α_4 and α_7 nACh receptors with age. Similarly, studies in schizophrenia show a substantial reduction in α_7 nACh receptors in hippocampus and frontal cortex. Therefore,

preventing or decreasing the loss of nAChR function may be therapeutically beneficial. In human trials, use of nicotine showed little efficacy in the improvement of AD symptoms. This may have been related to the initiation of treatment after the diagnosis of symptoms.

The loss of cortical cholinergic neurons has been well-documented in Parkinson's disease (PD) dementia and Lewy body dementia. There is less expression of α_7 nACh receptors in the frontal cortex of patients with PD dementia and Lewy body dementia. The reduction of these receptors in the temporal cortex of patients with Lewy body dementia was associated with delusions and visual hallucinations.

Drugs that are currently approved for AD include the acetylcholine esterase inhibitors (AChE), galantamine, donepezil, and rivastigmine. These drugs have also been evaluated for the improvement of cognitive decline and negative symptoms of schizophrenia, as well as PD dementia.

It is also important to note that because of the high expression of M1 mACh receptors in the cortex and hippocampus, it is postulated that M1 mACh receptor agonists possess the highest potential for the treatment of AD. However, despite various preclinical candidates, no M1 mACh agonist is yet available for the treatment of AD. This is thought to be due to a lack of selectivity for M1 mACh receptors, since these compounds bind the highly conserved orthosteric ACh-binding site. Recent discovery of a new class of agonists, which selectively bind the allosteric M1 mACh receptor binding site, shows promise.

Movement

PD is a progressive neurodegenerative disorder caused by a loss of dopaminergic neurons in the substantia nigra. Several studies suggest that acetylcholine receptors play a critical role in PD. In several animal studies, nigrostriatal damage caused a significant loss in $\alpha_6\alpha_4\beta_2\beta_3$, $\alpha_6\beta_2\beta_3$, and $\alpha_4\beta_2$ nACh receptors, and postmortem studies showed a significant decline in the nicotinic Ach receptors in the striatum of PD patients.

Extensive studies have also shown the specific involvement of α_4 and α_6 containing nACh receptors in improving abnormal motor activity in rodents.

Nicotine can induce dopamine neurons to release dopamine. It is suggested that this release is mediated through the activation of presynaptic nACh receptors that are located on the cell body or terminal regions of dopaminergic neurons. Therefore, it has been postulated that nicotine or nicotine receptor agonists that cause dopamine release from nerve terminals may have a higher physiological efficacy in stimulating postsynaptic dopamine receptors compared with the administration of L-dopa or dopamine receptor agonists. It is also possible that combination therapy with a nACh receptor agonist and L-dopa may allow to decrease the dose of L-dopa and reduce the frequency and severity of adverse effects usually reported with the use of L-dopa. Few studies have investigated the use of nicotine patch and an investigational nicotinic agonist SIB 1508Y in PD; however, no significant improvement in the PD symptoms were noted with the doses and duration of treatment chosen. The use of higher doses was limited by the occurrence of intolerable side effects.

One future therapeutic option includes developing drugs that specifically act on α_6 subunits of nACh receptors, which may play a significant role in regulating dopamine release in the striatum.

Stimulation of nACh receptors may also play a role in neuroprotection and against nigrostriatal damage. Epidemiological studies showed that heavy smokers are ~50% less likely to have PD. However, the results of animal studies have been inconsistent.

In PD, the destruction of dopaminergic neurons results in a higher level of acetylcholine in the striatum. Anticholinergic drugs have long been used to restore the balance between the cholinergic and dopaminergic systems in PD; however, the extensive central and peripheral adverse effects caused by these medications have limited their use, especially in older individuals. PD tremor, in particular, may be improved with anticholinergic medications. Recent research suggests a role for more selective cholinergic antagonists. Several animal studies suggest a role for M4 mACh receptor antagonists to improve tremor in PD.

Dystonia is characterized by sustained, prolonged muscle contractions and can produce abnormal, twisting body movements and postures. Imaging and postmortem studies have linked dystonia with lesions and dysfunction of basal ganglia. There have been reports of significant reduction in dopamine level in the substantia nigra and striatum in dopa-responsive dystonia (DRD). Patients with DRD usually show a significant improvement when treated with small doses of L-Dopa. Anticholinergic drugs such as trihexyphenidyl have shown efficacy and resulted in a significant symptomatic improvement in patients with young-onset dystonia, segmental dystonia, and generalized and secondary dystonia. Botulinum toxin types A and B have shown efficacy in the treatment of dystonia. Both type A and type B botulinum toxic act at the neuromuscular junction and inhibit the release of ACh at the presynaptic membrane paralyzing the striated muscles.

Addiction

Chronic use and addiction to nicotine have been related to changes in function and expression of nACh receptors.

Continued nicotine administration results in upregulation of high-affinity $\alpha_4\beta_2$ nACh receptors. Several genetic studies in mice have shown the important role of α_4 nAChR subunits in nicotine addiction. A mutant form of this subunit showed a higher sensitivity to nicotine, and a lower concentration of nicotine was required to enhance the activity of this receptor. Other studies indicate that $\alpha 7$ nACh receptors may control withdrawal symptoms and that tolerance to nicotine administration may be induced by $\beta 3$ and/or $\beta 4$ subunits.

M5 mACh receptors are the main subtype in the ventral tegmental area of the brain, which is involved in drug reward and addiction. Several studies have shown that activation of these receptors will increase dopamine levels in the nucleus accumbens and other limbic areas, reinforcing drug dependency. On the other hand, selective M5 mACh receptor antagonists inhibit dopamine release and may provide a novel therapeutic approach in the treatment of drug addiction.

See also: Alzheimer's Disease and Parkinsonism; Dementia, Movement Disorders; Dopamine Transporter: Aging and Parkinson's Disease; Parkinson's Disease: Definition, Diagnosis, and Management.

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Actigraphy

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Glossary

Accelerometer – A motion transducer that is sensitive to the acceleration of motion and earth's gravity.

Actigraph – A small portable motion transducer, usually an accelerometer, worn on the wrist or other body part for the purpose of recording the motor activity for one or more days.

Gravitational artifact – The portion of an accelerometer output signal that is produced by earth's gravity.

Gyroscopic transducer – A motion transducer that is sensitive to the velocity of the rotation of a body (i.e., angular velocity).

Rotational motion – Motion of a body that produces a change in orientation in space (i.e., spinning or rotation).

Translational motion – Motion of a body without any change in body orientation in space (i.e., without any spinning or rotation).

An actigraph is a small portable motion transducer that is worn on the wrist or other body part (e.g., ankle) for the purpose of recording the motor activity for hours or days. The motion transducer is usually an accelerometer with one to three axes of recording. These devices are about the size of a watch and contain integrated electronics for the processing and storage of digitized data. Data are downloaded from the actigraph to a digital computer for analysis.

The validity of these devices in recording a particular type of activity depends critically on the method used to process the accelerometric signal(s). Accelerometers are

extremely sensitive to all types of motion, including mechanical and gravitational artifact. Sudden jarring movements entail much larger accelerations than slow smooth movements, and the acceleration of repetitive movements (e.g., tremor) increases in proportion to the squared frequency of repetition (oscillation). Thus, the processing algorithm must take such issues into account when measuring motor activity, and the algorithm used in a particular device determines its utility and validity more than the characteristics of the accelerometer. An accelerometer on the wrist will detect the acceleration produced by all but very minute forces (muscle, gravitational, and external) acting on the wrist directly or indirectly through mechanical linkage with other body parts.

Actigraphy was first developed in the 1970s for analysis of rest–activity (sleep–wake) cycles. Sleep is deemed present when the quantity of movement (activity) per minute falls below an empirically defined threshold. Actigraphy is a reliable and valid method of detecting sleep in normal adults, but its reliability and validity are unestablished in patients with sleep disorders. The location of the actigraph has little, if any, effect on its reliability and validity.

Van Someren and colleagues developed an actigraph algorithm for long-term tremor recording, and this algorithm is incorporated into the Cambridge Tremorwatch (Cambridge Nanotechnology, www.camntech.com/h_aw_6.html). The integrated electronic algorithm in this device separates tremor from other movement by distinguishing the rhythmic high-frequency profile of tremor acceleration from the arrhythmic low-frequency profile of other movement. Tremor is quantified in terms of duration and amplitude. It has been validated in patients with Parkinson's disease but not other forms of tremor. The uniaxial accelerometer in this device is not sensitive enough to detect physiologic tremor, and the measurement of tremor amplitude is subject to the caveats discussed elsewhere.

The Cambridge Tremorwatch parses acceleration into tremor and nontremor activity. It is unclear to what extent this nontremor activity is a measure of bradykinesia or hyperkinesia in Parkinson's disease.

Salarian and colleagues developed an actigraph with gyroscopic sensors instead of accelerometers and were able to produce measures that correlated with the Unified Parkinson Disease Rating Scale (UPDRS) tremor and bradykinesia scores. Unlike accelerometers, gyroscopic sensors are not sensitive to their position on a body segment and are not subject to gravitational artifact.

Actigraphs are used in many other applications that are relevant to movement disorders. Kinetic energy is one-half the body mass times velocity squared, and velocity is the integral of acceleration. Thus, energy expenditure can be estimated with an accelerometric actigraph worn at the waist, near the body's center of mass. Actigraphs are also used to capture crude estimates of physical activity, postural sway, walking speed, walking cadence, limb motion during walking, and falls.

Actigraphs provide only crude measures of body motion regardless of the type of transducer used, because body motion usually consists of complex translational motion and rotation of multiple body segments in 3-dimensional space. Multiple transducers mounted strategically on multiple body segments are needed to quantify motion completely. The rhythmicity and frequency of pathologic tremors are useful in distinguishing tremor from other normal and abnormal movements. However, rhythmic normal movement, such as tooth brushing, can be mistaken for tremor. The complex movements produced by chorea, ballism, myoclonus, and dystonia cannot be distinguished with an actigraph.

In summary, users beware of the limitations of these devices! There is no actigraph that is suited for all applications, and actigraphs are becoming increasingly application specific. Transducer technology, data analysis algorithms, integrated electronics, wireless data transmission, and data analysis software are improving rapidly. Many options are available, and the internet is a good place to search for the best available option. Begin searching the internet using the following search parameters with and without your particular application (e.g., tremor, bradykinesia, falls) appended: actigraph, activity motor plus accelerometer, activity monitor plus gyroscope.

See also: Accelerometry.

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Akathisia

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Glossary

Diurnal pattern – Symptoms and signs that vary or fluctuate in intensity over a 24 h period for example, better in the morning and worse in the evening.
Drug holiday – A planned period of time in which the person stops a medicine and then resumes it.
Tactile hallucinations – A perception of being touched in the absence of any stimulus, such as a feeling of insects/bugs crawling on the skin (known as formication).

Definition and History

Akathisia is a disorder characterized by a subjective report of inner restlessness with an inability to sit still, relieved by moving about. The patient usually has repetitive movements, which involve primarily the legs and trunk, that occur predominantly when the patient is sitting.

The first documented description of a syndrome resembling akathisia has been attributed to the British physician and anatomist Thomas Willis (1621–1675). The term akathisia (from Greek, literally 'not to sit') was coined by Lad Haskovec (1902) to describe two patients with restlessness and an inability to sit still. Haskovec distinguished the disorder from chorea and regarded it as a nonorganic psychiatric disorder, a tradition that continued for the next two decades. Due to the Sicard's and Bing's descriptions of akathisia in association with parkinsonism in 1923, akathisia was recognized as a symptom of idiopathic or postencephalitic parkinsonism. An influential statement came from Kinnier Wilson (1940) who wrote that even though Haskovec used the term akathisia for cases of 'hysterical or psychopathic nature,' it could be applied to parkinsonian patients.

In 1947, Sigwald reported drug-induced akathisia in a patient with Parkinson's disease (PD), who developed restlessness when treated with promethazine, a neuroleptic drug. After antipsychotic drugs became generally available, a number of reports appeared in the literature of patients being restless, unable to sit, and marching like soldiers to abate the restless feelings. The similarity with the akathisia syndrome of the preneuroleptic era was recognized. In the early 1960s, akathisia was accepted as an 'extrapyramidal' side-effect of neuroleptic medications with dopamine receptor blocking properties. It was demonstrated that akathisia could occur in psychiatrically normal individuals when treated with neuroleptic drugs.

In modern psychiatry, akathisia is used synonymously with drug-induced akathisia, but the term's origin in the preneuroleptic era makes it clear that the syndrome has multiple causes.

Pathogenesis

Although numerous risk factors for akathisia have been described, the exact pathophysiology of akathisia is still unknown.

Drug-Induced (Iatrogenic) Akathisia

The most frequent cause of akathisia is exposure to antipsychotic medications, both typical, such as phenothiazines, thioxanthenes, and butyrophenones (e.g., haloperidol), and atypical, such as olanzapine and quetiapine (patients 1 and 4). Antipsychotic medications primarily act as competitive antagonists of central dopaminergic receptors.

Akathisia due to the use of neuroleptics can occur shortly after starting the psychotropic drug, termed acute akathisia, or after long-term use, termed tardive akathisia. In the former case, akathisia usually starts within days of starting or increasing the dose of an antipsychotic. In the latter case, the syndrome can develop after long-term, stable, or even decreasing doses of antipsychotic drugs. The common characteristic of these drugs is that they block dopamine D2 receptors in multiple areas of the nervous system. In line with this, metoclopramide, an antiemetic drug that is not only used in psychiatry but also with dopamine D2 receptor blocking actions, also causes akathisia. In addition, dopamine depleting drugs, such as tetrabenazine (patient 3) and reserpine (the latter is no longer in clinical use), can cause akathisia, suggesting that the syndrome relates to decreased activity of central dopaminergic mechanisms, but can have pre- or postsynaptic causes of dopaminergic antagonism. Rarely, akathisia is associated with antidepressants, particularly the selective serotonin reuptake inhibitors (SSRIs (patient 5)) and less often with tricyclic compounds.

Akathisia can also be due to certain recreational drugs such as γ-hydroxy-butyrate (GHB), methamphetamine, and 3,4-methylendioxymethamphetamine (MDMA). All these agents potentially influence dopaminergic neurotransmission.

Akathisia Associated with Neurodegenerative Disorders

Akathisia can be seen in a variety of neurodegenerative forms of parkinsonism such as idiopathic PD, corticobasal degeneration (CBD), and multiple system atrophy (MSA). It can also occur in the context of postencephalitic parkinsonism. In PD, akathisia can develop in untreated patients or in treated patients in need of higher daily doses of dopaminergic medication. Among PD patients with a fluctuating medication response throughout the day, akathisia can be a cyclic and distressing form of 'off' effects that occur when the dopaminergic drugs are not working well. However, other studies (see below) found no correlation in symptoms of akathisia with response to levodopa.

Although these observations suggest that blockade or reduced stimulation of dopamine receptors, especially D2 dopamine receptors, can cause akathisia, the exact mechanism is probably more complicated. Beta blockers and anticholinergics can relieve akathisia, suggesting nondopaminergic influences. Anticholinergics may work indirectly to modify dopaminergic transmission because there are well-established compensatory balances between cholinergic and dopaminergic function in several areas of the central nervous system. Beta blockers antagonize norepinephrine, and the mechanism underlying efficacy of these drugs is less clear. In addition, a role of iron has been suggested based on phenomenological similarities between akathisia and restless legs syndrome (RLS). In RLS, unpleasant sensations in the legs occur that worsen at rest or periods of inactivity and are relieved by movement. These, however, are primarily nocturnal, which is not the typical pattern with akathisia. The association between low serum iron and RLS is established and serum iron may also be lower than normal in patients with antipsychotic medication-induced akathisia.

Epidemiology/Risk Factors

The prevalence of akathisia in neuroleptic-treated people ranges between 20 and 75%, occurring more frequently in the first 3 months of treatment. It is usually related not only to acute administration of a neuroleptic but also to rapid dose increase. Currently, clinicians use newer, atypical antipsychotics, but these drugs also induce akathisia, though to a lesser degree than the traditional neuroleptic drugs: risperidone, 6.7–50%; olanzapine, 2.8–16%; quetiapine, 2–5%; clozapine, 0–39%. One of the causes for the wide discrepancy in the reported prevalence of akathisia may be under-diagnosis. The presence and severity of drug-induced akathisia can be measured using the Barnes Akathisia Scale (see **Table 1**).

Lang and Johnson performed an interview study using a questionnaire in 100 patients with idiopathic PD and found evidence for akathisia in 26; 17 patients complained of general restlessness. Akathisia most often started after initiation of levodopa. Comella and Goetz studied 56 idiopathic PD patients using an 'akathisia questionnaire.' Akathisia was defined as feelings of restlessness associated with an urge to move. Based on this definition, they concluded that 45% of patients had akathisia and motor restlessness predominantly affecting the legs and feet. This high prevalence may be due to the inclusion of other causes of restlessness in these patients, such as muscle stiffness and immobility and possibly RLS. In a recent prospective study by Wadia and colleagues assessing the prevalence of restlessness in parkinsonism, 16% of idiopathic PD patients and 19% of patients with atypical parkinsonism (MSA, Progressive Supranuclear Palsy (PSP), CBD, and vascular parkinsonism) had restlessness not due to stiffness and immobility but thought to be due to akathisia, in contrast to 6% aged matched healthy controls. This observation demonstrates that akathisia likely affects individuals with atypical parkinsonism as well as PD.

Restlessness and psychomotor agitation may also occur in a wide variety of diseases, for example, due to metabolic disturbances secondary to liver or kidney disease. However, an iatrogenic cause should not be overlooked. In a recent prospective study, in which cancer patients were referred to an outpatient department of psychiatry, 20 of 420 (4.8%) patients had developed akathisia from prochlorperazine, an antiemetic drug.

Clinical Features and Diagnostic Criteria

The typical motor phenomena in akathisia include complex motor activities that are repetitive or stereotyped. These include repetitive crossing of legs, tapping of legs or feet, squirming in a chair, and truncal rocking back and forward. Arm movements may include repetitive rubbing of the face or scalp. Patients find it hard to sit still in a chair and therefore get up and pace. In addition, some patients prefer to lie down rather than sit. Vocalizations are often associated, especially in tardive akathisia, including moaning, groaning, and humming (patient 4). Akathisia rarely involves a single limb or body part. The movements and vocalizations can be transiently suppressed by the person if asked.

Patients describe an inner sense of restlessness, inner tension, or even torment as well as other abnormal sensations such as burning or pain. However, frequently, they cannot describe the sensation. The motor activity provides some relief from the abnormal sensation.

Akathisia may range in intensity from a mild sense of disquiet or anxiety (which may be easily overlooked) to a total inability to sit still, accompanied by overwhelming anxiety, malaise, and severe dysphoria (manifesting as an almost indescribable sense of terror and doom). Akathisia can exacerbate psychopathology and lead to suicide.

Table 1 Rating scale for drug-induced akathisia (by Barnes)

Patients should be observed while they are seated, and then when standing while engaged in neutral conversation (for a minimum of 2 min in each position). Symptoms observed in other situations, for example, while engaged in activity on the ward may also be rated. Subsequently, the subjective phenomena should be elicited by direct questioning.

Objective

0 Normal, occasional fidgety movements of the limbs

1 Presence of characteristic restless movements: shuffling or tramping movements of the legs/feet, or swinging of one leg while sitting, and/or rocking from foot to foot or 'walking on the spot' when standing, but movements present for less than half the time observed

2 Observed phenomena, as described in (1) above, which are present for at least half the observation period

3 The patient is constantly engaged in characteristic restless movements, and/or has the inability to remain seated or standing without walking or pacing, during the time observed

Subjective

Awareness of restlessness

0 Absence of inner restlessness

1 Nonspecific sense of inner restlessness

2 The patient is aware of an inability to keep the legs still, or has a desire to move the legs, and/or complains of inner restlessness aggravated specifically by being required to stand still

3 Awareness of an intense compulsion to move most of the time and/or reports a strong desire to walk or pace most of the time

Distress related to restlessness

0 No distress

1 Mild

2 Moderate

3 Severe

Global clinical assessment of akathisia

0 Absent

No evidence of awareness of restlessness. Observation of characteristic movements of akathisia in the absence of a subjective report of inner restlessness or compulsive desire to move the legs should be classified as pseudo-akathisia

1 Questionable

Nonspecific inner tension and fidgety movements

2 Mild akathisia

Awareness of restlessness in the legs and/or inner restlessness worse when required to stand still. Fidgety movements present, but characteristic restless movements of akathisia not necessarily observed. Condition causes little or no distress

3 Moderate akathisia

Awareness of restlessness as described for mild akathisia above, combined with characteristic restless movements such as rocking from foot to foot when standing. Patient finds the condition distressing

4 Marked akathisia

Subjective experience of restlessness includes a compulsive desire to walk or pace. However, the patient is able to remain seated for at least 5 min. The condition is obviously distressing

5 Severe akathisia

The patient reports a strong compulsion to pace up and down most of the time. Unable to sit or lie down for more than a few minutes. Constant restlessness that is associated with intense distress and insomnia

Akathisia may be difficult to distinguish from psychotic agitation or anxiety, especially if the person describes a subjective experience of akathisia in terms of being controlled by an outside force. If the akathisia is mistaken for psychosis, the antipsychotic drug dose may be increased leading to worsening of the condition. Another pitfall is that a patient may suffer from neuroleptic-induced hypokinesia and akathisia at the same time.

In the study of Lang and Johnson, akathisia most often started after initiation of levodopa but was not clearly related to either 'on' or 'off' phases of the levodopa-induced motor response fluctuations. The authors did not find a diurnal pattern. Drug holidays led to a transient resolution of symptoms in individual cases. In the study of Comella and Goetz, half of the patients reported an association between their akathisia symptoms and the timing of their antiparkinson drugs. About 40% of their patients had akathisia only at certain times of the day. The syndrome may also occur when antiparkinsonian drugs are reduced or discontinued.

Differential Diagnosis

In psychiatric patients on neuroleptic drugs and displaying motor restlessness, akathisia may be difficult to distinguish from psychotic agitation, anxiety, and tactile hallucinations, especially if the patient interprets the sensation in terms of being controlled by an outside force. This is complicated by the possibility that movements may be suppressed by the medication (hypokinesia). The inner restlessness may not

be expressed voluntarily, and for patients with intellectual disability, it may be difficult to describe the sensations.

In PD, akathisia should be distinguished from muscle stiffness and immobility as well as from drug-induced dyskinesia. In this respect, the presence of inner restlessness may be the clue. As noted above, akathisia in PD patients with response fluctuations may be associated with the timing of the antiparkinsonian drugs in different manners; during 'on,' 'off,' 'wearing off,' or the 'onset of drug effect' phases, in a similar way to levodopa-induced dyskinesia that varies in phenomenology (chorea and dystonia) in relation to levels of levodopa.

Akathisia shares a number of features with RLS. Both disorders are accompanied by an urge to move. Compared to drug-induced akathisia patients, those with RLS more often have sleep disturbances, periodic limb movements, paresthesias, and worsening of the symptoms at nighttime and less often have inner restlessness. Many patients with akathisia prefer the recumbent position over the sitting position, while lying down often worsens the symptoms of RLS.

Other rarer disorders that may be mistaken for mild akathisia include 'painful legs and moving toes'; although the movements here generally do not alleviate discomfort.

Diagnostic Work-Up/Tests

Akathisia can be diagnosed through a careful history, in particular, drug exposure and physical examination. Patients should be observed while they are seated and when standing and asked to describe any abnormal sensations especially when trying not to move. However, patients may be able to voluntarily stay still for a short period of time, so they should not be prompted to sit still. The clinical context, such as the use of neuroleptics or the presence of PD, is important in this aspect. There are no ancillary tests such as laboratory or imaging studies that assist in making the diagnosis. Small case series have reported lower serum iron and ferritin levels in patients with akathisia, although the finding is inconsistent.

Management

The optimal management of neuroleptic-induced akathisia is prevention rather than treatment. In this regard, it is preferable to use the atypical antipsychotics and standardize titration, although these can also result in akathisia. Treatment options include discontinuation or reduction of dose of the causative agent, if possible.

Most commonly, anticholinergics and propranolol (or other lipophilic beta-blockers) are recommended for neuroleptic-induced akathisia. The rationale for using anticholinergics is that acute akathisia may be an extrapyramidal side-effect similar to dopamine D2 receptor antagonist induced rigidity and hypokinesia, and therefore should be treated in the same manner. However, Cochrane reviews have concluded that there is insufficient data to recommend either anticholinergics or beta-blocking drugs for akathisia. Case reports have suggested that mirtazapine may be helpful, possibly due to an anticholinergic property as well as 5-HT_2 receptor antagonism. Other 5-HT_2 receptor antagonists such as mianserin and cyproheptadine have been tried in small studies. High dose vitamin B6 (1200 mg day^{-1}) has also been shown to significantly improve neuroleptic-induced akathisia.

There is little information on the treatment of tardive akathisia. Publications on successful treatments are mostly case reports and include the discontinuation of neuroleptics for a long period of time. Other options include lorazepam, anticholinergics, propranolol, moclobemide, clonidine, ropinirole, and electroconvulsive therapy.

In PD, it seems reasonable to determine the relationship between the occurrence of akathisia and the timing of the antiparkinson medication and adjust the medication schedule accordingly, analogous to the treatment of the motor symptoms.

See also: Drug-induced Movement Disorders; Dystonia, Drug-induced (Acute); Motor Fluctuations; Neuroleptics and Movement Disorders; Parkinson's Disease: Definition, Diagnosis, and Management; Restless Legs Syndrome; Tardive Dystonia; Tardive Syndromes.

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Relevant Websites

www.movementdisorders.org – Movement Disorder Society.

Akinetic-Rigid Syndrome

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Glossary

Akinesia – Difficulty initiating movement.
Basal ganglia – A group of brain nuclei including the striatum, globus pallidus, subthalamic nucleus, substantia nigra, and its corticothalamic connections.
Bradykinesia – Slowness of movement.
Festination – A peculiar type of gait; short-stepped, shuffling, and propulsive.
Hypomimia – Reduced facial expression.
Parkinsonism – Aka 'akinetic-rigid' syndrome, any disorder presenting with the combination of bradykinesia and rigidity, with or without tremor.
PET – Positron emission tomography: a functional neuroimaging technique that allows the visualization of radiolabeled fluorodopa within the nigrostriatal system.
SPECT – Single photon emission tomography; a functional neuroimaging technique that allows the visualization of radiolabeled tracers bound to the dopamine transporter in striatal dopaminergic endings.
Syndrome – A combination of signs and symptoms that collectively indicate or characterize a disease or group of diseases.

Definition and History

Akinesia and rigidity are derived from the Greek word 'akinesis,' the prefix 'a' meaning without, and 'kinesis' meaning motion, and the Latin word 'rigor' meaning stiffness. The term 'akinetic-rigid syndrome,' also designated as 'parkinsonism,' encompasses a variety of disorders that present clinically with the characteristic combination of difficulty in initiating movement and slowness in the performance of voluntary actions (akinesia/bradykinesia), hypertonicity, or muscular stiffness, with or without associated tremor. It may also include postural abnormalities, and depending on the etiology, associated features that help in making a differential diagnosis among the different diseases presenting with this syndrome. Parkinson's Disease (PD) is the most frequent and representative disease within the spectrum of the 'akinetic-rigid' syndromes.

In James Parkinson's original monograph of 1817, 'An Essay on Shaking Palsy,' we can find the first comprehensive description of this syndrome. Parkinson defines the shaking palsy as a combination of rest tremor, lessened muscular power, abnormal truncal posture, and festinant, propulsive gait, without any mention of the presence of rigidity. Although he did not distinguish weakness from slowness of movement, he specified the presence of disabilities affecting writing and feeding and referred to the failure of the hand to respond to the dictates of the will, which in fact constitutes the essence of akinesia. The recognition of rigidity as one of the main features of PD came in the second half of the nineteenth century, when the French neurologist, Charcot, recognized it to be an integral part of PD. Based on his observations, he was able to distinguish bradykinesia as a cardinal feature of the illness, separating it from rigidity. Charcot and his students described the clinical spectrum of the disease, recognizing two forms of presentation, the tremor predominant and the akinetic/rigid form. This is perhaps the first mention in the medical literature of the peculiar combination of akinesia and rigidity, causing impairment in motor function.

Pathophysiology

Loss of dopaminergic innervation of the nigrostriatal circuits, leading to changes in tonic and phasic activity of basal ganglia output pathways, transmitted via cortical motor areas, results in akinesia, bradykinesia, and rigidity. As a result of nigrostriatal denervation, there is reduced inhibition of the globus pallidus internal segment (GPi) neurons via the direct pathway and increased neuronal activity in the subthalamic nucleus via the indirect pathway, both leading to increased activity of GPi neurons and causing excessive inhibition of thalamocortical and brainstem motor neurons. In combination, these physiological changes are felt to underlie the development of parkinsonian features. Although these changes have been studied extensively in PD, similar involvement of basal ganglia circuits probably constitutes the pathophysiological basis of the majority of disorders presenting with an akinetic-rigid syndrome.

Clinical Features and Diagnostic Criteria

In patients with an akinetic-rigid syndrome, there is slowness and poor movement (bradykinesia) and often

difficulty in initiating movement (akinesia). This problem typically manifests as hypomimia (masked faces), micrographia (handwriting becomes smaller), and hypophonia (reduction in speech volume). Additionally, the speech becomes monotonous, there is a reduced blink rate, and impairment of associated movements such as reduced arm swing while walking. There is a reduction in the speed and amplitude of repetitive hand and foot movements; there may be progressive fatiguing, and brief arrests of ongoing movement. The demeanor and overall bodily attitude convey the sense of labored slowness in akinetc-rigid syndromes. Muscle tone is frequently affected with hypertonicity (rigidity) of variable distribution depending on the specific disorder. There may be postural abnormalities like generalized flexion in PD, extensor posturing of the head and neck in progressive supranuclear palsy (PSP), disproportionate antecollis in multiple system atrophy (MSA), or asymmetric limb dystonia in corticobasal degeneration (CBD). Gait may be involved early or late, depending on the specific disorder. In PD, it usually occurs late in the course of the disease and is characteristically slow, with short shuffling steps and a tendency to propulsion and festination. In PSP and MSA, gait disorders are an early manifestation of the disease, presenting as frontal disequilibrium in the former, and ataxia in the latter. Some of the secondary causes of the akinetic-rigid syndrome may also have gait disorders; in vascular pseudoparkinsonism, a peculiar short stepped gait ('*marche à petit pas*') is frequently observed, while in normal pressure hydrocephalus, there is often a mixed pattern gait disorder (frontal disequilibrium, parkinsonian, ataxic gait). Clinical criteria developed by the United Kingdom Parkinson's Disease Society Brain Bank are used to establish a firm diagnosis of PD, in which the presence of an akinetc-rigid syndrome, with or without rest tremor, in the absence of atypical features (exclusionary criteria, see **Table 1**), and in the presence of prospective supporting clinical elements (e.g., asymmetry, presence of rest tremor, progressive course, etc.), establishes it with a high degree of certainty. A number of diseases included in the category of akinetic-rigid syndrome are also diagnosed on the basis of established criteria.

Differential Diagnosis

Table 1 provides a list of disorders in which the akinetic-rigid syndrome is the sole or predominant clinical feature or one of many other clinical manifestations. As a general rule, only in primary or idiopathic parkinsonism (PD) is the akinetic-rigid syndrome present as the exclusive clinical manifestation of the disease. Drug-induced parkinsonism may also be a pure akinetic-rigid syndrome; however, it is often associated with signs and symptoms of tardive dyskinesia.

Diagnostic Work-Up/Tests

Clinical examination is performed through the observation of general body movement, gait, posture, and the performance of repetitive alternating movements of the limbs (akinesia/bradykinesia), together with manual examination of muscle resistance to passive limb displacement (rigidity). The unified Parkinson's disease rating scale (UPDRS) and its updated revision, sponsored by the movement disorder society (MDS-UPDRS) are used to evaluate severity, and overall functioning and disability in primary parkinsonism. Other scales have been specifically developed for the evaluation of other forms of the akinetic-rigid syndrome (e.g., PSP, MSA, etc.).

In routine clinical practice, diagnostic tests are generally used to rule out disorders other than PD from within the spectrum of the akinetic-rigid syndrome (e.g., CT and MRI may help in confirming the presence of hydrocephalus, vascular lesions, brainstem atrophy, cerebellar atrophy, tumors, etc.). Functional neuroimaging, such as fluorodopa positron emission tomography (PET) scans and dopamine transporter single photon emission tomography (SPECT) scans, not used in routine clinical practice, may help in confirming the presence of nigrostriatal denervation.

Management

Pharmacological treatment using dopaminergic agents (levodopa, dopamine agonists, MAOB inhibitors, and COMT inhibitors along with levodopa), amantadine, anticholinergics, and functional stereotactic surgery (pallidotomy, thalamotomy, pallidal, or subthalamic deep brain stimulation) are predictably effective in the management of primary parkinsonism (PD). Some of these drugs may be used in the treatment of other akinetic-rigid syndromes, but in most cases, the positive effects are less marked than in PD. In the case of drug-induced parkinsonism, withdrawal of the offending drug is the treatment of choice, whereas in hydrocephalus, a surgically implanted drainage device may be effective. Physical therapy and motor and speech rehabilitation may also be helpful.

Prognosis

On the basis of the diversity of diseases presenting with an akinetic-rigid syndrome, it is almost impossible to

Table 1 Akinetic-rigid syndromes

Disease	*Distinguishing features*
Primary	
Parkinson's disease (sporadic, genetic)	Asymmetric akinetic-rigid syndrome, rest tremor frequent, excellent response to levodopa
Secondary	
Drug-induced	Usually symmetric presentation; frequently associated with tardive dyskinesia
Infectious	Oculogyric crises, dystonia, myoclonus, choreoathetosis, seizures, altered sleep-cycle, cognitive impairment
Metabolic	Hepatocerebral degeneration (similar to Mn intoxication), Hypoxia (pyramidal tract signs, dysarthria, cognitive disturbances). Parathyroid dysfunction (seizures, cognitive disorders, oculomotor disturbances, chorea, calcifications on neuroimaging)
Tumor	Focal signs, positive imaging findings
Hydrocephalus	Cognitive deterioration, mixed pattern gait disturbance, urinary incontinence
Toxic	Mn (cock walk, postural tremor, T1 hyperintensities), Organic mercury (visual loss, ataxia, paresthesias, cognitive dysfunction CO (delayed-onset parkinsonism and dystonia)
Vascular	*Marche a petit pas*, signs of pyramidal tract involvement, pseudobulbar palsy, imaging studies reveal vascular lesions
Atypical parkinsonism (Parkinsonism-plus)	
Progressive supra-nuclear palsy	Supra-nuclear gaze palsy, cognitive involvement of the frontal type, frequent falls, discordant axial rigidity, early dysarthria, superior peduncular atrophy on imaging
Multiple system atrophy	Cerebellar signs, early dysarthria, early signs of autonomic failure, pontocerebellar atrophy on imaging
Corticobasal degeneration	Asymmetric limb involvement, cortical sensory loss, dystonic posture, myoclonus, alien limb phenomenon, asymmetric frontoparietal atrophy on imaging
Parkinsonism associated to other neurodegenerative diseases	
Alzheimer's disease	Early dementia (cortical type), amnestic, aphasia, apraxia, temporal atrophy on imaging
Lewy body dementia	Early dementia, visual hallucinations, cognitive fluctuations, early falls, autonomic dysfunction
Akinetic-rigid form of Huntington's disease	Oculomotor disturbances, cognitive and psychiatric involvement, gait ataxia, cortical, and caudate nucleus atrophy on imaging
Spinocerebellar ataxias	Ataxia, oculomotor disturbances, cerebellar atrophy on imaging
Pantothenate kinase associated neurodegeneration (PKAN)	Early-onset (first/second decade), progressive rigidity, dystonia, dysarthria, swallowing disturbances, cognitive deterioration; 'eye of the tiger' sign on MRI
Neuroacanthocytosis	Arreflexia, elevated CPK, acanthocytes on blood smear, orolingual dystonia, facial grimacing, bite lesions, self-mutilation, chorea
Wilson's disease	Cognitive and behavioral disturbances, flapping tremor, dystonia, rictus sardonicus, Kayser–Fleischer ring, basal ganglia or thalamic lesions on imaging
Other	
Dopa-responsive dystonia	Lower limb dystonia, gait disorders (walking on the balls of the feet), diurnal fluctuations, dramatic response to levodopa
Neimann-pick type C	Childhood-onset, progressive deterioration, ataxia, dystonia, seizures, spasticity, myoclonus, supranuclear gaze palsy, dementia, psychiatric manifestations
Pallido-pyramidal degeneration	Kufor–Rakeb syndrome. Early-onset (first/second decade), rapidly progressive, absence of tremor, spasticity, upgaze paresis, dementia, visual hallucinations, facial–faucial–finger mini-myoclonus, oculogyric crises
Rapid onset dystonia-parkinsonism	Unusually rapid evolution of symptoms (abrupt or subacute, hours or weeks), dystonic cramps, gait disturbances, dysarthria, dysphagia

make general statements regarding prognosis. PD and drug-induced parkinsonism are perhaps the only disorders that entail a rather benign prognosis. In the majority of the remaining disorders, the prognosis is poor due to their progressively disabling nature, and the lack of effective treatment.

See also: Bradykinesia; Corticobasal Degeneration; Freezing of Gait; Multiple System Atrophy; Parkinson, James; Parkinson's Disease: Definition, Diagnosis, and Management; Primary Progressive Freezing Gait; Progressive Supranuclear Palsy; Rigidity.

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Alexander Disease

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Glossary

Alexander disease (AD) – A rare, progressive, degenerative disorder of the central nervous system presenting with a broad range of signs and symptoms, in all age groups.
Glial fibrillary acidic protein (GFAP) – A major astrocytic intermediate filament protein, forming cytoplasmic aggregations as part of Rosenthal fibers.
Leukodystrophy – A group of inherited diseases characterized by progressive degeneration of central nervous system white matter, with primary pathology in myelin or myelinating cells.
Megalencephaly – Abnormal brain enlargement beyond the average for age and gender, usually related to abnormalities of neuronal proliferation.
Rosenthal fibers – The pathologic hallmark of AD: eosinophilic inclusions found in astrocyte cytoplasm composed of protein aggregates, including GFAP.

Definition and History

Alexander disease (AD) is a rare leukodystrophy characterized by progressive neurologic impairment, typically affecting infants and children but occasionally presenting in adults. The first case was characterized in 1949 by W. S. Alexander, who described developmental delay, megalencephaly, vomiting, and continuous screaming in a 15-month-old boy, with rapid progression to death. Brain pathology revealed hypertrophic astrocytes with protein aggregates, later identified as Rosenthal fibers. The eponym for the disease was later coined by Friede in his description of the sixth similar case in 1964.

Pathogenesis/Pathophysiology

AD is a genetically homogeneous disorder: ~95% of cases have glial fibrillary acidic protein (GFAP) gene mutations on chromosome 17p21, which is the only known genetic abnormality associated with AD. Nearly all forms of the disorder are caused by heterozygous, dominant, missense GFAP mutations. The exact function of the intermediate filament GFAP protein is not clear. Mutations of two GFAP residues account for over half of all cases. Almost all cases are sporadic, with de novo mutations discovered in almost all infantile cases, although autosomal dominant transmission in some familial cases has been reported. Dozens of different GFAP mutations have been associated with AD, mostly affecting the conserved regions of the gene, resulting in a gain of GFAP function.

The pathologic hallmark of AD, regardless of the phenotype, is abundant, widespread accumulation of Rosenthal fibers, which are eosinophilic protein aggregates found in the cytoplasm of hypertrophic astrocytes. Rosenthal fibers are composed of mutant GFAP, α β-crystallin, vimentin, and heat shock protein 27. Rosenthal fibers are not specific to AD, being also found adjacent to CNS tumors, multiple sclerosis plaques, syringomyelic cavities, and in a association with Parkinsonism. However, Rosenthal fibers in AD are distinctly concentrated in periventricular, perivascular, and subpial astrocytes. They also may be distributed throughout deep brain structures in younger-onset cases. Histologic brain tissue examination also demonstrates varying loss of myelin and neurons.

Epidemiology/Risk Factors

AD is rare, with fewer than 500 cases reported. Prevalence has not been published. Male predominance is suggested in infantile cases, while there are more females reported in the adult form. Environmental or sex-related risk factors are unknown.

Clinical Features

The clinical and pathological signs of AD vary widely depending on the age of onset, and have been divided into three subtypes:

Infantile AD

With onset of symptoms before age 2, infantile AD comprises the majority of reported cases (~63%). Progression typically follows a rapid, lethal course. Seizures, psychomotor delay, bulbar dysfunction, and megalencephaly are the most common symptoms; dysphagia, emesis, spasticity, and ataxia may also occur. Pathologic examination shows a pronounced absence of myelin in the frontal lobes. Accumulation of Rosenthal fibers may lead to aqueductal stenosis and obstructive hydrocephalus.

Juvenile AD

Onset between age 2 and 12 years defines juvenile AD, and accounts for about 24% of cases. The clinical course may present in a manner similar to that of infantile AD or may occur in the setting of normal early development, with more bulbar or pseudobulbar signs. Intelligence may be relatively intact, with lower incidence of frontal lobe involvement or macrocephaly.

Adult-Onset AD (AOAD)

While Previously considered the rarest manifestation of AD, case reports of AOAD have been growing since the availability of genetic testing. Symptoms begin after age 12, with more variable clinical and radiologic presentations. Common features of infantile forms are absent. In genetically confirmed AOAD cases, bulbar dysfunction, particularly lower brainstem signs, accounts for the most common symptoms, including dysphonia, dysphagia, dysarthria, and ataxia. Palatal tremor is present in 41% and can be an important clue for the diagnosis. Fluctuations of symptoms may occur. Urinary dysfunction, pyramidal involvement, scoliosis, and cerebellar dysfunction are often present, while dysautonomia, endocrine dysfunction, or sleep disturbances such as obstructive sleep apnea are less common. Cognition is typically well preserved.

Differential Diagnosis

Differential diagnosis is broad given the nonspecificity and diversity of symptoms, and depends on the individual clinical phenotype and the age of presentation. In young-onset cases, consideration should be given to other leukodystrophies, inborn errors of metabolism, or mitochondrial disease. Later-onset cases may mimic multiple sclerosis, cervical myelopathy, or brainstem tumors and may have overlapping signs with other neurodegenerative disorders, including motor neuron disease, multiple system atrophy, or spinocerebellar ataxia.

Diagnostic Work-up/Tests

Neuroimaging

Five diagnostic MRI criteria for AD were reported in 2001, four of which must be met for an imaging-based diagnosis: (1) extensive, symmetric, frontal-predominant cerebral white matter abnormalities (including atrophy, swelling, or cystic degeneration); (2) a periventricular rim of high signal on T1-weighted images and low signal on T2-weighted images; (3) signal abnormalities in the basal ganglia and thalami (atrophy or swelling); (4) brainstem abnormalities, particularly in the medulla or midbrain; and (5) contrast enhancement of select white and grey matter structures. In typical patients, MRI criteria lead to an appropriate diagnosis and correlate highly with histopathologic findings (**Figure 1**). Unusual variants in MRI findings have been reported, particularly in those with juvenile or adult onset. Typical MRI findings in later-onset patients include prominent atrophy and signal change in the upper spinal cord and medulla, no or minimal cerebral white matter abnormalities, and predominant or isolated abnormalities in posterior fossa structures (**Figure 2**). Review of MRIs by neurologists

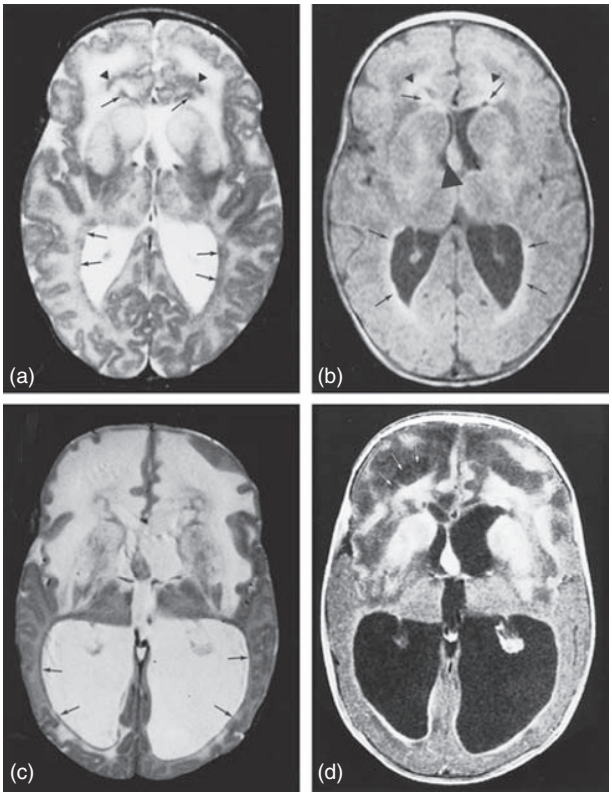

Figure 1 MR imaging of a patient with biopsy-confirmed infantile Alexander disease. (a and b): At the age of 1 1/2 months, the frontal white matter has a slightly higher signal intensity on T2-weighted images and slightly lower signal intensity on unenhanced T1-weighted images than does the remainder of the cerebral white matter, which has normal signal intensity for unmyelinated white matter. There is a periventricular rim of low signal intensity on T2-weighted images (arrows, a) and high signal intensity on T1-weighted images (arrows, b), with some extensions into the frontal white matter (arrowheads, a and b). The caudate nucleus and putamen have high signal intensity on T2-weighted images and are mildly swollen. (c and d): At the age of 3 months, a major increase in ventricular size is seen with extreme thinning of the posterior cerebral mantle. The frontal white matter has more abnormal signal intensity than the occipital white matter, appears markedly swollen, and shows early cystic degeneration (arrows, d). There is a thin periventricular rim of low signal intensity on T2-weighted images (arrows, c). The basal ganglia are now markedly atrophic. After contrast administration, enhancement occurs in the ventricular lining, caudate nucleus, putamen, frontal white matter, and parts of the frontal cortex (d).

or radiologists familiar with leukodystrophies is recommended before pursuing genetic testing.

Molecular Genetic Testing

GFAP gene testing is clinically available. Given the high rate of novel GFAP mutations reported in new cases, in many instances it may not be clear whether a novel coding change represents a benign polymorphism or a disease-causing mutation. In such situations, further familial genetic testing (best accomplished by testing both parents), comparison with control chromosomes, or assembly of abnormally expressed GFAP protein in cultured cells may provide further evidence that a particular coding change may cause AD pathology.

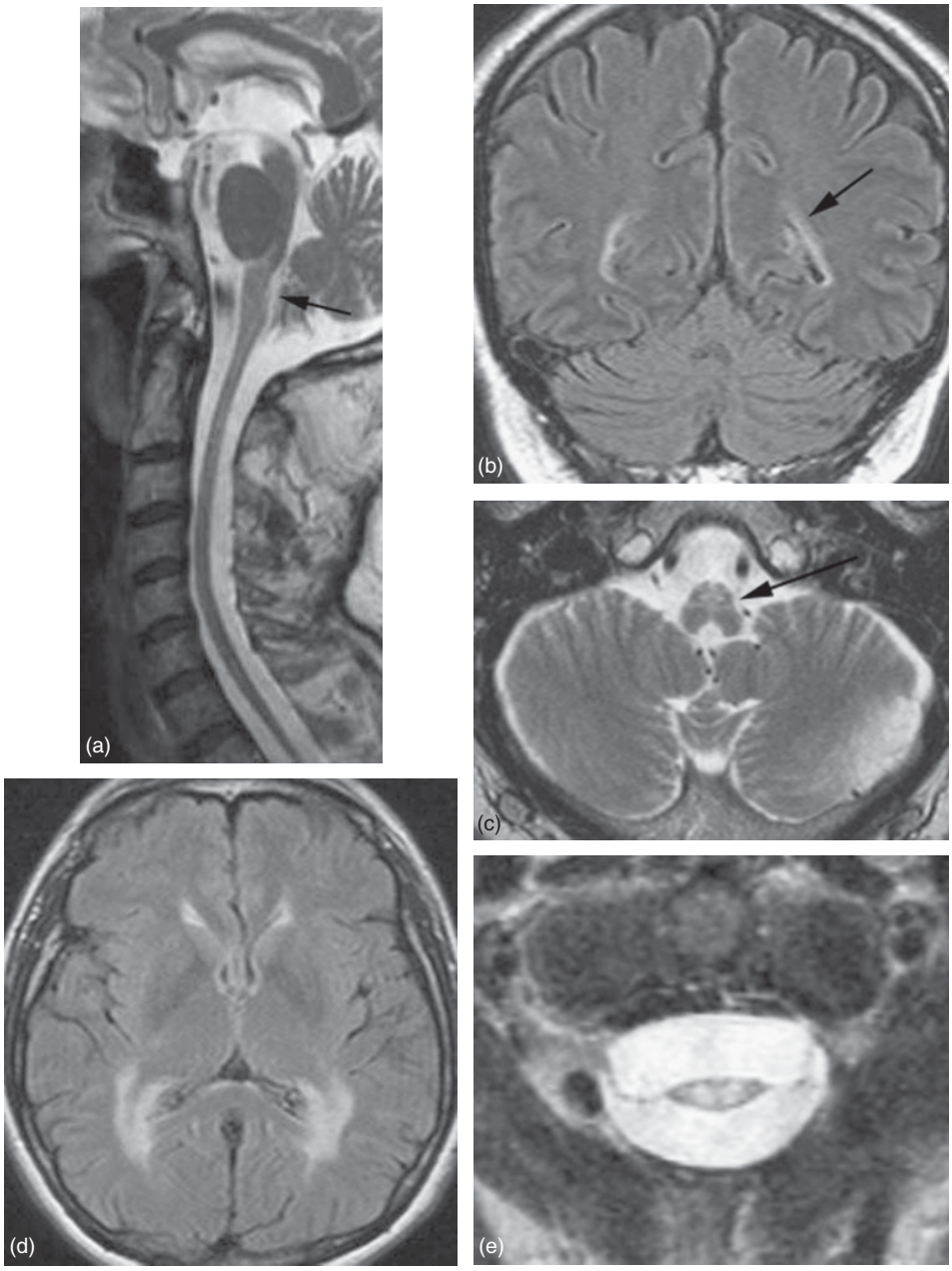

Figure 2 Representative MR images of characteristic lesions of AOAD from patients ranging in age from 43 to 64-years old. T2-weighted midline sagittal section shows (a) atrophy and signal abnormalities in the medulla oblongata (arrow); the hyperintensity fades away in the upper cervical spinal cord, whereas the entire spinal cord is also atrophic. Axial FLAIR image shows (b) increased signal intensity of the periventricular white matter, more extensive in the posterior regions. Coronal FLAIR section shows (c) very thin posterior periventricular abnormalities (arrow on the left) not detected by T2-weighted sequences (not shown). Axial T2-weighted section demonstrates (d) signal hyperintensities in the atrophic anterior part of the medulla oblongata (arrow). Axial T2-weighted section on the cervical spinal cord shows (e) severe atrophy and signal changes at C1–C2 level.

Histology

Before development of reliable MRI diagnostic criteria, definitive diagnosis was confirmed by the demonstration of astrocytic accumulation of Rosenthal fibers. Brain biopsy is now only indicated in atypical cases.

Management

Treatment is symptomatic as there are no curative or neuroprotective strategies. Bone marrow transplantation in one child did not change the disease course. Hydrocephalus may be treated with a VP shunt, and antiepileptic drugs help to alleviate seizures. Genetic counseling may be appropriate in later-onset cases. Secondary prevention of complications of disease may include screening for dysphagia and taking precautions for falls or complications of immobility. Physical, occupational, and speech therapy may assist with functional adaptation.

Prognosis

Prognosis is variable, with age of onset as an indicator of disease course. In infantile AD, death occurs within a decade, usually from respiratory complications, after an average of 3–4 years from symptom onset. In juvenile AD, progression is slower with a median interval to death of 8 years but some patients survive for decades. In AOAD, progression is highly variable, ranging from a few years to over 20 years.

See also: Ataxia; Cortical Tremor; Dysarthria; Palatal Myoclonus.

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Alien Limb

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Glossary

Agonistic apraxia – Agonistic apraxia is the execution of an act by one limb when the contralateral limb is asked to perform the act.
Autocriticism – Negative or astonished attitudes toward the alien limb.
Corticobasal degeneration (CBD) – Neurodegenerative disease typified by prominent apraxia, myoclonus, parkinsonism, and cognitive decline; pathologically characterized by cortical and basal ganglionic gliosis and atrophy as well as tau-positive astrocytic plaques.
Diagonistic apraxia – Diagonistic apraxia conflict between the performed act and the desired act.
Intermanual conflict – The phenomenon of one limb acting at odds with the other.
Magnetic or repellent apraxia – Magnetic or repellent apraxia is grasping or avoiding postures.

Definition and History

Alien limb refers to the phenomenon of alteration of self-perception of one's own limb, combined with abnormal involuntary movements of that limb. There are currently no formal consensus diagnostic criteria, but one basic element thought to be essential for making the diagnosis

of alien limb is that the patient's perception of the limb is altered in some form. In the prototypic case, patients do not recognize their limb as belonging to them.

An early case described in the literature by Goldstein in 1908 involved a 57-year old woman describing a left hand behaving on its own will, at some points choking her with great force. Autopsy revealed multiple infarctions, including one involving the corpus callosum. Originally coined *la main étrangère* ('the foreign hand') by Brion and Jedynak in 1972 describing patients with corpus callosal tumors, the term evolved into alien hand syndrome in part due to erroneous translation of the term 'étrangère' and in part to imply the behavior of a hand with independent will. Since the original descriptions, a variety of structural lesions have been associated with these abnormal movements, including medial frontal lobe lesions, with or without involvement of the anterior corpus callosum, posterior corpus callosal lesions, thalamic infarcts as well as parietal-occipital atrophy associated with corticobasal degeneration (CBD). Other degenerative conditions, such as Alzheimer's disease and Creutzfeldt–Jakob disease, have occasionally been associated with alien limb although not to the same degree as with CBD. In addition, a lower extremity can be affected as well, thereby generating the broader term, alien limb.

Clinical Features and Anatomical Basis

Biran and Chatterjee classified three aspects of alien limb behavior: (1) apparent conflict of the will of the limbs involved, (2) abnormal involuntary movements, and (3) the subjective attitude of the patient to the abnormal limb. A wide variety of terms describe the various behaviors that can be seen with alien limb. *Diagonistic apraxia* refers to the conflict between the performed act and the desired act. *Agonistic apraxia* reflects the execution of an act by one limb when the contralateral limb is asked to perform the act. *Intermanual conflict* is seen when one limb acts at odds with the other.

Several types of involuntary movements can be seen with alien limb. *Magnetic* or *repellent apraxia* refers to posturing seen as grasping or avoiding. Compulsive manipulation of tools is sometimes seen as well. The term *anarchic hand* has been used to describe the autonomous behavior of a limb in the absence of denial of ownership. This type of behavior is thought to result from damage to the supplementary motor area via a failure to modulate externally generated action from ipsilateral premotor area.

The patient's attitudes toward the alien limb vary. Some patients fail to recognize the limb as their own and are astonished by the behavior of the limb, referred to in the literature as *autocriticism* or *interhemispheric autocriticism.* Denial of ownership of the limb is seen in prototypic cases, but this feature is uncommon and is not considered by many to be essential for the diagnosis of alien limb. Various combinations of alien limb behavior have been seen, but the common element of alteration of self-perception runs through different types of subjective attitudes of patients to adopt in relation to the limb.

Debate continues on subcategorizing the various patterns of involvement, and correlating them with affected neuroanatomic structures. Alien limb can be seen with a variety of anatomical lesions. Variations in the clinical signs may exist depending on the location of damage. Part of the confusion derives from cases of alien limb that result from anterior cerebral artery territorial infarctions which variably involve supplementary motor area and the anterior corpus callosum. There may be three forms of alien limb with different patterns of behavior, originating from either frontal damage, callosal damage, or from posterior or subcortical involvement as in CBD. This disorder may present with a unique type of motor posturing, described as a 'wayward' or 'wandering' hand. In CBD, an asymmetric involvement of parietal and frontal lobes seems to play a role in the genesis of the phenomenon. An interplay of approach and avoidance behaviors have been advanced to explain the differences in limb movements. Frontal lobe lesions may facilitate approach behaviors mediated by the parietal lobe such as grasp reflex, while parietal lesions allow frontal avoidance behaviors to predominate such as abnormal overextended posturing of the hand. Fitzgerald et al. identified a left-handed patient with autopsy-proven CBD with bilateral asymmetric alien hand. The greater proportion of parietal to frontal atrophy was seen to correspond with contralateral avoidance behavior, while the relatively more preserved parietal lobe in the right hemisphere was associated with an approach behavior which they termed *tactile mitgehen.* It still remains unclear whether this parietal-frontal interplay hypothesis holds true in other patients with CBD. In most cases, it is believed that alien limbs in CBD patients tend to display more levitation and posturing relative to the perseveration commonly seen in medial frontal lobe damage. In contrast, alien limb phenomenon seen with callosal damage manifests as more complex purposeful movements in the nondominant hand.

Epidemiology and Differential Diagnosis

Estimates of prevalence of alien limb phenomenon among the general population are unknown, but it is reasonable to conjecture that it is more common in the chronic stroke population. In a large multicenter case series of CBD patients, 42% had alien limb syndrome. Dystonia occurred in 71% in this series making it feasible that alien limb can be mistakenly identified as dystonia.

When prominent posturing is present, botulinum toxin injections can be administered to provide relief from pain and spasm, but the more complex automatic behavior is not readily treated by either botulinum toxin or oral medications. Other conditions resembling alien limb phenomenon include dystonia and arm levitation each occurring without alteration of self-perception, both of which can be seen in atypical parkinsonism syndromes such as progressive supranuclear palsy and pure limb apraxia which can be differentiated by the absence of involuntary movements. When abnormal limb movements are present, especially when limited to one limb, imaging is important to identify the underlying structural lesions such as stroke, tumor, or lobar atrophy due to neurodegenerative conditions.

Management and Prognosis

Rehabilitative strategies have been employed with little success, perhaps depending upon the etiology. Alien limb phenomenon can be distressing to the patient and others, and in general has a poor prognosis for recovery. In some situations, placing a barrier or a cover on the affected limb has been effective for minimizing intrusive automatic behaviors.

See also: Apraxia: Upper Limb; Corticobasal Degeneration; Dystonia.

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Alpha-2 Adrenergic Agonists in Tic Disorders

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Glossary

Clonidine – This drug is used primarily to treat hypertension because of its action on central norepinephrine, but is also used to treat tic disorders and attention deficit hyperactivity disorder.
Guanfacine – This drug, pharmacologically similar to clonidine, but with distinct properties, is used primarily to treat hypertension because of its action on central norepinephrine, but is also used to treat tic disorders and attention deficit hyperactivity disorder.
Locus coeruleus – This brainstem nucleus is rich in noradrenergic cells.

Definition and History

The alpha-2 agonists were developed for the treatment of hypertension through their effect on noradrenergic receptors in the brain. Clonidine was introduced as a treatment for tic disorders in the late 1970s and for the treatment of attention deficit hyperactivity disorder soon thereafter. Guanfacine was introduced for these same indications in the 1990s. Currently, these agents are among the most commonly used medications in children with tic disorders. They are often used in combination with other medications such as stimulants or selective serotonin reuptake inhibitors. In September 2009, an extended release formulation of guanfacine was approved by the FDA for the treatment of children with attention deficit hyperactivity disorder (ADHD).

Mechanism of Action

Using clonidine as the model for the class, it has been shown that alpha-2 agonists reduce the firing of norepinephrine neurons in the locus coeruleus. The reduced firing of these neurons results in reduced norepinephrine

release in the prefrontal cortex. This regulatory effect on the noradrengeric system decreases arousal, resulting in decreased hyperactivity and impulsiveness. The introduction of guanfacine in the 1980s and a large body of preclinical data that followed prompted a revision in this proposed mechanism. Animal experiments and human studies have revealed important differences in clonidine and guanfacine. Although less potent than clonidine, guanfacine also reduces the firing of neurons in the locus coeruleus. In addition to indirect benefits on prefrontal function, guanfacine enhances prefrontal function through direct effect on alpha-2A receptors. According to this theory, prefrontal cortical dysfunction adversely affects attention, emotional regulation, and impulse control. Direct stimulation of alpha-2A receptors may improve attention, impulse control, and, perhaps, regulation of subcortical activity, including tics.

Clonidine for the Treatment of Tics and Attention Deficit Hyperactivity Disorder

Since it was introduced for the treatment of Tourette syndrome, clonidine had been evaluated in a few small randomized placebo-controlled and active comparator trials targeting tics. Taken together, these trials suggest that clonidine is modestly effective for tics, though results are not uniformly positive (**Table 1**).

There is more support for the efficacy of clonidine in children with ADHD. Two large scale trials have been conducted with clonidine, methylphenidate, their combination, and placebo in children with ADHD. In a sample of 136 children (age 7–14 years), the Tourette Study Group showed that each of the active treatments was superior to placebo on parent and teacher ratings of ADHD symptoms. The magnitude of benefit on ADHD outcomes was greatest for the combined treatment group. Tics showed modest improvement in all active treatment groups on average. However, in all treatment groups, including placebo, ~20% of subjects reported an increase in tics.

Using the same design in 122 children with ADHD uncomplicated by tic disorders, Palumbo and colleagues reported that neither clonidine alone nor methylphenidate alone was superior to placebo on the teacher ratings. After adjusting for the effect of placebo, combined treatment (clonidine plus methylphenidate) had a significant positive effect on teacher and parent ratings on ADHD. These two trials suggest that clonidine offers benefit of medium magnitude for children with ADHD (with or without tic disorders). Both trials showed additive benefit with the combination of clonidine and methylphenidate on ADHD outcomes. In the sample of children with tic disorders, clonidine, however, was not superior to placebo for tics.

Guanfacine

To date, only two placebo-controlled trials have been conducted with guanfacine in children with a tic disorder (Tourette Syndrome or Chronic Tic Disorder). Both trials were small and tic severity of these samples was relatively mild. Guanfacine was associated with about a 30% improvement in overall tic severity in both trials. This improvement was superior to placebo in the first trial but not the subsequent (smaller) trial (**Table 1**).

These two guanfacine trials also provided information on ADHD outcomes. Guanfacine was superior to placebo in an 8-week randomized controlled trial in 34 subjects with ADHD and a tic disorder on teacher measures of ADHD. In this trial, parent ratings of ADHD symptoms showed improvement, but were not significantly better than placebo. In the second trial involving 24 subjects (and only a subset met criteria for ADHD), guanfacine showed no difference from placebo on ADHD outcomes.

Adverse Effects of Alpha-2 Agonists

Clonidine is rapidly absorbed and, although it has a wide ranging half-life (6–24 h), peak effects occur as soon as 1 h after oral administration. Thus, some adverse effects can be tied to the time of administration. Common adverse effects include sedation, fatigue, lowered blood pressure and heart rate, irritability, and sleep disturbance (mid-sleep awakening). The sedative effects often reduce sleep latency, but the decline of peak effects after 3 or 4 h may contribute to mid-sleep awakening in some patients. Similarly, behavioral change across the day may coincide with peak and waning of acute drug effects. Slow upward dose adjustments and modifying the timing and dose increment is often required to achieve optimal benefit against minimal adverse effects. Abrupt discontinuation of clonidine is

Table 1 Dosing for immediate release alpha-2 agonists in children with tic disorders

Medication	*Starting dose (mg)*	*Rate of increase*	*Usual dose range (mg per day)*	*Doses (per day)*
Clonidine	0.025–0.05	every 4–5 days	0.15–0.30	3–4
Guanfacine	0.5–1.0	every 4–5 days	1.5–3.0	2–3

associated with a well-established withdrawal syndrome consisting of increased pulse and blood pressure, sweating, anxiety, and irritability. Findings by Daviss and colleagues suggest that concerns about cardiovascular adverse effects have been overstated. In healthy children with a negative cardiac history, no pretreatment medical testing appears necessary.

Guanfacine has a longer half-life ranging from 12 to 24 h and a slower rise to peak concentration. The longer duration of action and less marked peak effects often translates into fewer adverse events. However, decreased pulse and blood pressure sedation, fatigue, and mid-sleep awakening have also been reported with guanfacine and clearly influence the rate of dose increase. Studies in adults treated for high blood pressure show that abrupt withdrawal is less of a problem with guanfacine, but still should be avoided.

Special issues related to Guanfacine Extended Release formulation: A new extended release formulation of guanfacine has been developed, tested and approved for children with ADHD. In a study of 345 children aged 6–17 years with ADHD, (without a co-occurring tic disorder) children were randomized to one of four groups: placebo or guanfacine at 2, 3, or 4 mg per day for 5 weeks. Subjects randomized to active treatment were started on 1 mg per day for a week and then increased to 2, 3, or 4 mg in 1 mg increments each week. Thus, children on the 2 mg dose were observed for 3 weeks on stable dose, subjects on 3 mg were observed for 2 weeks, and subjects on 4 mg were observed for 1 week. Although each dose of active medication showed statistically significant improvement on the primary ADHD outcome measure at week 5, due to the design, the results provide few clinical implications. The most common adverse effects associated with guanfacine included sedation, abdominal pain, and fatigue. Most adverse effects were mild to moderate and time limited. Study withdrawal due to adverse events occurred in 9 of 87 patients taking 2 mg per day and 20 of 86 patients taking 4 mg per day.

Future Directions for Research

Clonidine and guanfacine have been used in clinical practice in children with tic disorders for many years. Thus, in many respects, their advantages and disadvantages are well known. Despite the common use of these drugs in clinical practice, however, it is remarkable that there are few large-scale trials in either drug focused on reducing tics in children with tic disorders. A large scale, so-called simple trial, might be considered as a way to confirm the validity of clinical practice.

Available data suggest that the alpha-2 agonists may be more effective for the treatment of hyperactivity, impulsiveness, and inattention than for tics. Clonidine has now been evaluated in two large-scale trials focused on ADHD outcomes. These trials show that the combination of clonidine and methylphenidate has advantages over either drug alone. Large-scale trials of guanfacine, especially the newer extended release product, are needed to evaluate the efficacy of guanfacine on ADHD outcomes and tic severity in children with tic disorders and ADHD. To be more clinically relevant, these trials should be longer than 5 weeks in duration and use flexible dose strategies.

See also: Tics; Tics, Complex; Tics, Simple; Tourette Syndrome.

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Relevant Websites

www.movementdisorders.org – Movement Disorder Society.
www.tsa-usa.org – Tourette Syndrome Association.

Alpha-Synuclein

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Glossary

Chaperone-mediated autophagy – A selective, lysosomal receptor-mediated process of degradation of cytosolic proteins.
Fibrillization – The process in which a protein starts assuming a beta-pleated structure.
Lewy body – A cytoplasmic neuronal inclusion comprising a radial fibrillar halo and a dense core, which stains positively with antibodies against α-synuclein and ubiquitin.
Oligomerization – The process in which multiple molecules of a single protein or polypeptide interact covalently with each other forming a larger globular structure.
Protofibrils – Soluble intermediates in the process of α-synuclein aggregation.

α-Synuclein: Structure and Physiologic Function

α-Synuclein is a member of the family of synucleins, comprising α-, β-, and γ-synuclein. The α-synuclein protein consists of 140 amino acids. In the N-terminal region, there are seven imperfect repeats of KTKEGV with an apolipoprotein lipid-binding motif, which are predicted to form amphiphilic helices. The central region, denominated non-amyloid component (NAC), is hydrophobic, whereas the C-terminus is characterized by the presence of acidic stretches. The NAC and the C-terminal region differentiate α-synuclein from the other members of the synuclein family, as within these areas, there is substantially reduced homology compared to the N-terminal region.

α-Synuclein does not have a defined structure in solution, and is therefore termed a natively unfolded protein. However, upon binding to synthetic membranes or certain lipid surfaces, its structure assumes an α-helical conformation. It is expressed predominantly in the neuronal cells and in the mature nervous system, where it is widely distributed; it is one of the most abundant neuronal proteins with preferential localization to the presynaptic terminal. Although the exact function of α-synuclein is unknown, it is thought to control vesicular trafficking and release, possibly through transient interactions with lipid vesicular surfaces. Knockout mice for α-synuclein do not demonstrate any obvious anatomical or behavioral abnormalities, but at least in the nigrostriatal dopaminergic system, they show an enhancement of response to paired electrical stimuli, suggesting that, α-synuclein normally negatively controls neurotransmitter release. This is consistent with studies in the chromaffin cells, which upon overexpression of α-synuclein show reduced evoked dopamine release, presumably through an effect at the level of the presynaptic membrane, downstream of vesicle docking. This could occur through interactions with the soluble *N*-ethylmaleimidesensitive factor attachment protein receptor (SNARE) complex, which regulates presynaptic release. Indeed, α-synuclein has been found to rescue the disassembly of the SNARE complex and the degeneration of neuritic terminals associated with lack of the presynaptic protein CSP-α (cystein string protein-α), suggesting that, possibly through a chaperone-like function, it normally helps in the maintenance of this presynaptic complex. α-synuclein also binds and inactivates phospholipase D2, and could thus influence synaptic membrane biogenesis through phosphatidic acid metabolism.

α-Synuclein is upregulated during late embryonic and early postnatal life in rodents and also during maturation of primary neurons in cell culture. As evidenced by the lack of obvious phenotype in the knockout mice, it does not appear to have a role in synaptogenesis per se, but it does appear to have a role in plasticity responses, as demonstrated by the fact that it is often upregulated as an adaptive response to various injuries, and most notably, during the period of song-learning in birds.

α-Synuclein has also been shown to bind to a number of other proteins, mostly cytoplasmic. It shares homology and binds to members of the family of 14-3-3 proteins, which have chaperone function within the cytosol. It has been reported to bind to a number of targets of 14-3-3 proteins and to regulate their function. Notably, α-synuclein may bind to tyrosine hydroxylase (TH) and inhibit its activity through effects on its phosphorylation status, and may thus affect dopamine metabolism. The physiological significance of these findings, mostly ascertained through overexpression in cellular systems, remains to be established.

Genetic Data Linking *SNCA*, the α-Synuclein Gene, with Parkinson's Disease

The first connection between α-synuclein and Parkinson's disease (PD) was the discovery that a missense point mutation, A53T, in the *SNCA* gene, encoding for α-synuclein,

was found to segregate with the disease in Italian and Greek families with autosomal dominant PD. Although the pathogenicity of this mutation was originally doubted, the identification of two further missense point mutations, A30P and E46K, in the *SNCA* gene in families with similar inheritance patterns in different populations, has conclusively shown the link with PD. Furthermore, more recently, it was discovered that multiplications of the gene locus for the *SNCA* gene are also linked to PD in other families with autosomal dominant inheritance. In fact, a gene dosage effect exists, in that individuals with triplication of the *SNCA* locus manifest the disease earlier and in a more severe form compared to those with duplications. However, it has to be noted that these families are very rare and only account for a very small proportion of PD cases worldwide. Therefore, it is especially important that genetic data exist linking *SNCA* with PD even in the large majority of cases with sporadic disease. In particular, the length of tandem repeats within the Rep1 polymorphic region ~10 kB upstream of the *SNCA* promoter has been conclusively shown through a series of studies, including a large meta-analysis, to confer risk of PD in sporadic cases. Alleles that confer risk were associated with increased α-synuclein mRNA expression in neuronal cells in one study, but it may be that the observed effect reflects the linkage disequilibrium with other critical regions within the *SNCA* gene. In support of this idea, other population studies have shown association of other polymorphic regions within or close to the *SNCA* gene, including areas within the 3′ UTR, with PD risk.

α-Synuclein Deposition in the Brain: The Concept of Synucleinopathies

Shortly after the discovery that α-synuclein is genetically linked to PD, another major discovery was made by Maria Grazia Spillantini and colleagues that α-synuclein was a main constituent of Lewy bodies (LBs), the cytoplasmic inclusions that represent the pathological hallmark of the disease. α-Synuclein antibodies characteristically label the ring of the LBs. On electron microscopy, the identified structures correspond to the filaments that characterize these structures. α-Synuclein antibodies normally demonstrate by immunohistochemistry predominantly punctate neuropil staining, indicative of the physiological localization to presynaptic terminals. In PD tissues, apart from LB staining, there appears to be a general increase of cytosoplasmic immunostaining in the substantia nigra (SN), as well as labeling of dystrophic neurites, termed Lewy neurites. In advanced PD as well as in Lewy body dementia (LBD), α-synuclein immunohistochemistry also identifies LBs throughout the cortex. With aging, there appears to be a general increase of cytoplasmic α-synuclein immunostaining in the SN. Immunohistochemistry with α-synuclein antibodies is now considered the gold standard for the pathological identification of Lewy pathology, as it is more sensitive than ubiquitin immunohistochemistry.

Immunohistochemistry with α-synuclein antibodies was used systematically by Heiko Braak and colleagues in a cohort of tissues from their brain bank. They discovered that a number of brains demonstrated abnormal α-synuclein accumulation and aggregation in lower brainstem areas, without involvement of the SN. Based on these studies, they surmised that α-synuclein aggregation and deposition initially start from the dorsal motor nucleus of the vagus and the olfactory bulb, and at later stages, follow an ascending route, eventually involving, at a third stage, the SN dopaminergic neurons. At stages 4–6, there is progressive involvement of the limbic system and cortical regions. This staging scheme has not been universally accepted, but it does seem to hold true for the majority of patients with sporadic PD. The Braak staging reinforces the idea that α-synuclein aggregation is an early event in the development of PD, and that it could be the main pathogenetic factor.

Beyond PD, it is now clear that aberrant intracellular α-synuclein deposition occurs in various neurodegenerative conditions, most notably multiple system atrophy (MSA), in which deposition occurs predominantly within glial cells, the LB dementia, and pantothenate kinase-associated neurodegeneration. Although there is no genetic link with α-synuclein in these cases, it is surmised that common pathogenetic mechanisms may lead to α-synuclein deposition in these disorders, collectively termed synucleinopathies, and that reversing this phenomenon may have therapeutic value.

α-Synuclein Aggregation

Biochemical studies of brain tissue of PD patients, including partially purified LBs, have revealed the presence of poorly soluble forms of α-synuclein, mostly in the form of SDS-resistant oligomers, which may appear as insoluble smears on the top of SDS/PAGE gels or as discrete multimers of α-synuclein. This tendency of α-synuclein to form oligomers and aggregates is thought to be the core of its pathological function. The purified α-synuclein protein, when incubated in an aqueous environment at 37 °C, gradually loses its disordered structure, and starts assembling into beta-pleated sheets. By electron microscopy, various structures can be identified as transition intermediates between the monomeric protein and the fully fibrillar amyloid-like structures of the mature α-synuclein fibrils. These intermediates appear as ring-like (annular) or spherical or chain-like 'protofibrils', and correspond to soluble oligomeric α-synuclein. The similarity of the end-products of this in vitro process of α-synuclein aggregation with human neuropathology, the conceptual kinship with the amyloid hypothesis proposed for Alzheimer's disease, the temporal correlation between α-synuclein

aggregation and the conferred toxicity in various cellular models, and the protective effects of antiaggregation strategies, all indicate that this process of aggregation is critical for α-synuclein-mediated toxicity. However, it is a matter of intense debate as to exactly which species within this aggregation pathway may be toxic. A related unanswered question is how such species may confer toxicity.

Which are the Toxic Species?

There is evidence that the soluble oligomeric protofibrils, and not the mature fibrils, are the toxic species. In particular, (1) the presence of such species, when compared to frank fibrillar inclusions, correlates better temporally with death in cellular models; (2) in cellular and in vivo models, the presence of frank inclusions is not a good predictor of toxicity; (3) dopamine and its metabolites act as inhibitors of the conversion of protofibrils to fibrils, thus favoring protofibril accumulation; this could help explain in part the selective vulnerability of dopamine neurons to α-synuclein-mediated toxicity; and (4) in vitro, the A53T and A30P mutants both lead to enhanced protofibril formation, whereas they have opposing effects on mature fibrils, suggesting that the common denominator of the mutants is the accumulation of soluble intermediates; however, this notion breaks down in the case of the E46K mutant, which leads to enhanced conversion of protofibrils to fibrils, and therefore this issue is not yet settled.

Mechanisms of Aggregation-Dependent Toxicity

In solution, protofibrils have structures resembling those of bacterial pore-forming toxins, and it has therefore been suggested that they may have a similar function, forming pores on cellular membrane, leading to deleterious alterations in ionic exchange or conductance, or on intracellular organelles. The hypothesis that protofibrils, through this pore-like mechanism on vesicles, may cause leakage of vesicular dopamine into the cystosol is especially attractive and supported by cellular data. This could provide a link between α-synuclein protofibrils and increased cytosolic dopamine, and thus, oxidative stress, leading to selective nigral neuron loss. Alternatively, protofibrils may interact aberrantly with cellular constituents and interfere with their function. A case in point is the effect of select soluble oligomers of α-synuclein on the 26S proteasome. Protofibrils may be deleterious especially when localized at the presynaptic level, as they may interfere with normal synaptic transmission. In one study, the presence of such soluble oligomers, but not frank inclusions, correlated with synaptic degeneration in brains of patients with LBD. Larger fibrillar inclusions may also exert toxic effects, through blocking of axonal transport or by causing other mechanical problems through bulk effects, or by sequestering normal cellular constituents, leading to loss of their function in the appropriate cellular compartment.

Factors that Influence α-Synuclein Aggregation

Given the importance of α-synuclein aggregation, it is critical to consider the factors that may influence it. An obvious factor is the amount of α-synuclein. It is clear that the higher the protein levels, the more likely the process of aggregation. This, in conjunction with the genetic data, especially the cases with *SNCA* multiplication, and the human PD α-synuclein pathology, gives rise to the 'α-synuclein burden' hypothesis, according to which the critical factor in idiopathic PD pathogenesis is the accumulation of α-synuclein, either because of enhanced transcription or through reduced degradation. A corollary of this hypothesis is that reducing α-synuclein levels may be a valuable therapeutic target. Although the factors regulating α-synuclein transcription in vivo are not known, a number of regulating transcriptional elements are beginning to emerge from cellular studies. The issue of α-synuclein degradation has been controversial, but it now appears that the bulk of degradation of at least monomeric wild type (WT) α-synuclein in neuronal cell systems occurs through the lysosomal pathways of chaperone-mediated autophagy (CMA) and macroautophagy. We and others have proposed that dysfunction of these degradation pathways may be a contributing factor to PD pathogenesis.

Posttranslational modifications of α-synuclein can also alter its propensity to aggregate. α-synuclein is constitutively phosphorylated at S129 in certain cell types, but in vivo in the CNS, such phosphorylated conformations occur only within LBs. This has led to the idea that S129 phosphorylation, which has now been shown to be mediated by Polo-like kinase 2 (PLK-2), may drive α-synuclein aggregation. However, the data supporting this idea are conflicting, and it now actually appears that S129 phosphorylation reduces α-synuclein aggregation, at least in vitro. Nitratively modified α-synuclein also occurs within LBs, and both nitration and oxidation may lead to enhanced aggregation, whereas glycation may also play a role.

The general consensus in the field is that α-synuclein, either through genetic or epigenetic influences, acquires a tendency to aggregate and to cause inclusions. Something along this pathway confers neuronal toxicity and leads to PD.

Beyond Aggregation: Other Mechanisms of α-Synuclein Toxicity

α-Synuclein may have other pathogenic effects which may not be dependent on aggregation. Susan Lindqvist and colleagues have discovered that in yeast, α-synuclein disrupts ER–Golgi trafficking, presumably due to misfolding,

and that enhancing ER–Golgi trafficking through overexpression of Rab5a leads to protection against α-synuclein toxicity in mammalian neuronal cell models and in the fly model of α-synuclein overexpression. ER stress may thus contribute to α-synuclein-mediated toxicity. The A30P and A53T mutants, as well as the dopamine-modified WT α-synuclein, lead to the inhibition of CMA, the same selective lysosomal process that is responsible in part for α-synuclein degradation, thus creating a potential feed-forward loop of cellular dysfunction. Aberrant interactions of α-synuclein with cytosolic proteins leading to activation of proapoptotic pathways have also been proposed. It should be noted that there is evidence that WT α-synuclein may even have antiapoptotic effects. This may depend on the levels of expression.

Animal Models of α-Synucleinopathies

Based on the idea that α-synucleinopathies are due to a toxic gain of function, animal models of these disorders have been created based on α-synuclein overexpression. Species targeted include *Caenorhabditis elegans*, *Drosphila*, mice, rats, and nonhuman primates. These are models of neuronal-specific expression, but a model of MSA has been created in transgenic mice with overexpression in ologodendroglia. In most cases, cellular dysfunction with phenotypic manifestations has been demonstrated. In some cases, neuritic degeneration, without neuronal cell body loss, has been shown. With the possible exception of the fly model, it has not been possible to replicate the classical fibrillar LBs. A particular problem with the transgenic mouse models has been the inability to recreate the dopaminergic degeneration that characterizes PD, despite abundant expression of the transgene in SN neurons. Models with lenti- or adeno-associated virus (AAV)-mediated transduction of rodent ventral midbrain neurons have been much more successful in this regard, and have the advantage that they can be extended to nonhuman primates. They are, however, technically challenging, and this prevents their widespread establishment and utilization for preclinical studies.

See also: Dementia with Lewy Bodies; Multiple System Atrophy; Parkinson's Disease: Definition, Diagnosis, and Management; Substantia Nigra; Synucleinopathies.

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Aluminum

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Glossary

Dopamine – A neurotransmitter occurring in a wide variety of animals, including both vertebrates and invertebrates. In the brain, this catecholamine functions as a neurotransmitter, activating the five types of dopamine receptors – D1, D2, D3, D4, and D5, and their variants. Dopamine is produced in several areas of the brain, including the substantia nigra and the ventral tegmental area.

Lewy bodies – Abnormal aggregates of protein that develop inside neurons. There are two morphological

types: classical (brain stem) Lewy bodies and cortical Lewy bodies.
Neurofilaments – Filaments found specifically in neurons.
Neurotoxin – A toxin that acts specifically on the peripheral or central nervous system usually by interacting with membrane proteins such as ion channels.
α-synuclein – A protein of unknown function primarily found in neural tissue, where it is seen mainly in presynaptic terminals. It is predominantly expressed in the neocortex, hippocampus, substantia nigra, thalamus, and cerebellum. It is predominantly a neuronal protein but can also be found in glial cells.

Chemical Structure

Aluminum is a trivalent trace element that is found in aluminum silicate, oxide, or halide. It is a common metal in the earth mined from impure ore, bauxite, which contains aluminum oxide, water, and iron. Metallic aluminum does not occur in nature, it occurs only after the electrolytic processing of the oxide from the ore.

Environmental Exposure

Aluminum is found in many products such as cosmetics, surgical bone cement, antacids, and antiinflammatory creams. It is commonly found in drinking water and teas and is used in leavening and antisticking agents in the baking industry.

Exposure can be nonoccupational such as dialysis, drinking water, and food, and occupational, including dust and vapors from mining, smelting, foundry, and fabrication work. Chemical manufacturing plants use organoaluminums as catalysts. Welders are vulnerable to exposure, as are miners exposed to 'McIntyre Powder,' a dust consisting of finely ground aluminum as oxides and used as a prophylactic agent for silicosis.

Clinical Signs of Intoxication

Aluminum exposure is usually not associated with any neurological problems. Aluminum is highly reactive and not known to perform any enzymatic or other function in the body. However, neurotoxicity related to aluminum has been reported. Metal flux across the blood–brain barrier (the primary route of brain metal uptake) and the choroid plexuses as well as sensory nerve metal uptake from the nasal cavity have been described. The controversial role of aluminum in Alzheimer's disease suggests that brain aluminum uptake occurs by transferrin-receptor-mediated endocytosis and of aluminum citrate by system Xc(-) and an organic anion transporter, suggestive of transporter-mediated aluminum brain efflux. Neurologic manifestations of aluminum toxicity include 'potroom palsy,' an acute syndrome characterized by lack of coordination, poor memory, and impairment of abstract reasoning as well as depression. It was first described in smelter workers, with loss of balance as the most frequent complaint noted. Aluminum has been also implicated in a syndrome known as dialysis encephalopathy since it has been found in dialysis water and is part of the oral aluminum-containing phosphate binding gels used to control blood phosphorus levels. Clinical manifestations start with fatigue, drowsiness, and disturbances of concentration, cognition, and mental activity.

Aluminum may also have a role in the pathogenesis of neurodegenerative diseases, since elevated aluminum levels have been found in subjects with amyotrophic lateral sclerosis and parkinsonism dementia complex of Guam. Animal studies have found induction of spinal neuronal degeneration after the injection with aluminum. The incorporation and accumulation of aluminum ions in the cells may also have a role for the transmissible spongiform encephalopathies due to an 'iron-overload syndrome' which highly promotes formation of hydrogen peroxide, which can be a main factor in causing serious damages to DNA and proteins (oxidative stress).

In experimental animals, a low calcium and magnesium/high aluminum diet induces neurofibrillary pathology characterized by the accumulation of phosphorylated neurofilaments in the anterior horn cells and neuronal loss most concentrated in the dopaminergic neurons in the substantia nigra. This diet over a prolonged period of 11–31 months induced loss of neurons and occurrence of tau-immunopositive neurons in the cerebral cortex. These findings may have implications to amyotrophic lateral sclerosis and parkinsonism–dementia complex where combinations of degenerating neurons occur. The isolation of this syndrome to Guam suggests that environmental issues may underlie at least part of the pathogenesis of this neurodegenerative disease.

The relationship between aluminum and idiopathic Parkinson's disease (PD) is unclear. In the majority of cases, it is proposed that environmental agents, modulated by the individual's genetic susceptibility, can contribute to the etiopathogenesis of PD. Several studies have implicated environmental factors, especially pesticides and metals, including iron and aluminum. In those studies, compared with controls, increased concentrations of aluminum in the substantia nigra of PD patients have been found. In a study of 200 PD patients and 200 age- and sex-matched controls, a marked and statistically

significant higher incidence of ulcers (diagnosed by X-ray or surgery) in the PD patients compared with the controls (14% to 4%) was found. As a result, it has been speculated that aluminum-containing antacids may contribute to the pathogenesis of idiopathic PD. Recently, it has been reported in the preliminary studies that certain pesticides and metals could accelerate the formation of α-synuclein fibrils both individually and synergistically. In experiments using higher α-synuclein concentrations, micromolar amounts of aluminum stimulated the rate of fibril formation. Since these agents also induce a conformational change in α-synuclein, it is likely that this partially folded conformation is a critical precursor to association and fibrillation. These observations suggest a possible underlying molecular basis for association of aluminum and PD and related Lewy body diseases, where these interactions between α-synuclein and environmental agents, in this case aluminum, could play a role in the pathogenesis of nigrostriatal degeneration, and thus, in the etiology of sporadic PD.

See also: Carbon Monoxide Poisoning; Cyanides; Mercury; Pesticides.

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Alzheimer's Disease and Parkinsonism

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Glossary

Alzheimer's disease – A common neurodegenerative disease of aging, associated with memory loss and cognitive decline, and motor decline including parkinsonism.

Episodic memory – Memory for learning and retention of specific events (episodes) embedded in an autobiographical, temporal context; deficit is the clinical hallmark of Alzheimer's disease.

Semantic memory – Previously acquired knowledge independent of the specific context in which the facts were learned.

Working memory – The ability to manipulate information held in short-term, limited-capacity, memory stores.

Consequences of Aging

The recent and marked increase in the detrimental impact, including personal, societal, and economic factors, of common conditions of aging on world populations is large and projected to worsen. Among the most common and disabling conditions of aging are neurologic conditions. In particular, two important consequences of aging are a decline in cognitive function and a decline in motor function. With the current demographic trends showing an increase in the life expectancy, age-related conditions, such as Alzheimer's disease, are increasingly common. Indeed, Alzheimer's disease is considered the most common cause of dementia.

Alzheimer's Disease

Important Public Health Issue

Over the last century, US national statistics show a trend of increasing life expectancy. In 2000, the average life expectancy at birth for all races and both sexes in the United States was 76.9 years of life. Because of the growing number of elderly persons, it has become increasingly crucial to understand and address the common diseases and problems experienced by this population group. One of the most prevalent diseases of old age is the neurodegenerative disease, Alzheimer's disease. Both the incidence and the prevalence of Alzheimer's disease are strongly related to age. Recent data estimate that Alzheimer's disease affects about 5 million Americans and that this will increase by slightly less than threefold by the year 2050. The annual number of incident cases of Alzheimer's disease is expected to more than double by 2050. Further, cognitive and motor impairments associated with aging will also become increasingly more common and become major public health concerns. Alzheimer's disease and cognitive and motor impairment are associated with greater morbidity and mortality. Because of the expected increase in the growth of the older age groups in the coming decades, the burden of cognitive and motor impairment, as well as other age-related conditions, is projected to increase dramatically for this sector of the population.

Clinical Features

Alzheimer's disease is characterized by an insidious onset and progressive decline in cognitive function. The most common early clinical manifestation is short-term memory loss, in keeping with a deficit in episodic memory. With disease progression, other cognitive systems are affected, including visuospatial abilities (resulting in disorientation and getting lost) and language abilities (with early anomia, and late global aphasia), and a full-blown dementia is observed.

In addition to decline in cognitive function, Alzheimer' disease is characterized by other clinical features. Patients have a decline in functional abilities, which may affect function in the work and home environment. Affect is often involved, with depression being common in the early stages of the illness. Behavior may become affected in the mid-late stages, with perseveration, apathy, and other abnormal behaviors. Significantly abnormal behavior, resulting in danger to the self or others (e.g., aggression), may result in institutionalization.

An increasingly recognized feature of Alzheimer's disease is the presence of parkinsonian signs. These manifest as bradykinesia, rigidity, and postural instability with inability to ambulate in late stages of the illness (see below).

Decline in Cognitive Function

Aging and Alzheimer's disease are characterized by progressive loss of memory and other cognitive abilities. Memory is the recording, retention, and retrieval of information and accounts for all knowledge gained through experience; it includes memories of specific events, knowledge of facts, and acquisition of skills. Although memory loss is recognized as the characteristic cognitive manifestation of Alzheimer's disease, extensive literature documents impairment in multiple other cognitive systems. Assessment of various cognitive systems is important, as risk factors may be associated with change in one or several systems, while showing little or no association with others. Such selective effects on cognitive function have already been found for various risk factors for Alzheimer's disease: genetic factors (e.g., apolipoprotein E ϵ4) and other factors (e.g., proneness to psychological distress) have been associated with decline in episodic memory, while vascular factors (e.g., diabetes mellitus) have been associated with decline in perceptual speed.

Episodic memory refers to learning and retention of specific events (episodes) embedded in an autobiographical, temporal context. Impairment of episodic memory is the clinical hallmark of Alzheimer's disease and may be the only clinically apparent deficit early in the disease. Recent studies suggest that persons with isolated episodic memory impairment (e.g., mild cognitive impairment) are probably exhibiting the earliest clinical manifestations of Alzheimer's disease. Semantic memory refers to previously acquired knowledge, independent of the specific context in which the facts were learned. It is represented primarily, though not exclusively, by language function. Working memory refers to the ability to manipulate information held in short-term, limited-capacity, memory stores. Perceptual speed refers to the speed with which perceptual comparisons can be made. Both working

memory and perceptual speed are involved, to some extent, in most forms of information processing. Both appear to decline with age independent of Alzheimer's disease.

Decline in Motor Function and Parkinsonism

Aging and Alzheimer's disease are also characterized by progressive loss of motor function. Age-related parkinsonian signs are common and changes in motor function, including gait disorder, rigidity, and bradykinesia, are often progressive. Both Alzheimer's disease and cognitive decline are associated with change in parkinsonian signs. Parkinsonian signs include signs of bradykinesia (e.g., slow, small amplitude, hesitant movements), gait disturbance (e.g., stooped posture, small tentative steps, postural instability), rigidity (e.g., stiff limbs), and tremor. Parkinsonian signs are associated with mortality in older persons with and without Alzheimer's disease. Parkinsonian signs are present in about half of people with Alzheimer's disease and become much more common as disease advances. Although parkinsonian signs progress in persons with Alzheimer's disease, the rate of this progression varies for the different signs, suggesting that risk factors may be associated with change in some signs but not others. Indeed, risk factors may be differentially related to change in one or several parkinsonian signs. Preliminary work suggests that some vascular factors common in aging and related to Alzheimer's disease are associated with change in parkinsonism signs, and may be related to some aspects of parkinsonism more than others. For instance, type 2 diabetes mellitus has been found to be associated with increasing rigidity and gait disturbance in older persons followed annually over about 6 years.

Relation Between Cognitive Decline and Parkinsonism

It has long been hypothesized that loss of cognitive function and progression of parkinsonian signs may share a common etiopathogenesis. For example, some diseases such as the Parkinsonian–Dementia Complex of Guam manifest clinically as cognitive impairment and parkinsonism. There is also data suggesting that age-related cognitive and motor impairment are related. First, about half of persons with Alzheimer's disease exhibit parkinsonian signs. Likewise, up to half of persons with Parkinson's disease develop dementia. Mild age-related parkinsonian signs are associated with risk of Alzheimer's disease. Further, in persons with and without Alzheimer's disease, rate of cognitive decline is associated with progression of parkinsonian signs. While many factors could account for the phenotypic overlap of cognitive decline and parkinsonian signs, including structural changes in cognitive and motor systems (e.g., cerebrovascular disease, Lewy bodies, neurofibrillary changes), shared mechanisms underlying selective vulnerability has also been hypothesized to play an important role, including oxidative stress and inflammatory processes, among others.

Recent studies have found that common age-related conditions, such as parkinsonism, increase the risk of dementia and Alzheimer's disease. Yet, little data are available on the relation of these conditions to neuropathology of dementia. Human postmortem data on a group of older community-dwelling persons with and without dementia who are well-characterized during life, allow for examination of potential mechanisms leading to dementia. Some clinical–pathologic data have suggested that neurofibrillary tangles (one of the key pathologies of Alzheimer's disease) in the substantia nigra (an anatomical location for pathology of Parkinson's disease) are contributing factors to gait disturbance and parkinsonism in old age. Further such studies are needed to examine the pathophysiologic basis of parkinsonism in old age and Alzheimer's disease.

Future Directions

Age-related conditions are increasingly common worldwide and are resulting in a large public health burden. Cognitive and motor impairment are among the most common conditions of aging. Identification of risk factors for decline in cognitive function and decline in motor function, particularly modifiable risk factors, could potentially have a large impact on our understanding of the underlying mechanisms of diseases of aging and on our ability to treat and, one day, prevent these conditions.

See also: Bradykinesia; Cognitive Assessments and Parkinson's Disease; MMSE - Mini-Mental State Examination; Neurofibrillary Tangles; Parkinson's Disease: Definition, Diagnosis, and Management; Substantia Nigra.

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Amyotrophic Lateral Sclerosis/Parkinsonism-Dementia Complex of Three Pacific Isolates

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Glossary

ALS (amyotrophic lateral sclerosis) – A universal and progressive disease with amyotrophy and spasticity of bulbar and limb muscles. On Guam, it was distinguished by familial occurrence, high prevalence, and linear retinopathy. Otherwise, its clinical features and immunohistology were like classical ALS elsewhere. Occurring among Guamanians for 200 years, it has declined on Guam during the past 40 years, and is now rare.
ALS/PDC (amyotrophic lateral sclerosis/ parkinsonism–dementia complex) – A unique familial tauopathy of three Pacific places with three phenotypes of ALS, parkinsonism, and dementia.
Dementia – A progressive disorder which impairs cognition and alters behavior. On Guam, when dementia is associated with parkinsonism, it is termed the parkinsonism–dementia complex. When it occurs independently, it is referred to as Guam dementia (GD) or Mariana's dementia (MD). Its clinical features include those of Alzheimer's disease (AD) and frontotemporal dementia (FTD).
Guam – A tropical and high island of 200 square miles, southernmost of the Marianas archipelago in Central and Western Oceania. Guam was a Spanish possession after its discovery in the sixteenth century until it was ceded to United States in 1898. As a US Territory, it remained an undeveloped island of subsistence and a Navy coaling station until its occupation by Japan from 1941 to 1944 during World War II. Since the War, United States has rapidly developed Guam as a main military and tourist center at its western extent.
Parkinsonism – A generic term for diseases involving the extrapyramidal system. On Guam, it is distinguished by clinical heterogeneity which includes features of atypical parkinsonism like postencephalitic parkinsonism (PEP), Parkinson's disease (PD), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD).
Postencephalitic parkinsonism – A progressive tauopathy accumulating the same hyperphosphorylated tau isoform as ALS/PDC and Alzheimer's disease which was epidemic for several decades after acute pandemics of encephalitis lethargica and Spanish influenza in the 1920s.

History and Background

The neuropathologist, Harry Zimmerman, was the first to recognize that amyotrophic lateral sclerosis (ALS) was unusually common in the Chamorros of Guam in 1945. He confirmed that diagnosis by autopsy, but because it was familial and of young onset, he called it an 'obscure

malady' (**Figure 1**). Thereafter, teams of Navy physicians confirmed that ALS was endemic in all parts of this small tropical island of 200 square miles, and in 1953, epidemiologist Leonard Kurland calculated that its overall prevalence was 100 times greater than elsewhere. His colleague, neurologist Donald Mulder agreed the clinical illness of Chamorros was the same as classical ALS, and he learned it had affected successive generations of the 'Q' family in Umatac village of southern Guam for more than 150 years. He also identified a second neurological syndrome of parkinsonism and dementia that was common among Guamanian Chamorros. It resembled postencephalitic parkinsonism and occurred in the same families with ALS. The neuropathologist, Nathan Malamud, identified neurofibrillary degeneration (NFD) in the substantia nigra of a patient with ALS and parkinsonism in 1958, and his new finding led Zimmerman to encourage Asao Hirano to study the neuropathology of both syndromes. In 1960, after a year of studies on Guam, Hirano and his colleagues concluded that ALS, parkinsonism, and dementia were phenotypes of a single disease with the histological hallmark of Alzheimer-type NFD. They called it the ALS/parkinsonism–dementia complex (ALS-PDC) of Guam, and since then it is known worldwide by this appropriate designation. Chamorros refer to it as lytico-bodig. (**Figure 2**). Since 1957, the National Institutes of Health (NIH) have honored a commitment to longitudinal studies of ALS/PDC on Guam.

Figure 1 Guam, Mariana islands.

Once described, ALS/PDC was recognized in two other places. In 1975, neurologist Yoshiro Yase and neuropathologist Hirotsugu Shiraki described ALS with NFD among the residents of two clusters, each involving five small and adjacent mountain villages in the Kii peninsula of Honshu island. One cluster, along the Koza river, was called the Kozagawa focus, and the other cluster, 200 km away was the Hobara focus on the Iseji river. There were no cases of ALS in the villages between these two clusters, in other parts of the Kii peninsula, or in Japan. The disease there is called 'muro' and it is also familial. It was first recorded in a document of 1693, and its high prevalence was recognized by the pioneer neurologist Kinnosuke Kimura after he learned of ALS from Jean-Martin Charcot in Paris. Since 2001, neuropathologist Shigeki Kuzuhara and his colleagues at Mie University have confirmed that the epidemiology, clinical features, and immunohistology of ALS/PDC in Hobara are identical to those of ALS/PDC on Guam.

Figure 2 Chamorro patients with ALS (left) and the parkinsonism–dementia complex (right).

In 1982, Nobel Laureate Carleton Gajdusek described a syndrome of ALS and parkinsonism among 7000 head hunting tribes people living in riverside villages of coastal mud flats in West New Guinea. Although not pathologically verified, its clinical features and epidemiology are similar to ALS/PDC on Guam and in Japan.

Materials for this Review

This review article is based on 1093 probable cases of ALS/PDC in Guamanian Chamorros during 50 years. For 25 years and from 1957 to 1982, neurologists at the NIH Guam Research Center identified 389 ALS, 306 PDC, and 39 mixed ALS and PDC cases. During the next 25 years and from 1983 to 2008, Steele and his colleagues have identified 64 ALS, 282 PDC, and 13 mixed ALS and PDC cases by the same NIH criteria.

Clinical Manifestations

ALS/PDC is progressive and fatal. Its average duration is 3–4 years, but the disease may be fulminant with death in 6 months or prolonged for more than 25 years. ALS/PDC is more common in men than women and has the same ratio of 1.7:1 in both ALS and PDC phenotypes.

ALS is clinically and immunopathologically identical to classical ALS in other parts of the world. Its age of onset, in this series and by pathological confirmation is from 20 years (in 1951) to 71 years (in 2005). The last born case was in 1951 (Patient AG).

Parkinsonism usually manifests as progressive bradykinesia, flexion posture, postural instability, and symmetrical rigidity that does not respond to L-dopa. Tremor is seldom severe. Less often, and in early stages, Guam parkinsonism may mimic Parkinson's disease (PD) presenting with asymmetric or even unilateral signs with prominent rest tremor, and responsivity to dopaminergic drug treatment. A small number of Chamorros exhibit classical syndromes of progressive supranuclear palsy (PSP), first described by Tanner and Steele in 1987, and corticobasal degeneration (CBD), described by Gwinn Hardy in 2000. The onset of parkinsonism is later than ALS, and its age of onset in this series and by pathological confirmation is from 32 years (in 1956) to 82 years (in 1998). The last born case was in 1951 (patient BT).

The dementia of ALS/PDC is referred to as Mariana's dementia (MD) by some and Guam dementia (GD) by others. It may precede, accompany, or be independent of parkinsonism. Different examiners report different characteristics. Thus, Douglas Galasko of UC San Diego finds that GD is clinically indistinguishable from Alzheimer's disease (AD), but Thomas Bak of Cambridge University, using different psychometric tests, concludes that a combination of amnestic and frontal-executive symptoms distinguish GD from AD. In 2004, an NIH-sponsored community survey diagnosed 12.2% (243 cases) of Chamorros 65 years and older with all types of dementia. The majority (174 cases and 72%) were diagnosed with probable (128) or possible (46) GD. GD and parkinsonism (i.e., PDC) were present in only 29 (12%) of all 243 cases of dementia. The probable age of GD was 79.4 ± 7.1, and greater than the age of 76.0 ± 5.9 for PDC.

Since 1983, Steele has identified 96 cases of GD. The age of onset is later than ALS or PDC and is from 53 years (in 2001) to 89 years (in 2004). Its prevalence increases exponentially with age, and it is three times more common in women than men. The eldest case had characteristic changes of ALS/PDC at autopsy without AD or beta-amyloid deposits. The last born case in 1947 (Patient RY) has the youngest age of onset (53 years) and is still alive in 2008. Her diagnosis of GD is probable. She has a family history of ALS/PDC and has not developed parkinsonism during the 7 years of observation.

Latent ALS/PDC remains common among senescent Guamanian Chamorros, but it is rare in Chamorros younger than 65 and in those born after the 1940s. Forty years ago, in subjects dying between 1968 and 1974 without neurological symptoms, Leung Chen identified NFD in a few Chamorros in their 20s who were born in the 1950s (14%), and Anderson observed it in some subjects in their 30s who were born in the 1940s (29%). Both agreed the histopathology was like ALS/PDC and not AD, and both found that NFD was increasingly prominent and widespread as subjects were older and their year of birth was earlier. Daniel Perl in 2003 confirmed that latent ALS/PDC was also a cohort which was ending when he examined asymptomatic Chamorros dying between 1988 and 1996. At that time, and 20 years after the reports by Chen and Anderson, the youngest subject of his series was 41 years of age, there were far fewer subjects under 50 years, and NFD was less intense. Those subjects who were older than 50 years and born before the 1940s still showed greater prominence of NFD with advancing age.

Pathology

In 1963, Hirano visited Jerzy Olszewski and Clifford Richardson in Toronto as they were describing PSP, and agreed that its neuropathology was remarkably similar to ALS/PDC. Thirty years later, Jean Geddes and her colleagues compared ALS/PDC with PSP and postencephalitic parkinsonism (PEP), and found that the histopathology and topography of all three tauopathies were so similar that they could not distinguish between them (**Figure 3**). Most recently, in 2008, neuropathologist Judith Miklossy and Patrick McGeer confirm that tau deposition dominates the pathology of ALS/PDC, but Aβ, α-synuclein, ubiquitin, and TDP-43 proteins are also present and implicated in

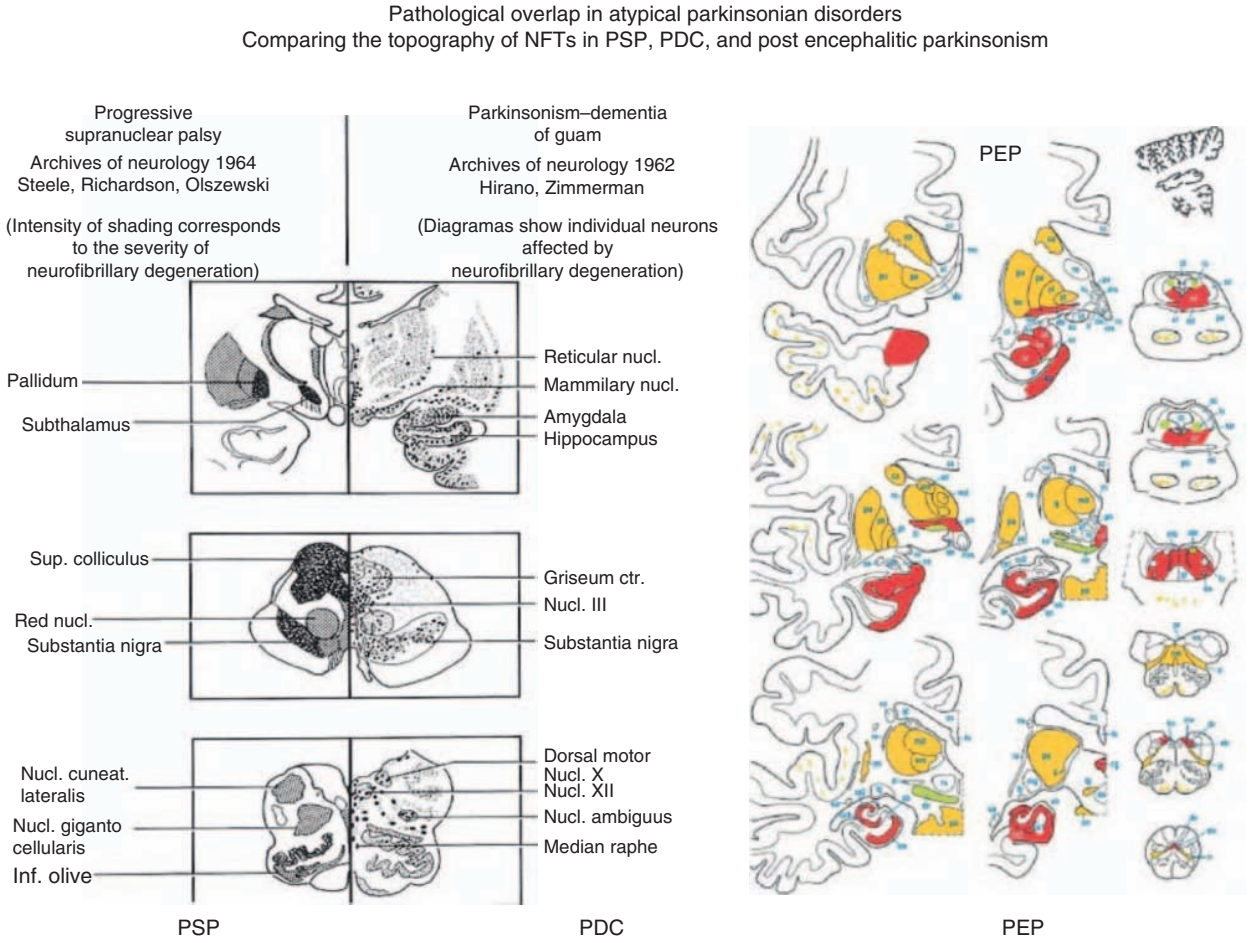


Figure 3 Pathological overlap in atypical parkinsonian disorders.

pathogenesis. The neurofibrillary tangle (NFT) pathology of ALS/PDC, first noted by Malamud and Hirano, shares similarities with AD and PEP, Lewy bodies are identical to those of PD, and the tau-positive glial pathology of ALS/PDC has similarities to PSP, CBD, and frontotemporal dementia (FTD). Tau-positive NFTs, coiled bodies, hazy granules, astrocytic plaques, thorn-shaped astrocytes, and the association of coiled bodies with hazy granules with nerve fiber tracts occur in all ALS/PDC phenotypes and confirm that they are likely variants of the same disease. In their immunohistological study of 35 ALS/PDC cases from 1946 to 2006, Miklossy and McGeer found that the qualitative features are the same in all cases, but they observed an increasing age of autopsy by 4.5–5 years per decade. They concluded that immunoproteins including ubiquitin, α-synuclein, and TDP-43 were not new but had always been involved in the neuropathogenesis of ALS/PDC.

Natural History

The etiology of ALS/PDC is not known, and it remains unclear if there is a single or multifactorial precipitant. It is, however, very clear that the phenotypic expression is age-dependent and that the age of onset can be from 20 years (ALS), to middle/late life (parkinsonism), to senescence (GD). The majority of cases are familial, and within a given family, siblings often express phenotypes of ALS, parkinsonism, and dementia that depend on the age of onset. (**Figure 4**).

During the past 50 years, the clinical and pathological features of ALS/PDC have remained the same, but there are no new cases of ALS, parkinsonism, or dementia in Chamorros born after 1951 or in non Chamorro migrants to Guam after 1956. Since that date and during the past 40 years, ALS/PDC has steadily declined, its age of onset has slowly increased, and its phenotypes have altered. Differences in the age of onset and latency of its different phenotypes are likely to account for these changes (**Figure 5**).

By example, ALS has the youngest age of onset (20 years) and affects the youngest siblings in families with ALS/PDC (**Figure 4**). Its longest latency, recorded by Ralph Garruto in 1980 is 34 years in a Chamorro who left Guam in 1935 and did not develop ALS until age 59 when in California. Because its onset is at the youngest age and its latency is the shortest, ALS was the first

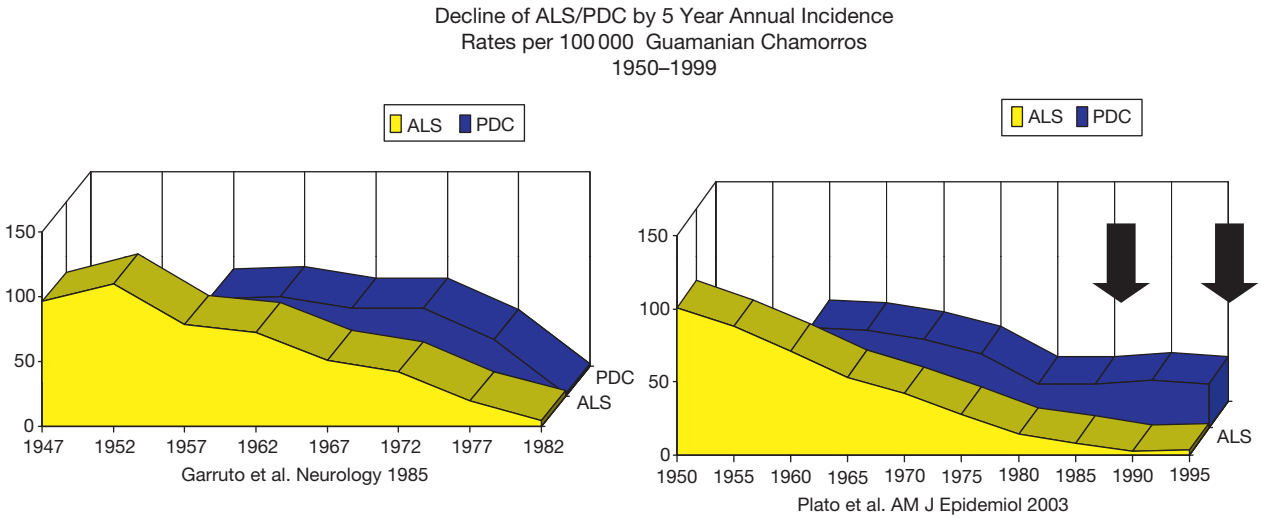
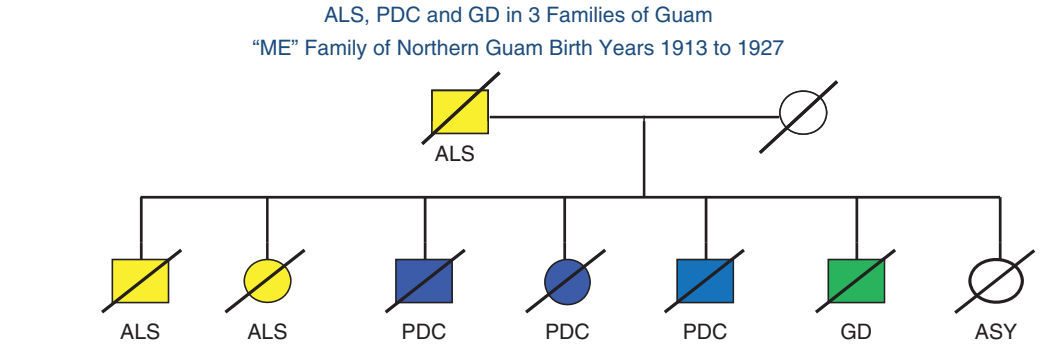


Figure 4 Three Chamorro families from different parts of Guam with ALS, PDC, and GD in siblings.



Family "M.E." northern Guam: years of birth 1913 through 1927. ALS, amyotrophic lateral; PDC, parkinson-ism dementia complex; GD, Guam Dementia, ASY, no neurological symptoms at time of death

Figure 5 Decline of ALS/PDC by annual 5 year incidence rates per 100 000 Guamanian Chamorros 1950–1999.

phenotype to show a steady decline in those born after 1951. By 2008, it is now rare.

Parkinsonism likewise is declining. The youngest age of onset of PDC is 32 years of age, 12 years later than ALS, and among affected siblings, it begins in middle or late life, and at a later age than ALS (**Figure 1**). In 1969, Eldridge reported a latency of 46 years in a Chamorro who left Guam in 1918 and lived thereafter in California until 1964 when he developed pathologically verified PDC. That latency is 12 years longer than the longest latency of ALS.

GD has been the last phenotype to alter. The youngest age of onset is 51 years, and it affects the eldest siblings in families with ALS/PDC (**Figure 4**). The NIH community survey, reported in 2007, indicates it is still common in senescent Chamorros.

Non Chamorros who migrated to Guam before 1957 are also apparently at risk for ALS/PDC. Majoor-Krakauer has recently identified American servicemen who were in Guam for only 1–2 months at the end of World War II, but who did not develop ALS until 1989–1991 when in New York City. Garruto has also reported Filipino construction workers migrating to Guam between 1946 and 1950 who developed ALS/PDC after long latencies. For example, ALS with NFD was identified in a Filipino beginning

17 years after arrival, and PDC is pathologically confirmed by Hirano, Perl, and Dickson in four cases whose onset was 20–55 years after arrival. Two nonmilitary Caucasians who went to Guam in 1952 and 1956 developed fulminant ALS 41 and 39 years later, and both were suspected to have ALS/PDC because of NFD by Hirano and Perl.

This ending of ALS/PDC in Chamorros born before 1952 and non Chamorro migrants coming before 1957, indicates the ending of its likely environmental cause which had been common and endemic in all parts of Guam for more than two centuries. Because ALS/PDC predominates in Chamorros and in families, its cause is likely to be in the traditional, pre-World War II subsistence life style of Chamorro families. But the cause must also involve genetic or other factors very specific to individual Chamorro families to explain why some are severely affected and others are spared, though they live in the same small village and share a common environment. Despite 60 years of intense study, Zimmerman first identified in 1945 that the disease remains an obscure malady.

Pathogenesis

In a review article of 2008 and correspondence that followed it, Steele and McGeer discuss the various hypotheses proposed for ALS/PDC during the past 60 years. These include genetic inheritance, neurotoxins of *Cycas circinalis* (cycad), seeds which may also be present in flying foxes, and geochemical deficiencies of calcium and magnesium. None is proven and each hypothesis is plagued by a mixture of supporting and refuting evidence. In 2009 evidence for genetic predisposition is provided by Sieh, Schellenberg and colleagues who find three susceptibility loci in Chamorros with ALS/PDC. Steele and some colleagues favor a postinfectious, immunologically mediated pathogenesis akin to postencephalitic parkinsonism. They notice the tau isoform of ALS/PDC, and its histology and topography are identical to PEP, the clinical phenotypes of parkinsonism and ALS are similar, and the long latency of ALS/PDC occurs also in PEP. Furthermore, the silent exposure and long latency of ALS/PDC very much resemble chronic cerebral infections like kuru, Jacob–Creutzfeldt's disease, and subacute sclerosing panencephalitis (SSPE).

Future Perspectives

In 1986, neurophthalmologist Cox reported a significant association between ALS/PDC on Guam and a unique linear retinopathy. It was present in one half of ALS/PDC patients and had the appearance of a worm migration in the retinal pigment epithelium. It was asymptomatic and detected only by indirect ophthalmoscopy. Three hundred sixty cases of this linear retinal pigment retinopathy (LRPE) are now identified in Guam since 1982. It does not alter over time, often precedes the onset of ALS/PDC, and may be the marker of its etiology. Yasumasa Kokubo in 2006 reports that it is also present in case of ALS/PDC in the Kii peninsula, but till date, it is not reported from any other part of the world. Knowing the cause of this unique retinopathy in these two places can advance understanding of the ALS/PDC pathogenesis.

Umatac village, the site of Guam's discovery and Ferdinand Magellan's landing in 1521, has been the epicenter of ALS/PDC for two centuries. In the 1950s, Kurland and Mulder observed ALS had 3–4 times the prevalence of adjacent villages. Now, 50 years later, most of its 33 residents of age 65 and older suffer dementia and some also have parkinsonism, but none is young or middle aged, and none has ALS. Like Rosetta town where the understanding of Egyptian hieroglyphics was revealed by the study of an ancient stone, Umatac village remains a place for neurological understanding and discovery. But time is running out and Oliver Sacks wonders; "Will the quarry, hotly pursued for fifty years now, with all the resources that science can bring, elude them finally, tantalizingly, by disappearing at the moment they are about to grasp it?".

See also: Amyotrophic Lateral Sclerosis/Parkinsonism-Dementia Complex of Three Pacific Isolates; Dementia, Movement Disorders; Frontotemporal Dementia-Parkinsonism; Progressive Supranuclear Palsy; Synucleinopathies; Tauopathies.

Further Reading

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Anticholinergics and Movement Disorders

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Definition and History

The anticholinergics are a class of drugs with antimuscarinic effects in the central nervous system. They were commonly used in the treatment of Parkinson's disease (PD), especially before the introduction of levodopa and other antiparkinsonian drugs. Currently, they are used, to a lesser degree, in PD although there is considerable geographic variability with respect to prescribing patterns. They are still used in the treatment of dystonia, especially in children.

Mechanism of Action

The exact mechanism of action of anticholinergic drugs in the relief of parkinsonian motor problems remains undetermined, although their effect is centrally mediated and they are believed to counteract the imbalance between striatal dopamine and the acetylcholine activities caused by the degeneration of dopaminergic nigrostriatal neurons. Anticholinergics are used for treating parkinsonism block muscarinic receptors. In addition, some agents have been shown to inhibit striatal dopamine reuptake in animal models of PD. In dystonia, the mechanism of action of anticholinergics is incompletely understood, but they are thought to work centrally within the basal ganglia circuits rather than at the neuromuscular junction.

Anticholinergics for the Treatment of Parkinson's Disease

Charcot was the first to note the beneficial effects of a belladonna alkaloid containing atropine on the parkinsonian motor signs. His observation was reported by his student, Ordenstein, in 1867. Subsequent investigators, including Gowers in the late nineteenth century, also found that antimuscarinic substances such as Indian hemp, scopolamine, and hyoscyamine were effective in mitigating tremor and muscular rigidity in patients with PD. Similarly, these drugs were used in the pandemic of encephalitis lethargica at the beginning of the twentieth century. In 1945, Feldburg discovered that acetylcholine is a central neurotransmitter abundant in the striatum at synaptic nerve terminals. He suggested a central effect for anticholinergic drugs. For over half a century, the belladonna alkaloids formed the mainstay of the medical management of PD. Since 1950s, these natural products have been replaced by synthetic substances, but anticholinergics remained the only drugs available for the symptomatic treatment of PD for nearly a century until the introduction of levodopa. The anticholinergics most commonly used in the treatment of PD are listed in **Table 1**.

Efficacy: Parkinsonian Motor Signs

A systematic review by the Cochrane Collaboration investigated the literature dealing with anticholinergics

Table 1 Most commonly used anticholinergics and their recommended daily doses in the treatment of PD

Substance	*Recommended daily dose in PD (mg)*
Benztropine	1–6
Benzhexol = trihexyphenidyl	2–15
Biperiden	2.5–15
Bornaprine	2–12
Orphenadrine	150–300
Procyclidine	5–20

for the treatment of PD and identified nine eligible randomized-controlled studies published between 1954 and 1986. The overall number of patients randomized into these studies was 221. Two studies dealt with benzhexol, three with bornaprine, one with orphenadrine, one with benztropine, and one with methixene; one compared benzhexol and benapryzine with a placebo. Seven studies investigated anticholinergics as an add-on to other antiparkinsonian drugs and two as monotherapy. Nearly all studies were double-blind; all were cross-over in design; and their duration ranged from 5 to 20 weeks. These studies were performed prior to the development of modern methodologies and each has significant limitations. Eight of the nine studies reported a significant improvement from baseline in at least one motor function or activity of daily living in patients on an active drug, but the magnitude of these changes was usually moderate. Only four studies reported whether the difference between drug and placebo was statistically significant. Despite limitations with respect to the quality of performing and reporting these clinical trials, the existing data provide evidence of a superior antiparkinsonian effect of anticholinergics as a group compared with a placebo in short-term application, both as monotherapy and as an adjunct to other antiparkinsonian drugs. There is no information from the literature on whether the use of anticholinergics as initial treatment of PD has any effect on the emergence of motor complications, which can be delayed by using dopamine agonists. There are also no long-term studies comparing the symptomatic effects of anticholinergics with other antiparkinsonian drugs.

There is a widespread belief among clinicians that anticholinergics have a more pronounced effect on tremor than on rigidity and bradykinesia and that the major benefit derived from their use is related to a tremorolytic effect. Although a small single-dose study found a better effect of benzhexol on tremor compared with pergolide, two recent systematic reviews indicate that data suggesting such a tremor-specific effect are inconclusive. In the Cochrane review performed on anticholinergics in PD, information on tremor as well as on other parkinsonian features was available from five studies. The results available from these studies do not argue in favor of a preferential effect of anticholinergics on tremor compared with other parkinsonian features such as rigidity and bradykinesia.

Anticholinergic drugs have been reported to alleviate dystonic spasms in PD associated with chronic levodopa administration, especially early-morning OFF dystonia. A challenge with procyclidine in nine fluctuating PD patients with OFF foot dystonia resulted in abolition of dystonia in six; amelioration in one; and no effect in two patients. In de novo-PD patients presenting with foot dystonia – as is sometimes seen in younger patients – the use of benzhexol has been reported to improve dystonia as an early motor sign.

The efficacy of anticholinergics in patients on long-term levodopa therapy with associated motor complications such as fluctuations or dyskinesias has not been investigated in randomized studies. Clinical experience suggests that there may be some benefit in this approach, and the use of anticholinergics as part of a combination regime in patients with advanced PD has been recommended by some authors, provided there are no contraindications, in particular with respect to age and cognitive function. The role of anticholinergics in the management of patients with advanced PD remains worthy of further research.

Other Manifestations of PD: Hypersalivation

Drooling and poor handling of saliva are frequent problems in PD. Despite the fact that drooling is primarily due to decreased swallowing and increased mouth opening, anticholinergics are occasionally used in an attempt to reduce saliva production. No randomized-controlled studies have investigated the systemic use of anticholinergics in this regard and the spectrum of adverse effects often precludes their use in patients with advanced disease. A small cross-over study using sublingual ipratropium bromide found a small subjective but no objective benefit compared with a placebo.

Comparison of Different Anticholinergic Drugs in Parkinson's Disease

Only one of the studies included in the Cochrane review involved two different anticholinergic drugs, benzhexol and benapryzine, in patients on levodopa therapy. The outcome measure was a total disability score based on functional disability, tremor, rigidity, akinesia, posture, and autonomic dysfunction. No significant improvement compared with placebo was found on using either drug.

Overall, there are insufficient data to draw conclusions on the differences among individual anticholinergic drugs, either in efficacy or in safety. It is likely that therapeutic differences among the various anticholinergics are minor, but some patients may tolerate one better than another.

Anticholinergics in the Treatment of Dystonia

The same range of anticholinergic drugs discussed for the treatment of PD have a role in the symptomatic management of many types of primary and secondary dystonia. One randomized-controlled cross-over study investigated benzhexol in 31 patients with various forms of primary or secondary dystonia. Improvement occurred in 22 patients. At doses up to 30 mg day^{-1}, the drug was better tolerated by patients below 19 years, whereas adverse effects

were dose-limiting in older patients. All other studies performed to date have been open-label or retrospective, but they support these findings. A large retrospective study reported good response in 43% of dystonic patients and again, younger patients being able to tolerate higher doses, with better efficacy and fewer side effects. As a rule, much higher doses can often be used in dystonia than in PD, because patients as a group are younger and usually cognitively intact. For example, most patients require a maximum dose of benzhexol of 40 mg day^{-1}, but in children, daily doses of up to 100–120 mg have been used and well tolerated. Overall, younger patients and patients with mild disease and short disease duration tend to show better responses to anticholinergic drugs. Both primary and secondary forms of dystonia may respond, and generalized and segmental dystonia tend to respond better than focal dystonia, which is often preferentially treated with botulinum toxin injections. There is some evidence that the initial effect of anticholinergics tends to wear off over months to years.

Safety and Tolerability of Anticholinergics

Clinical practice has shown that compared with some other antiparkinsonian drugs, anticholinergics carry a greater risk of adverse events. Side effects considerably limit their clinical use in many patients.

The abrupt withdrawal of anticholinergic drugs may lead to rebound effects with marked deterioration of parkinsonism and severe agitation in PD patients. In both PD and dystonic patients, these drugs should always be discontinued gradually over a period of weeks to months.

Due to their peripheral antimuscarinic action, anticholinergics are contraindicated in narrow-angle glaucoma. Caution must be exercised in elderly male patients with prostate hypertrophy, due to a high risk for urinary retention. They may cause blurred vision due to accommodation impairment, urinary retention, nausea, tachycardia, and dry mucous membranes. Gingivitis and caries, sometimes leading to loss of teeth, may occur, and reduced sweating may interfere with body temperature regulation. They impair gastrointestinal motility and may impair the absorption of other drugs, including levodopa. Constipation may occur, rarely leading to paralytic ileus. These effects are reversible with discontinuation of the drug, and can show some tolerance after prolonged exposure.

The most relevant limitation to the clinical use of anticholinergics is caused by their central anticholinergic effects. Effects on the cholinergic system, specifically in the nucleus basalis of Meynert, likely form the basis of the cognitive changes induced by anticholinergics. Impaired mental function, mainly involving immediate memory and memory acquisition, is a well-documented central side effect that resolves after drug withdrawal. Acute confusion, sedation, restlessness, poor concentration, and psychiatric disturbances, including hallucinations and psychosis, may also occur. Anticholinergics may lead to an exacerbation of frontal lobe dysfunction in patients with PD. These central adverse effects are more common in older and cognitively impaired patients, but they have also been demonstrated in patients without preexisting cognitive impairment. A recent small pathological study showed a significantly greater degree of Alzheimer-type pathology in PD patients who had been on long-term anticholinergic treatment. The findings have not yet been replicated, but in keeping with the clinical adverse effect profile, suggest that this class of drugs should be used with caution.

There are a few reports of dyskinesias brought on or increased by anticholinergics when used in PD, either when used as monotherapy or in combination with levodopa. Some dystonic patients will develop dyskinesia when anticholinergics are used to treat the dystonic symptoms.

Future Directions of Research

The available literature demonstrates a symptomatic effect of anticholinergics on PD and dystonia, but a clear delineation of the receptor populations involved in this benefit has not been accomplished. Further, pure centrally active anticholinergics that target only the needed receptors have not been developed, and therefore, many patients cannot tolerate these drugs because of central and peripheral side effects. Although anticholinergics are occasionally used in initial treatment in the early stages of PD and throughout the course of dystonia in many patients, they are no longer used as first line drugs for PD. There are no controlled data for anticholinergic use in the management of motor fluctuations in PD, but this area could be studied further in future research efforts. Anticholinergics are still sometimes recommended in patients in whom other therapies have failed to sufficiently control tremor. Definite data to confirm a special role for anticholinergics in the management of tremor are lacking, but the literature on this class of drugs dates back to times when performance and the reporting of clinical trials differed from today's standards, precluding firm conclusions. With the development of actigraphy and other automated tools to assess tremor longitudinally, very focused studies on tremor response to anticholinergics are feasible research programs for the future. Although the discussion of anticholinergics has focused on antimuscarinic agents, a second primary central cholinergic system involves nicotinic pharmacology. The development of pure nicotinic and antinicotinic agents would allow the study of the cholinergic/anticholinergic impact of nicotinic receptor manipulation in both PD and dystonia.

See also: Acetylcholine; Cholinesterase Inhibitors in Parkinson's Disease; Dystonia; Parkinson's Disease: Definition, Diagnosis, and Management.

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Antidepressants and Movement Disorders

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Glossary

Apathy – Lack of emotion, as distinguished from depression.
Augmentation – Adding a medication to increase the response already achieved by another.
Mania – Increased energy and decreased need for sleep, often associated with irritability and agitation.
Remission – Lack of daily signs or symptoms of depression versus response, which is only an improvement.
Sexual side effects – Decreased libido, impotence, and difficulty in reaching orgasm or anorgasmia.
Suicidality – Thoughts of wanting to kill oneself, if a plan or intent exists the patient will likely need emergency psychiatric help.
Withdrawal effects – Most often flu-like symptoms with severely depressed mood, even suicidality.

Antidepressant Application Overview

Mood or behavioral symptoms are very common in movement disorders. Patients with Parkinson's disease are more likely than the general population to have depression and anxiety. Tourette's syndrome and obsessive–compulsive disorder are known comorbidities. Irritability is extremely common as one of the first psychological symptoms of Huntington's disease. Behavioral symptoms adversely affect the quality of life, as well as motor symptom-related disability and level of social support. Anxiety can result in more 'off' time in Parkinson's disease patients. A Huntington's disease patient with irritability can end up with little family support and be institutionalized sooner than would be necessary otherwise. Behavioral and mood problems in movement disorders may be under-recognized and undertreated. Whether for depression, anxiety, or irritability, the antidepressants may be useful for patients with movement disorders. Treatment helps more than just the psychological wellbeing of the movement disorder patient, but can often improve the physical manifestations of their illness.

Many of the antidepressants and other medications discussed here can cause movement disorders, usually of minor significance. These movement disorders are most commonly tremor or myoclonus, or rarely neuroleptic malignant syndrome. Please see the suggested reading and chapters on these subjects for further information.

Antidepressant Medication Classes

Serotonin Selective Reuptake Inhibitors

This class of medications includes fluoxetine, fluvoxamine, citalopram, sertraline, paroxetine, and escitalopram. The side effect common to the entire class and of similar frequency among each is sexual side effects. These sexual side effects consist of decreased libido, impotence, delayed orgasm, or anorgasmia. **Table 1** summarizes usual dosing, side effects, and other important considerations of these medications.

Choosing which SSRI

Serotonin selective reuptake inhibitors (SSRIs) are one category of antidepressants without life-threatening or organ-damaging side effects with normal use, although nearly every one has drug–drug interactions that can be serious. For this reason, they are agents of first choice for depression. There is controversy over their (and other antidepressant) use with Parkinson's medications of the monoamine oxidase inhibitor (MAOI) family, but combination can be done with close monitoring, preferably by both a psychiatrist and the neurologist. The choice of initial SSRI is based on desirable and undesirable side effect profiles, past history of efficacy with a particular drug, family history of drug efficacy, drug interaction potential, and cost. If one SSRI is not effective, there is a 75% chance another one may be effective. After two failures, a switch to another category of antidepressants is recommended.

SSRIs' interactions with movement disorders

While there were early concerns that SSRIs could worsen parkinsonism, this is not usually the case. SSRIs can worsen restless leg syndrome, but again, monitoring case by case seems to be the best approach.

The other concerns with SSRIs lie in the overall treatment of elderly patients. The anticholinergic effects of paroxetine, as well as particular other SSRI effects such as decreased appetite, sleep/wake disruption, and hyponatremia, are all concerns when using SSRIs in the elderly.

Serotonin Norepinephrine Reuptake Inhibitors

Serotonin norepinephrine reuptake inhibitors (SNRIs) include venlafaxine, duloxetine, and desvenlafaxine. Information on dose, adverse effects, and other features is contained in **Table 2**. These agents are serotonergic and noradrenergic. The noradrenergic component may be helpful in patients who experience apathy or emotional numbness from the SSRIs, those who do not respond to SSRIs, or for patients when poor energy and physical symptoms are chief symptoms of depression.

Norepinephrine and Dopamine Reuptake Inhibitor

The norepinephrine and dopamine reuptake inhibitor comes in two generic forms: budeprion XL and bupropion SR. Dosing information, common side effects, and other information are reported in **Table 3**. In particular, this type of medication counteracts apathy and enhances energy, attention, and wakefulness.

Table 1 Selective serotonin reuptake inhibitors

Drug	*Dose*	*Common side effects*	*Other information*
Fluoxetine	20–80 mg daily	Fatigue, weight gain, weight loss, apathy; sexual side effects, headaches	Calming; rarely causes agitation, akathisia more common than other agents
Fluvoxamine (only available as brand name Luvox CR)	100–300 mg daily	Insomnia, fatigue, sexual side effects, headaches	May be best SSRI for obsessive–compulsive symptoms, may need high doses, many drug interactions
Sertraline	100–250 mg daily	Initial anxiety, loss of appetite, insomnia, nausea, sexual side effects, headaches	Can be started at very low dose, benzodiazepine may be needed early in therapy
Paroxetine	20–60 mg daily	Sedation, weight gain, dry mouth, constipation, confusion, sexual side effects, headaches	Withdrawal rapid and severe, avoid in patients with poor compliance
Escitalopram	10–40 mg daily	Sedation, increased appetite, dry mouth, sexual side effects, headaches	Few medication interactions
Citalopram	20–80 mg daily	Minimal, weight and sleep neutral, headaches, sexual side effects	Not the generic for escitalopram and those on escitalopram may not respond

Table 2 Serotonin norepinephrine reuptake inhibitors

Drug	*Dose*	*Common side effects*	*Other information*
Venlafaxine	150–375 mg daily	Insomnia, anxiety, loss of appetite, hypertension, irritability (especially in Huntington's disease); sexual side effects and headaches	Not a good choice for noncompliant patients, withdrawal rapid and severe
Duloxetine	60–150 mg daily	Liver failure (rare), weight neutral, fewer sexual side effects	Calming, avoid in patients with ethanol abuse
Desvenlafaxine	50–100 mg	Similar to venlafaxine	Crumbles when cut, FDA approved only at 50 mg, minimal drug interactions

Noradrenergic and Specific Serotonin Antidepressant: α-2 Antagonist

Mirtazapine is a noradrenergic and serotonergic antidepressant that is also an α-2 antagonist. Mirtazapine is likely underused outside of the elderly population. However, it can be combined with other antidepressants and has a low incidence of sexual side effects. In the elderly population, the use of mirtazapine minimizes negative side effects and maximizes positive side effects of the antidepressants. Mirtazapine is given 15–75 mg once daily, usually at night. It may cause sedation, weight gain, dry mouth, and constipation and is very rarely associated with aplastic anemia. At low doses, sedation and weight gain may be significant. Mirtazapine has a calming effect, and its effects on insomnia and weight loss make it a very good choice in Parkinson's disease patients.

First Generation Antidepressants

A discussion of first generation antidepressants is very complicated. A selection of agents is discussed here. While there is evidence to support the use of amitriptyline and nortriptyline for treatment of depression in Parkinson's disease, current practice is to use newer agents with more favorable side effect profiles, especially in an older population. First generation antidepressants may be used to treat symptoms other than depression. For example, low-dose amitriptyline and trazodone are often used to treat sleep disturbances. Information on dose, side effects, and other salient features is included in **Table 4**.

Other treatment modalities

Monoamine oxidase inhibitors

The use of nonselective MAOI is quite complex and can be best managed by consultation with a psychiatrist or neuropsychiatrist. The three main monoamine oxidase inhibitors (MAOIs) in use by psychiatrists at this time are eldepryl, phenylzine, and tranylcypromine. The doses of MAOIs used in psychiatry are eldepryl: 10 mg orally and patch form in 6, 9, and 12 mg, phenylzine: 30–60 mg, and tranylcypromine: 20–60 mg. With phenylzine, tranylcypromine, eldepryl oral, and any eldepryl patch above 6 mg, careful dietary and medication precautions are required to prevent hypertensive crisis. These are irreversible MAOIs and 14 days must pass after use of any other antidepressants (5 weeks for prozac) and starting an MAOI or 14 days after the MAOI is stopped before starting another antidepressant. Dextromethorphan and meperidine are well known contraindicated medications with MAOIs, and levodopa/carbidopa are as well.

Table 3 Norepinephrine and dopamine reuptake inhibitor

Drug	*Dose*	*Common side effects*	*Other information*
Budeprion XL	150–450 mg daily	Insomnia, decreased appetite, fidgeting, tremor, risk of seizures – rare except if history of seizures, head trauma, or current electrolyte imbalance (purging in bulimia, renal)	Activating antidepressant, may activate mania in Huntington's disease, not very good for anxiety, irritability or impulsivity; generic XL may not be as reliable as brand name (Wellbutrin XL), lower seizure risk
Bupropion SR	200–400 mg daily in two divided doses	More likely to cause insomnia, remainder as above	Better choice than generic XL, higher seizure risk than brand name XL

Table 4 Selected first generation antidepressants

Drug	*Dose*	*Common side effects*	*Other information*
Amitriptyline	10–25 mg daily for insomnia 150–300 mg daily for depression	Excessive morning sedation, dry mouth, constipation, orthostatic hypotension, dizziness, arrhythmia, hyponatremia, seizures	Useful for sleep at low doses, can be useful in patients with pain at moderate doses, treats depression and anxiety at higher doses, second most fatal medication in completed suicides
Nortriptyline	75–150 mg daily	Dry mouth, sedation, orthostatic hypotension (less than amitriptyline)	Avoid grapefruit juice, longer half-life than amitriptyline, better tolerated in elderly
Clomipramine	100–250 mg daily	Weight gain, headaches, insomnia, sedation, arrhythmia, hyponatremia, seizures	Used for obsessive–compulsive disorder, most serotonergic of the first generation antidepressants
Trazodone	25–150 mg	Morning sedation, dry mouth, orthostatic hypotension	Works best in depression-altered sleep, higher doses do not increase efficacy for sleep, not very effective as antidepressant/antianxiety agent

Orthostatic hypotension, weight gain, edema, and, as in other antidepressants, sexual dysfunction are the more common and troublesome side effects. MAOIs are thought to be most helpful for the depression with hypersomnia, hyperphagia, and mood reactivity, and worse for bipolar depression.

Electroconvulsive shock therapy

Electroconvulsive Therapy is an alternative therapeutic strategy for depression. This therapy is usually outside the scope of neurological practice, and therefore, requires referral to a psychiatrist.

Other biological therapies

Other nonmedication biological therapies also exist. See additional reading for more information.

Maximizing Treatment with Antidepressants

Before moving from the first few categories to trying a first generation or MAOI antidepressant, there are other options that may be helpful and have fewer side effects. These can be referred to as 'boosters,' although in the psychiatric literature they are called 'augmentation strategies.' The difficulty, if the SSRIs, SNRIs, mirtazapine, or bupropion are not working, is in deciding whether it is better to increase the dose, use an augmentation strategy or combination, or switch antidepressants. The goal is complete remission from mood disorder. Without complete remission, patients can relapse sooner, and most often the relapse of depression will be more difficult to treat than the original episode.

Decision Making

Guidelines are generally stated as follows: if the patient is showing some decrease in symptoms of depression and at least 3–6 weeks have passed, the physician can increase the dose of the current medication (unless already at the suggested maximum dose in the earlier table). If there is no room for increasing the dose and the patient has only shown partial response, one can augment that current antidepressant (consultation with a psychiatrist may be helpful here, see Further Reading) or use a combination approach. If there has been little to no response over at least 8 weeks to the current antidepressant (dosed in the 'effective' dosing range as listed earlier), there are two options. If time permits, the physician can increase the dose of antidepressant once and wait 4 weeks, then, if no results, switch antidepressants or simply switching antidepressants is also reasonable.

The most commonly used combinations include mirtazapine or bupropion/budeprion combined with selective serotonin reuptake inhibitors or with SNRIs. Mirtazapine and bupropion/budeprion can also be added to tricyclic antidepressants.

Aripiprazole is the only FDA-approved augmentation agent for depression. Because of the risks of chronic antipsychotic therapy (drug-induced parkinsonism, tardive dyskinesias), it is not used except to manage treatment-resistant depression. In this context, psychiatric consultation can be very valuable.

Managing Side Effects

Another reason to switch antidepressants, or augment and keep the original medication dose lower, is that the patient suffers from significant side effects. Movement disorder patients with degenerative brain disorders are very sensitive to side effects in general. Often times, keeping doses of medications low, but using combinations or augmentation, can allow them to be fully treated with antidepressants.

Sexual side effects are the easiest to treat and very common in the usual patient. Common 'antidotes' used are bupropion/budeprion addition for sexual dysfunction in men and women, taken at usual dose daily; Buspirone can be added for sexual dysfunction in women at a dose of 15–30 mg bid; or Sildenafil or similar impotence medication for sexual dysfunction in men and women, taken as needed. Benzodiazepines can also be of assistance to treat other side effects.

Length of Treatment

In major depression, the recommendation is a full year of treatment dated from full remission before tapering a patients with no prior history of depression off of their antidepressant (although some say 6 months). Another area where patients/physicians make decisions about medication is the lowering of the dose of medication, augmenting agent, or antidepressant itself; however, this could be the same as removing it entirely. In addition, sometimes starting the same antidepressant regime again does not treat a new depression. Patients with degenerative brain disorders will likely be having fewer neurosubstrates to work with over time. Lifelong medication treatment, and frequently, increasing doses of medication over time or augmentation (rarely having to switch medications) are often necessary.

Follow-up

Being familiar with antidepressants adds to a neurologist's practice of medicine. Knowing when to start an antidepressant or when to consult a psychiatric colleague can be very helpful. It is a black box warning recommendation that patients started on antidepressants must be

monitored closely for emergence of clinical worsening, suicidality, or unusual behavior. The current standard of care in psychiatry is that patients are being seen between 2 and 3 weeks after they are started on an antidepressant. This could pose a difficult situation for a neurologist who usually follows patients on a less intensive schedule. However, if the physician takes the time to have the patient check in on the phone regularly, and can arrange for short-term monthly follow-up, the comfort of the patient being able to stay with their primary neurologist for treatment of mood or behavior is important for compliance. The initial follow-up appointment is only to check on side effects and suicidality or evidence of mania, and can usually be managed over the phone, if collateral information can be obtained from a family member.

Antidepressants do not start to work for 4–6 and sometimes 8 weeks after they are at an effective dose. It is important to see a depressed, anxious, or irritable patient who has been started on an antidepressant on a more frequent schedule initially, but once well treated and in remission, moving to an every 3–4 month appointment is acceptable. In the acute phase of treatment, when an antidepressant is first started, it might be necessary to use a psychiatrist, if only to follow the patient more closely, and then have the patient return to you for their psychiatric care once the crisis has passed and medication stabilization has been accomplished.

Conclusion

A neurologist who uses antidepressants in practice is making an excellent decision and patients with movement disorders are among the most psychiatrically ill of neurological patients. In addition to medication, the physician should also refer to the psychological elements of mood or behavioral treatment, such as social work assistance, counseling, or family, individual, or caretaker psychotherapy. Being familiar with the common side effects, effective dose ranges, and decision making involved in using antidepressants helps a physician to be more confident in treating this aspect of the patients' movement disorder. Consultation for full care or for assistance should be available from a psychiatrist for every movement disorders practice. Many movement disorders are neurodegenerative and little can be done for the patient's movement, but often the psychiatric aspects of the patient's disorder are a major factor and can be greatly helped by antidepressants.

See also: Drug-induced Movement Disorders; Serotonin and Tryptophan; Serotonin Syndrome; Tremor: Drug-induced.

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Applause Sign

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Definition and History

The 'applause sign' describes an abnormal tendency for a patient to initiate an automatic program of applause when asked to imitate three claps. It is included in the spectrum of clinical signs that can be identified at the bedside in patients with frontostriatal cognitive dysfunction. It was originally described as a clinical sign that differentiates progressive supranuclear palsy from Parkinson's disease and frontotemporal dementia.

Bruno Dubois is the neurologist who has contributed most to the development and study of the applause sign. His work on cognitive neurology, with colleagues from the Hôpital de la Salpêtrière, has established him as an expert in the area of subcortical cognitive dysfunction. Some refer to this sign as 'Dubois' applause sign.'

Pathophysiology

The frontostriatal cognitive pathways subserve the motor and cognitive functions via circuits that involve the dorsolateral prefrontal cortex, orbitofrontal and cingulate regions of the prefrontal cortex, and basal ganglia. Lesions in any of these regions can produce a dysexecutive syndrome characterized by poor attention, decreased working memory, diminished planning and reasoning, and depression. Although anatomically different, the basal ganglia and the frontal lobes are so closely involved in executive function that extensive neuropsychological evaluation is required to demonstrate the neuropsychological differences between lesions in these areas. They do, however, differ in their control of motor acts: the frontal lobes are involved in the voluntary control of actions and subcortical structures intervene in more automatic components of action.

The applause sign probably reflects lesions in the subcortical structures, and is more often seen in patients with these lesions than in patients with predominantly frontal lobe dysfunction. Although unproven, this sign is thought to be caused through an inability to stop an automatic activity once it has been released (because of the dysfunction of the basal ganglia). Other explanations for this behaviour include frontal lobe problems of perseverative behavior or decreased ability to plan specific motor programs.

Clinical Features and Diagnostic Criteria

The sign is usually elicited as part of the cognitive bedside assessment. The examiner first says to the patient 'Clap three times after me' and then demonstrates three claps (in <1 s). The patient is observed and the number of claps produced is counted and scored. The performance of the subject is normal when he or she claps only three times (score $= 3$) or abnormal when he or she claps four times (score $= 2$), 5–10 times (score $= 1$), or when he or she initiates a program of applause that he or she cannot stop (score $= 0$).

Normal controls always clap three times. Patients with subcortical cognitive dysfunction clap more than three times. In patients with progressive supranuclear palsy, there was no correlation between the severity of cognitive dysfunction and the degree of abnormality in the applause sign. The applause sign has been studied in only small samples of patients with Parkinson's disease and no correlation with cognitive function (mini-mental state examination) was observed but a negative correlation with motor severity (Unified Parkinson's Disease Rating Scale, section III) was identified.

Differential Diagnosis

The applause sign has been shown to be a common clinical feature in patients with neurodegenerative parkinsonism, including corticobasal syndrome, progressive supranuclear palsy, and multiple system atrophy, and has been described in a patient with nondegenerative subcortical lesions. The applause sign occurs less often in Parkinson's disease, Huntington's disease, and rarely in frontotemporal lobar dementia syndromes. The sign is not sufficiently sensitive or specific to contribute to the differential diagnosis of patients with Parkinsonism.

See also: Dementia, Movement Disorders; Huntington's Disease; Parkinson's Disease: Definition, Diagnosis, and Management; Progressive Supranuclear Palsy.

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Approximate Entropy

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Glossary

Autocorrelation – A method to quantify the correlation of a variable at one time with itself at another time.
Essential tremor – A movement disorder that primarily causes tremor of the extremities, and is considered the most prevalent movement disorder in the world. The tremor can occur during a posture, during movement, and when holding an object. The tremor does not occur when the limb is at rest.
Frequency – Frequency describes the number of cycles per second. Fourier analysis is a method that transforms a data time series into the frequency domain to determine which frequency content is within the data time series.
Parkinson's disease – A neurodegenerative disorder that causes motor symptoms such as tremor, rigidity, and bradykinesia.
Tremor – An involuntary, approximately rhythmic, and roughly sinusoidal movement that occurs in Parkinson's disease, cerebellar disease, essential tremor, and other movement disorders.
White Gaussian noise – Each data point in a time series is independent to the past and future data points. The power spectrum of white Gaussian noise is flat.

Definition and History

Approximate entropy (ApEn) is an algorithm that examines the structure of a data time series in the time domain. ApEn was originally developed by Steven Pincus. This was a seminal paper that has been cited 576 times as of writing this entry. In general, ApEn measures the regularity of a time series by examining the predictability of future values in a time series on the basis of previous values. For example, consider a sine wave where there are accurate short- and long-term predictions of future values in a time series. ApEn tends toward a value of 0. For a randomly generated signal such as white Gaussian noise, each value in the time series is generated independently of the other time series values. ApEn increases to a value near 2. Thus, the ApEn algorithm returns a value tending toward 2 for highly irregular signals, and becomes close to 0 for a more regular signal.

In the field of movement disorders, ApEn has been used to study tremor. This is because tremor in healthy individuals takes on a broad band of frequencies, but during pathology, tremor becomes more rhythmical at a fixed frequency. ApEn can be more sensitive than frequency at detecting tremor in Parkinson's disease. An example of the independence of ApEn in relation to the frequency and amplitude of tremor is shown in **Figure 1**. **Figure 1(a)** shows an accelerometer recording of tremor from the index finger of a healthy individual in the time domain (left), frequency domain (middle), and autocorrelation (right). In the middle figure, the classic peak ~10 Hz is observed, as is a high frequency peak between 20 and 25 Hz. This is consistent with the original description of healthy physiological tremor by Stiles. The signal in **Figure 1(a)** has a standard deviation (SD) of 0.38 and an ApEn value of 0.90. In **Figure 1(b)**, the time series was converted into the frequency domain, and the phases associated with each frequency were shuffled. The signal was then converted back into the time domain. This process randomizes the orderliness or regularity of the signal, but preserves the linear qualities of the signal. Thus, as shown in **Figure 1(b)**, the SD remains at 0.38 (left), the frequency spectrum remains very similar to **Figure 1(a)** (middle), and the autocorrelation looks very similar (right). The ApEn value has increased to 1.24. This demonstration illustrates why ApEn can be more sensitive than the other measures that rely on the first and second moments at detecting tremor.

ApEn is reduced in patients who have essential tremor and Parkinson's disease. Also, deep brain stimulation of the ventral intermediate nucleus of the thalamus increases the ApEn value of tremor in patients with essential tremor. Deep brain stimulation of the subthalamic nucleus increases the ApEn value of tremor in patients with Parkinson's disease. ApEn has also been used to study posture and force steadiness in other motor control studies. Although ApEn has not been used in electrophysiological studies of brain function, it is a very reasonable approach if one is interested in regularity. ApEn is beneficial because it can be calculated on time series that are short, with only a few hundred data samples. There is one cautionary point regarding ApEn. The ApEn value is dependent on the number of samples. Thus, if one wants to compare ApEn values across studies using the same type of time series (e.g., local field potential, tremor acceleration), the sampling rate and length of the recording need to remain constant. More recent developments which build on ApEn have been developed in the form of sample entropy.

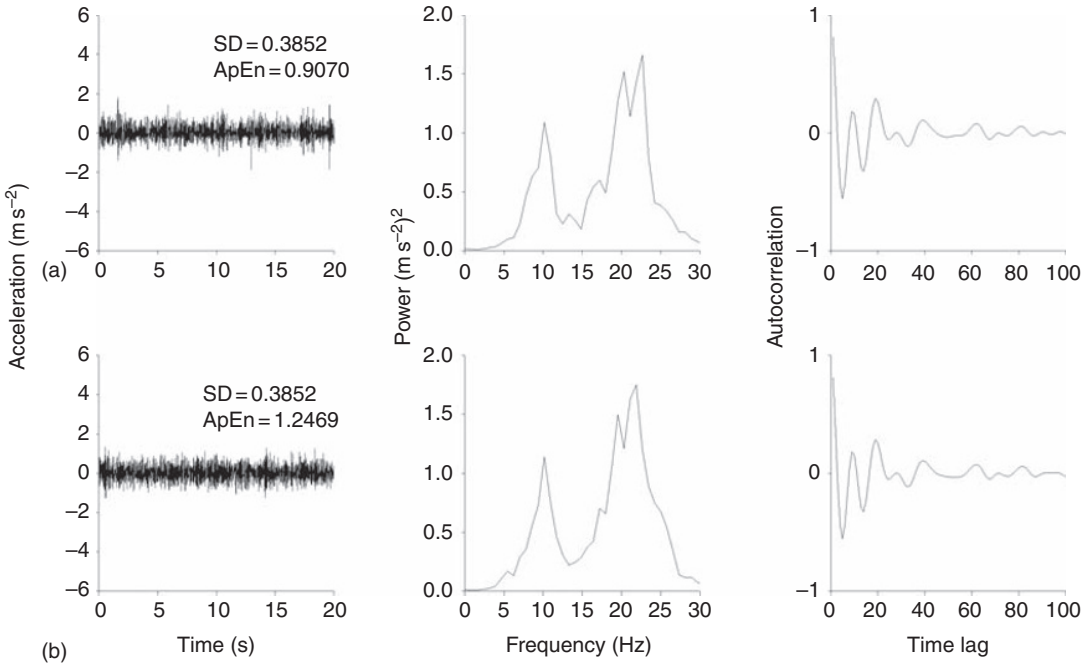

Figure 1 The figure shows a recording of physiological tremor from an accelerometer attached to the middle finger of a healthy adult. (a) The acceleration time series (left panel), power spectrum of the acceleration (middle panel), and autocorrelation of the acceleration (right panel). (b) The phase-randomized surrogate transformation of the acceleration signal in A. The surrogate time series (left panel), power spectrum of surrogate time series (middle panel), and autocorrelation of surrogate time series (right panel) all appear qualitatively similar to the original time series. As is shown in (a) and (b) left panel, the ApEn values distinguish the two signals whereas the SD does not distinguish the two signals.

Sample entropy is independent of the number of data samples.

The following steps are adapted from Slifkin and Newell and used in the calculation of ApEn. A more formal mathematical account of the required calculations is available in Pincus and Pincus and Goldberger.

Step 1: Two input parameters, m and r, need to be specified. The value of r is multiplied by the SD of the time series and, as is discussed in more detail, provides tolerance limits for assessing the nearness of adjacent data points in the time series. The m value represents a vector length comprising m consecutive data points. Typical values used in the literature include $r = 0.2 \times \text{SD}$ and $m = 2$.

Step 2: The calculation of ApEn begins with the identification of the first vector in the time series, $[u(1), u(2)]$, which comprises the first and second data points. This vector is termed as the template vector. The calculation of ApEn entails a determination of the similarity of other vectors in the time series to the template vector. Beginning with the first data point, $u(1)$, limits are established around it that extend across the time series. The limits are determined by multiplying r by the SD. If, for example, $r = 0.2$ and the $\text{SD} = 0.10$, a value of ± 0.02 around the first data point is established. These limits are extended over the entire length of the time series. Then, according to the same procedure, limits are established for the second element, $u(2)$.

Step 3: The next step is to identify all other vectors of adjacent m length points, $x(i) = [u(i), u(i+1)]$, in the time series that are close to the template vector, $[u(1), u(2)]$. The first element, u(i), in all other vectors, $x(i)$, is close to $u(1)$ if the element falls within the limits around $u(1)$. The second element, $u(i+1)$, of each vector is close if it falls within the limits around $u(2)$. Thus, all vectors that are close to $[u(1), u(2)]$ will have their first element within the boundaries of $u(1)$ and their second element within the boundaries of $u(2)$. These are called the conditioning vectors. The number of conditioning vectors becomes the denominator of a ratio that is the central calculation for ApEn. Another way of thinking about this procedure is that it identifies other vectors that are similar to the template vector, and the value of r determines the threshold or criterion for stating that other vectors are similar. For instance, decreasing the value of r decreases the range of the limits around template vector elements, and would result in fewer vectors qualifying as conditioning vectors.

Step 4: The next element of the template vector is identified, which in this example is $u(3)$. According to the procedure in Step 2, limits are constructed around it as previously described for $u(1)$ and $u(2)$. Then the

conditioning vectors with $u(i+2)$ values that are close to $u(3)$ – within the limits around $u(3)$ – are identified. The initial conditioning vectors, $u(\mathrm{i})$, that were close to the template vector, $[u(1), u(2)]$, and that still have $u(\mathrm{i}+2)$ values close to $u(3)$ of the template vector become the numerator of the ratio.

Step 5: The ratio forms a conditional probability of the likelihood that runs of two adjacent data points in the conditioning vectors that were close to the first two values of the template vector and will remain close to the template vector on the next incremental comparison – to $u(3)$. In other words, given the number of runs of adjacent values that are a similar distance away (A), what is the likelihood that those runs will still be similar when the number of values have been incremented to three (B)? The natural logarithm of the conditional probability, A/B, is then calculated. Thus, compared with a highly periodic process (e.g., a sine wave), white Gaussian noise will have a low probability of finding conditioning vectors in the time series that are close to the first two elements in the template vector, and that will still be close at the next incremental comparison.

See also: Accelerometry; Actigraphy; Concentric Needle EMG; Cortical Tremor; Deep Brain stimulation; Dyskinesias; Electromyography (EMG); Interspike Interval; Intra-Individual Variability in Movement; Motor Output Variability; Motor Unit Synchronization; Postural Tremor; Primary Orthostatic Tremor; Rest Tremor; Tremor; Tremor, Essential (Syndromes).

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Aprataxin

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Glossary

APTX – Gene coding for aprataxin, mutated in Ataxia with oculomotor apraxia type 1 (AOA1) patients.
Aprataxin – Protein implicated in DNA repair.
Ataxia – Symptom or syndrome consisting of abnormal coordination caused by an altered function of the cerebellum or its connections.
Base excision repair (BER) – Mechanism responsible for removing DNA damaged bases.
Oculomotor apraxia – Dissociation of eyes and head movements when looking toward a lateral target.
Single strand brake – DNA discontinuation in one filament produced during base excision repair or after reactive oxygen species (ROS) damage.

Definition and History

Ataxia with oculomotor apraxia type 1 (AOA1) was first described in Japanese and Portuguese families. AOA1 is characterized by early-onset ataxia, peripheral neuropathy, and oculomotor apraxia. Linkage analysis localized the causative gene to chromosome 9p13.3. The sequencing of the region revealed missense, nonsense, and frameshift mutations in the *FLJ20157* gene. Nucleotide changes were not found in unrelated and unaffected individuals. The gene was successively named *APTX* and the protein, Aprataxin (*APTX*).

Pathogenesis

DNA single-strand breaks (SSBs) are the most abundant DNA lesions produced by reactive oxygen species (ROS).

Experimentally, SSBs can be generated after UV irradiation and hydrogen peroxide (H_2O_2), methyl methane sulfonate (MMS), or camptothecin administration. SSBs are also produced during base excision repair (BER) as repair intermediates. BER is responsible for removing DNA bases that are oxidized or alkylated, which can occur during inflammation and UV light exposure, and after endogenous alkylating agents' exposure. The first step in BER is the recognition and removal of damaged bases and the incision in the phosphodiester bond operated by glycosylases. At this point, the DNA filament is opened and a SSB is generated. During SSB formation, abnormal 3′or 5′ terminals can arise, especially if SSBs are generated directly by ROS. To be correctly repaired and polymerized, they must be repaired to 5′-phosphate and 3′-OH. At this stage, the recognition of SSBs is operated by poly-ADP ribose polymerase-1 (PARP-1), which assembles the repair machinery interacting with DNA polynucleotide kinase–phosphatase (PNKP), XRCC1, polymerase-β, ligase-III, tyrosyl-DNA phosphodiesterase 1 (TDP1), and aprataxin.

APTX consists of 7 exons and is ubiquitously expressed in human tissues. Mutations have been reported in exons 5, 6, and 7. Lymphoblasts of patients carrying truncating mutations show reduced levels of APTX mRNA up to 57% of controls. Exon 3 is alternatively spliced, generating two transcripts. The longer, in frame transcript of 342 amino acids, is the major form found in human cell lines, whereas the shorter is present at lower levels. Aprataxin contains three functional domains: A N-terminal forkhead-associated (FHA) domain (exons 1–3), a central histidine triad (HIT) domain (exons 4–6), and a C-terminal divergent zinc-finger (exon 7). Aprataxin is also predicted to have a potential nuclear localization signal between the FHA and HIT domains. Aprataxin is believed to interact with PARP-1 and XRCC1 through its FHA domain, allowing a close interaction at BER sites. Aprataxin's HIT domain is able to catalyze the nucleophilic release of adenylate groups linked to 5′-phosphate termini, as well as the removal of 3′-phosphoglycolate and 3′-phosphate ends.

AOA1 lymphoblastoid cell lines (LCL) display an altered sensitivity to genotoxic stress. H_2O_2, MMS, and camptothecin, all SSB inductors, cause genomic instability and reduce cell survival compared with control LCL. Enhanced sensitivity to H_2O_2 can be reduced by transfecting AOA1 LCL with wild-type aprataxin. SSB repair is also impaired after UV light irradiation, resulting in cell death. Antioxidants have been shown to be useful in this model.

Together this information indicates an active role of Aprataxin in BER and SSB repair. Mutations may result in unrepaired SSBs and apoptosis, followed by neuronal loss and cerebellar atrophy.

Clinical Features

AOA1 is an autosomal recessive neurodegenerative disorder, first described in the Japanese and Portuguese population. Relative frequency, as estimated through molecular screening of non-Friedreich early onset (<25) progressive autosomal recessive ataxia, ranges from 6 to 9%, representing the most frequent recessive ataxia in the Japanese population. The most frequent AOA1 phenotype is associated with early-onset cerebellar ataxia with cerebellar atrophy, areflexia, and axonal sensorimotor neuropathy. The onset of the disease ranges from 2 to 18 years, although late onset (>25) has been reported. Hypoalbuminemia and hypercholesterolemia are variable and late features, and thus, not present in all patients. Choreic movements are frequent at onset, but often disappear during the course of the disease, except for those patients with A198V mutations that show persistence up to 10 years after onset. Mild cognitive impairment may also be present, and represents a frequent finding in Japanese families. In contrast, Portuguese and Tunisian families showed no mental deterioration despite long disease duration.

AOA1 presents with square wave jerks, saccadic pursuit, gaze-evoked nystagmus, and hypometric saccades. In addition, patients show normal vestibulo-ocular reflex (VOR), but cancellation is defective. Dissociation of eyes and head movements when looking toward a lateral target in the head-free condition is present in 80% of the patients. It closely resembles oculomotor apraxia (OMA).

Genome-wide analysis was performed in a family with ataxia and coenzyme Q10 deficiency, showing linkage to chromosome 9p13. *APTX* mutations were identified, indicating that coenzyme Q10 deficiency may contribute to the pathogenesis of AOA1.

Postmortem examination has revealed severe loss of Purkinje cells and degeneration of the posterior columns, spinocerebellar tracts, and anterior horn cells of the spinal cord. Nerve biopsies show marked loss of small and large myelinated fibers, with preservation of small unmyelinated fibers.

Brain MRI shows cerebellar atrophy in all patients. Cerebellar hypoperfusion was present in SPECT imaging. Dopamine transporter density was studied with (FPCIT)-SPECT in four patients. It showed a slight bilateral and uniform reduction of the average striatal DAT density, impairment that occurred even in the absence of extrapyramidal features, suggesting a subclinical involvement of the basal ganglia.

Differential Diagnosis

Differential diagnosis is usually made among Friedreich's ataxia (FA), ataxia-telangiectasia (A-T), chorea, and hereditary neuropathies. The absence of oculo-conjunctival telangiectasias, cancer predisposition, immunodeficiency, and normal α-fetoprotein levels can allow exclusion of A-T. FA patients show extensor plantar reflexes, altered electrocardiograms, and cardiomyopathy without marked cerebellar atrophy or OMA. The presence of involuntary movements in AOA1 may pose a differential diagnosis with other

choreas. Cerebellar atrophy at MRI and the presence of peripheral neuropathy may be helpful in the diagnosis.

Management

Coenzyme Q10 administration ($>600\,\mathrm{mg\,day^{-1}}$) to AOA1 patients was reported to be beneficial and well tolerated, but future clinical trials are warranted to confirm this finding. Idebenone, a Q10 synthetic analog used in Friedreich' ataxia, could also be proposed. Beneficial effects of antioxidants on SSBs in cellular models suggest that their clinical use should be studied.

See also: Ataxia; Ataxia-Telangiectasia; ATM Gene; Coenzyme Q_{10}; Idebenone and Friedreich Ataxia.

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Apraxia: Upper Limb

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Glossary

Apraxia – A loss of the ability to perform purposeful skilled movements that cannot be accounted for by weakness, sensory loss, abnormal movements, impaired comprehension, or cognitive disorders.

Body part as tool error – Patients with ideomotor rather than pantomiming tool use will often use their fingers and hands as the tool.

Callosal apraxia – Injury to the corpus callosum that prevents motor programs stored in one (dominant) hemisphere from reaching the other hemisphere (nondominant) such that the hand contralateral to the nondominant hemisphere has a loss of the ability to perform skilled purposeful movements.

Conceptual apraxia – A loss of mechanical knowledge including tool–object relationships, tool–action relationships, and mechanical advantage of tools.

Deftness-dexterity – Ability to make precise, independent, but coordinated finger–hand movements.

Dissociation apraxia – An inability to correctly use the upper limb in response to a stimulus of one type or in one modality (e.g., verbal command) with preserved ability to perform in response to stimuli in a different modality (e.g., vision).

Ideational apraxia – A loss of the ability to perform a correct sequence of acts leading to a goal.

Ideomotor apraxia – Making spatial and temporal errors when using tools, pantomiming or imitating purposeful acts.

Limb-kinetic apraxia – A loss of deftness. This disorder is also called innervatory apraxia.
Premotor areas (including supplementary motor area) – Regions in frontal lobe, anterior to motor cortex, that is thought to translate spatial temporal movement representations to motor programs.
Supramarginal gyrus – Portion of the inferior parietal lobe that, when damaged, often induces ideomotor apraxia. This area is thought to store movement representations.

Introduction

Only organisms that perform goal-directed actions have brains, and hence one of the most important functions of the brain is to program movements that will allow the organism to successfully alter the environment or themselves. In humans, it is primarily the upper extremity or forelimb that we use for performing these goal-directed actions. The joints and muscles of the human forelimb allow people to perform almost any type of movement, and the corticospinal system that activates specific motor units can mediate an almost infinite number of movements. Thus, in order to successfully interact with the environment, the corticospinal neurons in the cerebral cortex must be guided by instructions or movement programs. Disorders in the implementation of these programs are termed apraxia.

There are many forms of apraxia, and this term has been used to describe abnormal control of movements of the eyes, mouth (e.g., buccofacial apraxia and apraxia of speech), and the legs (e.g., apraxia of gait). We, however, confine our discussion to apraxia of the forelimbs. There are two major forms of forelimb apraxia: task specific and general. Task-specific apraxia includes dressing and constructional apraxia, which will not be discussed in this article. We discuss general forms of forelimb apraxia, which can impair almost all purposeful movements made by the forelimb.

Apraxia is defined both by what it is not and what it is. After Liepmann's seminal papers in the early part of the twentieth century, there was little interest in this disorder until Geschwind's classic paper on 'Disconnexion Syndromes,' in which he resurrected interest in this disorder. Geschwind defined apraxia as a disorder in which a person makes clumsy movements as a result of a neurological disease, but this disorder is not considered as an apraxia if clumsiness is caused by weakness, abnormal movements such as tremor, chorea, ballismus, and myoclonus, severe sensory-perceptual deficits, or cognitive impairments such as an impaired comprehension or attention. There are several types of general forelimb apraxia, which are characterized by the errors made by the patients. In this article, we discuss five different forms of general forelimb apraxia including (1) conceptual, (2) ideomotor, (3) ideational, (4) dissociation, and (5) limb-kinetic. In addition to briefly describing the clinical aspects of these five forms of limb apraxia, the pathophysiologic disorders that might account for these deficits are also briefly discussed.

The five forms of general limb apraxia, which are discussed in this article, can be induced by a variety of diseases. Some of these diseases cause focal damage, such as that caused by a cerebral infarction, but apraxia can also be associated with degenerative diseases where the brain pathology is more widely distributed such as Alzheimer's disease or corticobasal degeneration. The specific diseases that can induce apraxia, however, will not be fully discussed in this article.

Conceptual Apraxia

Clinical

When a person is presented with a situation that requires forelimb actions to alter either themselves, such as combing hair, or objects in their environment, such as fixing a flat tire, the first thing a person must do is to see what is needed. Although there are animals that use tools and rare examples of animals that actually fabricated tools, it is primarily humans who develop and use tools to alter themselves and their environment. There are, however, patients who, when presented with a problem that requires an action, sometimes cannot recognize the required action, the required tool, or both. In addition, there are also patients with conceptual apraxia who might not recall the type of actions associated with specific tools, utensils, or objects (i.e., tool–object action associative knowledge) and therefore, make content errors. For example, when asked to demonstrate the use of a screwdriver by either pantomiming or using the tool, the patient without a visual agnosia might pantomime a hammering or pounding movement or use the screwdriver as if it were a hammer.

Patients with conceptual apraxia might be unable to recall which specific tool (e.g., hammer) is associated with a specific object (e.g., nail), thereby revealing impaired tool–object associative knowledge and a loss of mechanical knowledge. For example, when attempting to drive a nail into a piece of wood, if there is no hammer available, the patient with conceptual apraxia might select a screwdriver rather than a wrench. In addition, since mechanical knowledge is also important for tool development, patients with conceptual apraxia are often unable to correctly develop tools.

Pathophysiology

While Liepmann thought that conceptual knowledge is stored in the caudal parietal lobe, DeRenzi and Luccelli

located these representations in the temporal–parietal junction. There are two forms of evidence that these representations are stored in the hemisphere contralateral to the preferred hand. Patients with a callosal disconnection demonstrate conceptual apraxia of the nonpreferred (left) of their left (nondominant) hand. Heilman et al. studied right-handed patients who had either right or left hemisphere cerebral infarctions and found that conceptual apraxia was more commonly associated with the left than the right hemisphere injury. Although these investigators attempted to learn the locus of injury that induced conceptual apraxia, no specific anatomic region appeared to be critical. This might be related to having an inadequate number of subjects, or that each subtype might have a different localization, or that in right-handed people, mechanical knowledge may be widely distributed in the left hemisphere. As mentioned, conceptual apraxia can be associated with diseases that cause focal brain damage, such as stroke, but it is commonly seen in patients suffering from Alzheimer disease.

Ideomotor Apraxia

Clinical

Patients with ideomotor apraxia (IMA) make primarily spatial errors that cannot be attributed to a loss of deftness (LKA). Three types of spatial errors can be observed: (1) postural or internal configuration errors, in which patients fail to put their hand and arm in the position that would enable them to correctly hold a tool or implement. Often, patients use their hand and fingers as the tool, and unlike normal subjects, will continue to use a body part as tool even when corrected; (2) spatial movement errors, in which patients either move the incorrect joint or joints or do not properly coordinate joint movements and therefore move the hand and arm incorrectly through space; and (3) spatial orientation errors, in which patients do not consistently orient the tool-implement at the target-object. The most sensitive test for IMA is asking patients to gesture (pantomime) to verbal command. Patients with IMA often perform more poorly with transitive ('Show me how you would scramble eggs with a fork') than intransitive acts ('Wave bye-bye.'). Although patients with IMA typically improve when imitating the examiner pantomime a transitive act, their performance often remains impaired. In addition, when using actual tools, their performance might improve even further, because they are provided with visual and tactile cues, but their performance often remains abnormal.

When one forelimb has an elemental sensorimotor disorder that would preclude meaningful testing, the opposite ipsilesional limb should be tested. When possible, both forelimbs should be tested. In addition to testing gesture to command, imitation, and use of actual objects, patients should also be tested to learn whether they can comprehend the examiner's pantomimes of transitive movements and the examiner should also perform correct and incorrect pantomimes to learn whether the patient can discriminate.

Pathophysiology

IMA is almost always induced by left hemisphere lesions in patients who are right-handed and is associated with injury to several structures, including the inferior parietal lobe and the premotor cortex (supplementary motor area and convexity premotor cortex) as well as the corpus callosum. Subcortical lesions that involve the basal ganglia, the thalamus, and the white matter connecting these areas with the cortex can also be associated with IMA.

Callosal disconnection

Liepmann and Maas reported Ochs, a right-handed patient with a lesion of his corpus callosum, who was unable to correctly pantomime to commands with his left arm. Unfortunately, this patient's right hand could not be tested because he had a right hemiparesis from a pontine lesion. Paul Broca had demonstrated that in people who are right-handed, the left hemisphere is dominant for mediating language. Although Ochs' inability to pantomime to verbal command with his left hand could be attributed to a disconnection between language mediated by the left hemisphere and the right hemisphere's motor areas (a language–motor disconnection), a language–motor disconnection could not explain why this patient could not imitate or use actual tools. Instead, Liepmann and Maas suggested that the left hemisphere of right-handed people contains movement formulas (i.e., the spatial temporal patterns required to make purposeful skilled movements) and that the callosal lesion disconnected these movement representations from the right hemisphere's motor areas.

Watson and Heilman, as well as Graff-Radford and colleagues, reported patients similar to Ochs, who could not correctly pantomime or imitate transitive acts, but unlike Ochs, these patients had infarctions limited to the corpus callosum. These patients did not have weakness of their right hand and performed tasks such as pantomiming to command, imitation, and the use of actual objects, flawlessly with their right hand. These patients' behaviors suggest that not only language but also spatial-temporal movement representations (movement formula) were stored in the left hemisphere, and callosal injury disconnected these movement representations from the right hemisphere.

Left hemisphere injury

Liepmann studied a population of right-handed patients who had damage to either the left or the right hemisphere. While none of the patients with right hemisphere damage

had apraxia, about 50% of the patients with left hemisphere injury had IMA. Many patients with IMA are also aphasic, and some have thought that both aphasia and apraxia are symptoms of asymbolia, an inability to use signs. Liepmann noted, however, that some apraxic patients did not have aphasia and some aphasic patients were not apraxic. These behavioral dissociations provide evidence against the postulate that apraxia is a form of asymbolia.

Parietal lobe

Liepmann noted that many patients with IMA had injury to the inferior parietal lobe, especially, the supramarginal gyrus. In order to explain why lesions in this region would induce IMA of both hands, Geschwind posited that, the lesions in the left hemisphere could induce a disconnection syndrome. Thus, when a patient is given a command to perform a gesture, the incoming verbal message is decoded in Wernicke's area, but this message must then be transmitted to the left premotor convexity cortex for the command to be implemented by the left primary motor cortex. According to Geschwind, the lesion of the supramarginal gyrus injures the white matter pathway that connects Wernicke's area, located in the posterior–superior temporal lobe, with the left hemisphere's convexity premotor cortex. The left hemisphere's premotor cortex connects with the motor cortex of the left hemisphere as well as the premotor cortex of the right hemisphere. According to Geschwind, when carrying commands with the right hand, people use the former pathway and when using the left hand, the latter pathway; interruption of this pathway in the parietal lobe would cause IMA of both hands.

When attempting with either hand to imitate or use actual objects patients who have IMA from left inferior parietal lesions are impaired. Although the left hemisphere disconnection hypothesis of Liepmann–Geschwind can account for failure to correctly pantomime to command, this disconnection hypothesis cannot account for these imitation and actual tool-use disorders. Although the left hemisphere lesion might have also disconnected visual association cortex from motor areas, these patients' right hemispheric connections (between the anterior motor areas and the posterior visual areas) are intact and these patient should be able to normally imitate and use tools and implements with the left forelimb.

An alternative hypothesis was advanced by Heilman et al. and Rothi et al., who suggested that, in right-handed people, the movement formula or representations that contain the spatial and temporal parameters of purposeful actions are stored in the left parietal lobe. If these movement representations are degraded or destroyed, not only should there be deficits of pantomiming to command, imitating, and using actual objects, but these patients should also have gesture/pantomime comprehension deficits and a loss of the ability to discriminate between correctly and incorrectly performed purposeful actions. In order for these spatial temporal movement representations to guide-program purposeful actions, they have to have access to the premotor and motor cortex. Thus, injury to the projections from these movement representations to the premotor cortex or injury to the premotor cortex would be expected to also induce IMA. However, unlike left hemisphere inferior parietal lesions that destroy the movement representations, the anterior lesions should not induce gesture comprehension and discrimination disorders. To test this hypothesis, Heilman et al. and Rothi et al. tested patients with anterior and posterior left hemisphere cerebral lesions by attempting to learn whether they had IMA and whether they had a disorder of pantomime comprehension and discrimination. We found that while both the anterior and posterior groups of patients had the production deficits typical of IMA, only the patients with damage to the inferior parietal lobe had comprehension and discrimination disturbances.

Halsband and coworkers replicated Heilman et al. and Rothi et al.'s findings. In addition, Haaland et al. studied the localization of lesions that induce and those that do not induce apraxia. They found that, in addition to patients with frontal convexity lesions, patients with IMA most often had lesions in the region of the intraparietal sulcus (the top of the supramarginal gyrus), but also in the superior parietal lobe (Brodmann's area 7). Haaland et al. also found that many of their patients had subcortical damage that disconnected the pathways between the occipital and frontal cortex. However, these patients were able to normally imitate. Convergent evidence for the postulate that the left inferior parietal lobe stores movement representations comes from functional imaging studies performed with normal right-handed subjects.

Supplementary motor area

The movement representations that are stored in the left inferior parietal lobe are probably stored in a three-dimensional supramodal (temporal, visual-spatial and temporal kinesthetic-spatial) code. Before the neurons in the motor cortex are properly activated, the stored spatial-temporal movement representations have to be transformed into a motor program. The supplementary motor area receives projections from parietal neurons and projects directly to the motor cortex (Brodmann's area 4). Studies have revealed that neurons in the supplementary motor cortex (SMA) discharge before neurons in the primary motor cortex. The SMA also projects to convexity premotor cortex, the basal ganglia, and directly to the motor neurons in the spinal cord. Functional imaging studies of cerebral blood flow, an indicator synaptic activity, have revealed that simple repetitive movements increase the activation of the contralateral primary motor cortex. In contrast, complex movements increase flow in contralateral motor cortex and in the supplementary

motor area. When subjects remain still and think about making complex movements, however, the blood flow to the SMA increases but not to the primary motor cortex. Watson et al. reported several patients with IMA from left-sided medial frontal lesions that included the supplementary motor area. These patients with SMA lesions, unlike patients with left inferior parietal lesions, could both comprehend pantomimes and discriminate between correctly and incorrectly performed pantomimes.

Convexity premotor cortex

While Liepmann did not believe that injury to the convexity premotor cortex induced IMA, Geschwind posited that when a person pantomimes to command, the information from Wernicke's area travels to the convexity premotor cortex via a white matter pathway that parallels but is superior to the arcuate fasiculus. Faglioni and Basso, however, mention that they had difficulty in finding well-documented cases in which patients suffered from apraxia because of injury to the convexity premotor region; Kolb and Milner, Barrett et al., and Haaland et al. did report patients with frontal premotor injury who appeared to have an apraxia.

In Haaland et al.'s study, the investigators used the lesion overlap method for localization of the premotor lesions that are associated with IMA and found that the middle frontal gyrus appeared to be the critical area. Freund and Hummelsheim studied patients with convexity premotor lesions and also found that these patients were apraxic but had limb-kinetic, rather than IMA.

Basal ganglia and thalamus

Although IMA is most commonly associated with cortical lesions, there have been reports that IMA can also be associated with subcortical lesions. Pramstaller and Marsden performed a meta-analysis of 82 cases of apraxia that were reported to be induced by subcortical lesions and concluded that lesions confined just to the basal ganglia (putamen, caudate nucleus and globus pallidus) rarely, if ever, cause apraxia.

In many of these studies reviewed by Pramstaller and Marsden, the subjects were tested with imitation and scored as correct versus incorrect, which may have limited the qualitative analysis of errors. To better elucidate the role of the basal ganglia in the production of learned skilled movements, Hanna-Pladdy et al. compared patients with cortical and subcortical strokes. Both groups made apraxic errors, but the patients with cortical lesion were more severe and had discrimination deficits. The subcortical group made more postural errors, but the patients with cortical lesions made more sequencing and content errors. These behavioral dissociations suggest that the subcortical structures make an independent contribution to the praxis processing system.

There have also been several case reports of patients who developed apraxia from lesions of the left thalamus in the region of the pulvinar nucleus. This nucleus is strongly connected with the inferior parietal lobes and this thalamic cortical network might be important for normal parietal lobe functions.

Dissociation Apraxia

Clinical

Patients with dissociation apraxia are unable to carry out a transitive act in response to stimuli in a certain modality, but are able to normally respond when the stimulus is presented in another modality. For example, Heilman described three patients who when asked to pantomime to verbal command, looked at their hand but failed to perform any recognizable actions. However, when shown the implement or tool, they had no trouble correctly performing the transitive pantomime. They also had no trouble while imitating the examiner or using actual tools and implements. As mentioned, patients with IMA have impairment even when they see the tool or object upon which this tool works as well as with imitation and use of objects. Subsequently, DeRenzi et al. reported patients similar to those reported by Heilman, but also patients who did not have a visual agnosia but who could not perform correctly when seeing a tool. However, they performed normally to verbal command. Other blindfolded patients had a similar modality-specific defect in the tactile modality.

Merians et al. described a patient with a left ventral temporal occipital lesion, who was impaired at imitation, but not pantomiming to command, suggesting another form of dissociation apraxia, which has also been called 'visuo-imitative apraxia' and 'conduction apraxia.' The patients described by Heilman and DeRenzi et al. demonstrated this modal-specific apraxia in both hands; Geschwind and Kaplan as well as Gazzaniga et al. described patients who could not perform normally to verbal command with their left hand but who could perform normally with their right hand. Unlike patients with callosal IMA described earlier, these patients could normally imitate and use actual objects with their left hand. Thus, these patients with callosal disconnection had a 'verbal callosal dissociation apraxia.'

Pathophysiology

We have suggested that the patients with verbal callosal dissociation apraxia have their brains organized differently than those patients who have an IMA of their left forelimb induced by injury to the corpus callosum. Whereas in the former patients (verbal callosal dissociation apraxia), their left hemisphere mediates speech-language, and their movement representations are stored

bilaterally. In contrast, the right-handed patients who have both language and movement formula represented in their left hemisphere may show a combination of verbal disassociation and IMA of their left forelimb as a result of a callosal lesion. Hence, when asked to pantomime with their left hands, they may look at them and perform no recognizable movement (disassociation apraxia), but when imitating or using actual tools and objects, they may demonstrate the spatial and temporal errors seen with IMA. The patients reported by Heilman and DeRenzi and associates who had dissociation apraxia of both hands probably had left hemisphere injury that induced either a hemispheric language-movement formula disconnection, a vision-movement formula disconnection, or somesthesic-movement formula disconnection. Thus, depending on the location of the lesion, stimuli from one of these modalities (e.g., speech-language) were not capable of activating the movement representations, but stimuli in other modalities (e.g., vision) were able to activate these representations. Unfortunately, the anatomic loci of the lesions that cause many of these intrahemispheric disassociation apraxias remain unknown.

Ideational Apraxia

Clinical

The term ideational apraxia has been used to label many different disorders. For example, it has been used for the syndrome we now call dissociation apraxia. It has been used for patients with what we now call conceptual apraxia and finally patients with IMA who are impaired when they use actual tools and implements. In this article, as proposed by Leipmann, this term will be used for the disorder, first described by Marcuse and Pick, in which patients have an inability to correctly sequence a series of acts, an ideational plan. Thus, the most important test for making the diagnosis of ideational apraxia is having the patient perform a task that requires several sequential motor acts (e.g., making a sandwich).

Pathophysiology

Most often, the patients with ideational apraxia have some form of degenerative dementia. This disorder, however, has not been systematically studied in the various forms of degenerative dementia. Liepmann thought that lesions in the left occipital parietal region induced this disorder, but support for this hypothesis is not strong.

Injury to the prefrontal regions, especially in the left hemisphere, is commonly associated with temporal and sequencing processing deficits, but as mentioned, the critical anatomic focus of dysfunction in ideational apraxia remains unknown.

Limb-Kinetic Apraxia (Melokinetic Apraxia, Innervatory Apraxia)

Clinical

In addition to understanding the nature of the problem that requires action, having the knowledge of the tool required to successfully perform this action as well as the knowledge of the postures, joint movements, speeds, and forces that are needed to perform the purposeful act, a person needs to have the ability to make precise, independent, coordinated movements (dexterity or deftness). A loss of this deftness has been called limb-kinetic apraxia by Liepmann.

There are many tests of deftness or dexterity, but we have found the coin rotation task, in which the patient is asked to rotate a nickel between their thumb, index, and middle fingers, as rapidly as possible for 20 revolutions, to be easy to perform and very sensitive. Typically, patients with hemispheric damage have a contralateral loss of deftness. However, Heilman, Meador and Loring, as well as Hanna-Pladdy and colleagues have found that people with right hand preference are more likely to have an additional ipsilateral loss of deftness (LKA) with left than right hemispheric injury.

Pathophysiology

Liepmann thought that the lesion that induces limb-kinetic apraxia includes the primary sensorimotor cortex. More recent support for this postulate comes from the work of Lawrence and Kuypers, who demonstrated a loss of precision grasp in monkeys with corticospinal tract lesions. However, several studies have suggested that portions of the convexity premotor cortex are also important for programing deft movements. Freund together with Hummelsheim as well as Fogassi and colleagues showed that damage to the premotor cortex is associated with LKA. Nirkko and coworkers provided converging evidence, using fMRI, demonstrating that discrete unilateral distal finger movements were associated with activation of the convexity premotor cortex.

As mentioned, left hemisphere injury in right-handed people can induce ipsilateral LKA and patients with right hemisphere dysfunction have LKA primarily limited to their left hand. These observations suggest that the left hemisphere might have stronger ipsilateral control of spinal motor neurons than does the right hemisphere. While physiological studies appear to support this postulate, it remains unclear whether this control is mediated by ipsilateral corticospinal pathways or via the corpus callosum.

Summary

This article describes the clinical characteristics that define the five forms of forelimb apraxia and also discusses

the possible neural mechanisms. Based on this information, we have proposed an anatomically distributed modular network that is responsible for mediating purposeful skilled movements. When a person determines that something needs to be altered, he/she must decide whether a tool is needed, and if so, what tool can best accomplish this goal. The person must also know what action that tool performs. When the correct tool is not available or a new tool is needed, the person also needs to know the mechanical advantage that tools afford and how this could be accomplished by alternatives. A loss of this knowledge is called conceptual apraxia. In right-handed people, this knowledge is stored in the left hemisphere, but the exact locations of these representations are unknown. After a person selects a tool, he/she has to have the knowledge of the posture needed to hold and use this tool as well as the egocentric movements that permit this tool to be properly moved through space and the allocentrically oriented movements that allows the tool to work on objects that require action. In this model, movement (temporo-spatial) representations are stored in the left parietal lobe, and degradation of these movement representations or damage to the premotor cortex that translates these spatial-temporal representations into motor programs induces IMA. These movement representations have to be activated by auditory (speech), visual, or kinesthetic systems input. If one of these input modalities cannot activate these movement representations, there is a modality-specific deficit in performing these learned skilled acts, and this disorder is called dissociation apraxia. The motor program formulated by the premotor cortex must be implemented by the motor cortex that activates the motor neurons in the spinal cord. Injury to the corticospinal system induces a loss of deftness, which is called limb-kinetic apraxia. Many goals require a series of independent acts that must be performed in a specific temporal sequence; an inability to correctly sequence a series of acts to achieve a goal is called ideational apraxia, which might be a sign of frontal-executive dysfunction.

See also: Corticobasal Degeneration; Dementia, Movement Disorders.

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Aromatic Amino Acid Decarboxylase Deficiency

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Glossary

Aromatic L-amino acid decarboxylase (AADC) – Enzyme that catalyzes the conversion of 5-hydroxy-tryptophan and levodopa into serotonin and dopamine, respectively.
Biogenic amines – Naturally occurring monoamines that act primarily as neurotransmitters. They include serotonin and catecholamines (dopamine, epinephrine, and norepinephrine).
Oculogyric crisis – Paroxysmal dystonia characterized by eye deviation associated or not with axial and limb dystonia. It is characteristic, thought not exclusive, of inherited disorders leading to dopamine deficiency.

Pediatric neurotransmitter diseases – Group of genetic disorders involving the metabolism of neurotransmitters.

Definition and History

Aromatic L-amino acid decarboxylase (AADC) deficiency is an autosomal recessive inborn error of metabolism that involves the biosynthesis of monoamine neurotransmitters. This disorder was first described in 1990 by Hyland et al. in two twin boys who presented early in life with motor, extrapyramidal, and autonomic symptoms; decreased monoamine metabolites in cerebrospinal fluid (CSF), and severely reduced AADC activity in plasma. Since then, ~75 patients have been diagnosed. In 1998, the first mutations in the AADC gene were reported and it became evident that the spectrum of mutations is heterogeneous.

Pathophysiology

Monoamine neurotransmitters include serotonin and the catecholamines dopamine, adrenaline, and noradrenaline. These compounds have multiple functions including modulation of psychomotor function, cardiovascular, respiratory and gastrointestinal control, sleep mechanisms, hormone secretion, body temperature, and pain.

AADC plays an important role in the synthesis of monoamines. It is a pyridoxal-phosphate-dependent enzyme that converts levodopa to dopamine and 5-hydroxytryptophan to serotonin. The catabolism of monoamines leads to the formation of 5-hydroxyindolacetic acid (5-HIAA) from serotonin, homovanillic acid (HVA) from dopamine, and 3-methoxy-4-hydroxyphenylethyleneglycol (MHPG) from norepinephrine (**Figure 1**).

Decreased activity of AADC leads to decreased production of the monoamine neurotransmitters and to the accumulation of their precursors 5-hydroxytryptophan and levodopa. It also leads to the accumulation of 3-*O*-methyldopa, which is the result of methylation of levodopa (**Figure 1**).

The clinical manifestations in AADC deficiency derive from the deficiency of monoamine neurotransmitters in the developing brain and in the peripheral nervous system. Reduced levels of dopamine are thought to be the origin of the motor symptoms. Norepinephrine and epinephrine deficiency are responsible for the manifestations of autonomic sympathetic dysfunction, while serotonin deficiency is associated with sleep disturbances. Yet, some manifestations cannot be attributed to one specific neurotransmitter deficit, such as cognitive and behavioral

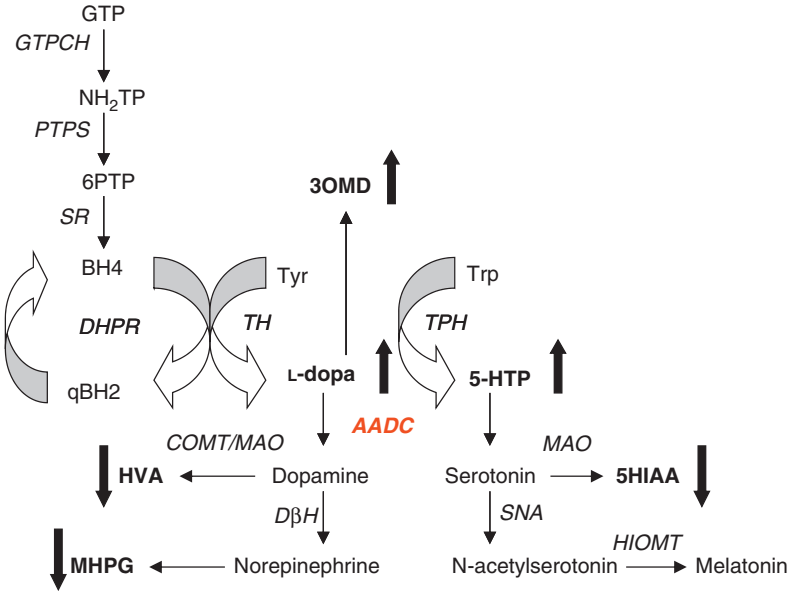

Figure 1 Central synthesis and catabolism of the catecholamines and serotonin. GTP: guanosine triphosphate; GTPCH: GTP cyclohydrolase; NH_2TP: dihydroneopterin triphosphate; PTPS: 6-pyruvoyltetrahydropterin synthase; 6PTP: 6-pyruvoyltetrahydropterin; SR: sepiapterin reductase; BH4: tetrahydrobiopterin; DHPR: dihydropteridine reductase; qBH2: quinonoid dihydrobiopterin; Tyr: tyrosine; Trp: tryptophan; 5-HTTP: 5-hydroxytryptophan; TH: tyrosine hydroxylase; TPH: tryptophan hydroxylase; COMT: catechol-O-methyltransferase; DβH: dopamine β-hydroxylase; AADC: aromatic L-amino acid decarboxylase; 3OMD: 3-O-methyldopa; 5HIAA: 5-hydroxyindoleacetic acid; MAO: monoamine oxidase; HVA: homovanillic acid; MHPG: 3-methoxy-4-hydroxyphenylglycol; SNA: serotonin n-acetyltransferase; HIOMT: hydroxyindole-O-methyltransferase. The large black arrows show an increase or decrease in the cerebrospinal fluid marker metabolites for AADC deficiency.

disturbances. Given the role of monoamines in hormonal function, evidence of endocrine dysfunction is also characteristic. Other factors implicated in the pathophysiology of this disorder are neurotransmitter imbalance and changes in receptor sensitivity.

Epidemiology

Currently, ~75 patients have been diagnosed with AADC deficiency. Over half of the total patients are in Asia. The largest single population is in Taiwan, with ~30 patients. A common splicing mutation has been identified in 81.3% of patients from Taiwan, and haplotype analyses have been consistent with a common ancestral origin. The calculated allele frequency for this mutation among the Taiwanese population is 1:508.

Clinical Features and Diagnostic Criteria

Clinical onset occurs within the first months of life, with more than half of patients presenting some symptoms during the neonatal period, including feeding difficulties, hypotonia, autonomic dysfunction, and/or hypoglycemia.

The majority of patients come to medical attention due to motor symptoms and paroxysmal events. The motor symptoms include axial hypotonia with fluctuating appendicular tone, decreased spontaneous movements with poor facial expression, and delayed motor development. The latter is so severe that patients fail to make any motor acquisition. Although tremor is not often seen in these infants, their striking hypokinesia and their fluctuating limb tone with rigidity, at times, are consistent with infantile parkinsonism.

The majority of patients develop paroxysmal dystonic events within the first months of life. These events are oculogyric crises. They are characterized by eye deviation upward, convergent, or to the side, that may occur on and off from minutes-to-hours. They may be associated with prolonged dystonic posturing of the limbs and/or the trunk. During these events patients are conscious but distressed. Seldom, some patients with AADC deficiency suffer from generalized tonic–clonic seizures.

Often, AADC-deficient patients show other types of movement disorders, especially dystonia, in particular limb, stimulus-induced and segmental cranial dystonia. They may also show prominent startle, myoclonus, and distal chorea. Less often patients develop choreoathetosis, nonepileptic flexor spasms or tremor.

Aggravation of neurologic symptoms late in the day and/or improvement by sleep is noted in many patients. Additionally, the occurrence of oculogyric crises is mainly in the afternoon or in the evening.

The majority of patients show some feature of autonomic dysfunction including ptosis and miosis, excessive diaphoresis, nasal congestion, temperature instability, and gastrointestinal dysmotility. Recurrent episodes of cardiorespiratory arrest with painful stimuli, hypersensitivity to exogenous cathecolamines and cardiac arrhythmias may also occur.

Sleep disturbances including increased sleeping time, frequent awakenings at night and insomnia are often noted. Also common are dysphoric mood with inconsolable cry, irritability, and moodiness. The majority of patients are nonverbal, though they are often able to interact with the environment. Cognitive testing in the more functional patients indicates mild-to-moderate mental retardation. Seldom, autistic syndrome and features of pervasive developmental disorders have been identified.

Although endocrine dysfunction is not documented very often, AADC-deficient patients can show recurrent episodes of hypoglycemia early in life, probably due to the lack of catecholamines as anti-insulinergic hormones. Delayed bone maturation and short stature reported in some patients is considered to be due to the lack of induction of growth hormone by catecholamines. Hyperprolactinemia due to dopamine deficiency is also documented.

Other features include failure to thrive, small hands and feet, hypersensitivity to light stimulation, tendency to breath-holding and apneic spells.

There have been occasional reports of patients with variable milder phenotypes. A few patients showed development of axial control by 2–3 years; while one showed independent gait by at 2½ years of age with remarkable fatigability.

Differential Diagnosis

The differential diagnosis of AADC deficiency includes neuromuscular disorders given their profound hypotonia and hypokinesia. The possibility of congenital myasthenia was raised in a mild case with ptosis, fatigability, and weakness of the cranial musculature.

Prolonged oculogyric crises associated with limb and/or axial dystonia may be misdiagnosed as seizures, while temperature instability during the neonatal period may be considered as an early sign of a serious infection. Hypoglycemia early in life may raise the diagnosis of an inborn error of intermediary metabolism, while prominent startle response may raise the diagnosis of hyperekplexia.

The clinical manifestations of other pediatric neurotransmitter disorders may be very similar. The pattern in CSF of monoamine metabolites and pterins, together with enzymatic and molecular analysis, points to the precise diagnosis.

A CSF pattern suggesting AADC deficiency has been detected in some patients with a severe infantile epileptic encephalopathy due to pyridoxamine 5′-phosphate oxidase deficiency. This disorder leads to decreased production of the biologically active form of pyridoxine; consequently the pyridoxine-dependent enzyme AADC is secondarily affected.

Diagnostic Work Up

The measurement of monoamine metabolites in peripheral fluids is generally uninformative, while their levels in CSF reflect the turnover of serotonin and catecholamine neurotransmitters within the brain. So, when there is clinical suspicion that a patient suffers from a pediatric neurotransmitter disease, a spinal tap is necessary. The diagnosis of AADC deficiency is based on the pattern of monoamine metabolites in CSF showing reduced levels of HVA, 5-HIAA, and MHPG; increased levels of the precursors levodopa and 5-hydroxytryptophan; and increased levels of 3-*O*-methyldopa (**Figure 1**).

Urine organic analysis searching for elevation of vanillactic acid, the result of 3-*O*-methyldopa transamination, may be used to further support the diagnosis. Amino acid analysis in blood is usually noninformative in AADC deficiency. However, if differential diagnosis with disorders of tetrabiopterin metabolism is raised, measurement of phenylalanine levels and analysis of tyrosine and phenylalanine levels after a load of phenylalanine may be of help.

Definite diagnosis with the analysis of AADC activity in plasma is done in a few laboratories, while molecular analysis of the AADC gene is more easily available in research and commercial laboratories. Analysis of AADC activity in plasma reveals residual activities ranging from undetectable to 8% of control values. When enzyme analysis is not available, diagnosis can be made with molecular analysis of the AADC gene. Screening of the gene has led to the identification of a number of mutations and the majority correspond to missense mutations. Patients are either homozygous for a given mutation or compound heterozygous. Recently, a common splice site mutation has been detected in a group of patients from Taiwan.

Neuroimaging studies are often normal, though in some cases they may show brain atrophy. F-18 Dopa positron emission tomography scan has shown virtually absent uptake of tracer. EEG studies are either normal or they show nonspecific findings. Epileptiform discharges have been reported in patients with epilepsy.

Treatment

The main goal in the management of AADC deficiency is to potentiate monoaminergic transmission. The main drugs used are dopamine agonists and monoamine oxidase (MAO) inhibitors, often administered in combination. Early patients were treated with the dopamine agonists bromocriptine and pergolide. Given the potential adverse effects associated with these medications (severe fibrotic reaction), more recently ropirinole and pramipexole have been used instead. MAO inhibitors include the nonselective inhibitors tranylcypromine and phenelzine and the MAO B inhibitor selegiline.

Treatment with levodopa is not given, since deficient AADC activity precludes monoamine production and administration of levodopa would promote further accumulation of the precursor. However, levodopa provided a favorable response in three siblings who had a mutation in the AADC gene that involved the enzyme-binding site for levodopa.

Because pyridoxine is a cofactor of AADC, patients are generally supplemented with pyridoxine. However, no significant clinical response is usually noted.

A number of other of therapeutic strategies have been used erratically in AADC-deficient patients, including anticholinergics, melatonin, buspirone, serotonin reuptake inhibitors, indirect cathecholaminomimetics, amine reuptake inhibitors, ergotamine and local sympathomimetics.

Some patients show elevated plasma homocysteine and low CSF 5-methyltetrahydrofolate levels due to reduced methylation capacity, since *S*-adenosylmethionine is the methyl donor for the methylation of levodopa to 3-*O*-methyldopa. For this reason, folate supplementation is given in some patients.

Finally, because of the risk of cardiac arrhythmia and abnormal responses to pressors in AADC-deficient patients, anesthesia procedures in these patients should be conducted with close cardiac and hemodynamic monitoring.

Prognosis

Treatment with dopamine agonists and/or MAO inhibitors offers variable degrees of improvement in tone and hypokinesia, reduces the frequency and duration of oculogyric crises and improves autonomic dysfunction. In general, response to the other therapeutic strategies has not been encouraging, because of poor clinical response or poor tolerance.

Many patients, despite the improvements noted above, are not able to make meaningful motor development; while a few are able to make significant developmental progress, become verbal, ambulant, and responsive to educational interventions.

Earlier series of AADC-deficient patients suggested better response to treatment and prognosis in males than in females, but this has not been supported with the description of further cases. It appears that patients with

milder presentations show better response to treatment; thus neurological status at the time of diagnosis is an important prognostic factor.

Early onset of treatment appears to be a favorable prognostic factor. However, numerous patients who started treatment early in life show poor motor progress. On the other hand, tolerance to treatment also has prognostic implications. Patients may show drug-induced dyskinesias such as chorea or dystonia; or they may develop prominent adverse effects. Generally these patients show a poorer clinical outcome and it is unclear whether they would have shown a favorable response if they had been able to tolerate higher doses of medication, or whether they represent a subtype of AADC deficiency with a worse clinical phenotype.

Monoamine metabolite concentration in CSF and residual AADC activity in plasma do not appear to correlate with prognosis. It is unknown if there is any correlation between specific mutations and the severity of the clinical manifestations.

Acknowledgments

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See also: 6-OH Dopamine Rat Model; Movement Disorders: Overview.

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Asterixis

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Glossary

Asterixis – An involuntary jerking movement typically considered to be a form of subcortical negative myoclonus and characterized by variable rhythmic EMG-silent periods without any detectible standard electroencephalographic (EEG) correlate.
Miniasterixis – A variant of asterixis with jerk rates of 6–12 Hz.
Myoclonus – Shock-like movements that can be generated at the spinal cord, brainstem, or cortex from a variety of causes including toxic-metabolic, drug effects and neurodegenerative diseases.
Negative myoclonus – A form of myoclonus involving lightning-like jerks due to rapid loss of postures.

Clinical Syndrome

Asterixis is derived from the Greek words 'a' meaning 'not' and 'stērixis' meaning 'fixed position,' and was used to describe the rhythmic motor phenomenon reported by Adams and Foley in 1949 for a bilateral flapping tremor of

3–5 Hz in the setting of hepatic encephalopathy. Although the frequency is known to be highly variable, it is best described as a momentary lapse of sustained posture. The movement is asynchronous and typically involves the wrist, metacarpophalangeal joints, hip joints, and feet. Asterixis can also involve muscles of the face and tongue. In its most dramatic presentation, asterixis of the lower extremities results in drop attacks and falls without loss of consciousness. Asterixis in the upper extremities can be elicited when the arms are held in extension with the wrists dorsiflexed like a 'stopping traffic' posture. A transient loss of extensor tone results in the flexion of the wrist and the fingers. It can be elicited in the lower extremities when the hip and the knees are flexed and slightly abducted. The loss of adductor tone in the legs results in an intermittent abduction of the lower extremities.

Over time, the phenomenon has been described in the setting of many metabolic encephalopathies, as a side effect of medications and as a result of structural lesions. A variant with faster rates of 6–12 Hz with postural lapse may be referred to as 'mini asterixis' by some people. The precise neuroanatomic details of asterixis remain unclear. Case studies and electrophysiologic studies have shed light on the role of the central and peripheral nervous systems in asterixis. It is classified as a type of negative myoclonus.

Negative myoclonus can be classified clinically or etiologically. It is divided into four clinical categories: asterixis, physiologic negative myoclonus, postural lapses, and epileptic negative myoclonus (ENM). Based on etiology, negative myoclonus is divided into three distinct entities: asterixis seen with metabolic derangements, unilateral asterixis noted with focal neurological lesions, and ENM.

Anatomy and Pathophysiology

Asterixis by itself provides poor neuroanatomic localization, and much of the information on the possible pathways involved in the generation of asterixis is ascertained from case reports. It can be associated with a variety of lesions in the neuraxis. As a general rule, discrete structural lesions produce unilateral asterixis, while metabolic or toxic causes generally result in bilateral asterixis. Lesions of the posterior fossa and subcortical and cortical structures have also been reported to produce this phenomenon, which is generally believed to be subcortical in origin.

Negative myoclonus can be localized to the subcortical areas, including the brainstem, pons, thalamus, and internal capsule. Cortical regions such as the parietal and medial frontal areas can also be involved, and the frontal circuitry likely includes the supplementary and premotor regions. It is believed that this circuitry receives input from the inhibitory motor suppression regions. In the brainstem, there is input into the circuit from the reticular activating system, which likely accounts for the altered mentation frequently seen with asterixis.

The underlying mechanism for asterixis is extrapolated from the neuropathologic effects of hepatic and renal dysfunction, as both conditions are frequently associated with asterixis. Fluid shifts cause swelling of Alzheimer type II astrocytes and metabolic derangements, leading to compromise in the blood–brain barrier, upregulation of peripheral benzodiazepine receptor, and the production of neurosteroids. The exact mechanism of how the metabolic derangements lead to asterixis and why this circuitry is particularly vulnerable are unclear.

Since its initial description in patients with hepatic encephalopathy, asterixis has been reported in numerous metabolic encephalopathies, including uremia, sepsis, cardiac, or pulmonary dysfunction, and electrolyte abnormalities. It has been reported in malabsorption syndromes such as Whipple's disease when electrolyte abnormalities or nutritional deficiencies occur. Asterixis has even been reported in the setting of bariatric surgery and Wernicke's encephalopathy due to nutritional deficiency. In addition, it has been reported in acute alcohol withdrawal. Asterixis can be present concomitantly with positive myoclonus in the setting of anoxic encephalopathy (Lance Adams Syndrome).

Medications and toxins can also produce asterixis. The most common are sedatives such as benzodiazepines and barbiturates, and anticonvulsants such as phenytoin, carbamazapine, valproic acid, and gabapentin. Phenytoin is the most prominently reported antiepileptic culprit. Asterixis due to phenytoin is referred to as 'phenytoin flap.' Phenytoin can unmask latent unilateral asterixis due to structural lesions. Lithium is associated with asterixis at both toxic and therapeutic plasma drug levels. Asterixis occurring in patients with Parkinson's disease, hallucinations, and high levodopa doses usually remits with lower levodopa. Ceftazidime, a third generation cephalosporin, has been associated with truncal asterixis in the setting of renal failure. Asterixis likely relates directly to ceftazidime, because a case history demonstrated that it remitted when the antibiotic was discontinued even though renal function continued to worsen. The penetration of ceftazidime into the central nervous system has been postulated to be responsible for asterixis in this setting.

Unilateral asterixis is generally due to focal lesions, most commonly of the thalamus. Other lesions involve the internal capsule, corona radiata, anterior cerebral artery territory, primary motor cortex, and parietal lobe lesions. In the posterior fossa, cerebellar and midbrain lesions are implicated in asterixis. A prominent case has been reported of a mesencephalic stroke producing bilateral asterixis.

Electrophysiology

Asterixis is typically considered a subcortical negative myoclonus and characterized by rhythmic EMG silent periods without any detectible standard electroencephalographic (EEG) correlate. Jerk-locked back-averaging techniques and measurement of silent period-locked back-averaging have been applied to studying asterixis, but these studies typically have not demonstrated any associated cortical phenomenon. Early components of cortical potentials, measured by standard somatosensory evoked potentials, also appear to be un-enhanced in asterixis. Coherence studies averaging the EEG and EMG signals in patients with asterixis have demonstrated the presence of giant sensory evoked potentials and C reflex in some situations, but overall, the evidence of cortical involvement is uncommon. Electrical stimulation of the internal capsule can produce negative myoclonus.

Treatment

In order to treat asterixis effectively, it is paramount to treat the underlying condition. For example, in situations where hepatorenal dysfunction appears to be the culprit, effective treatment of the dysfunction slowly leads to the resolution of the motor phenomenon called asterixis.

See also: Myoclonus.

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Ataxia

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Glossary

Anticipation – Increased symptom severity and earlier onset of symptoms in subsequent generations.
Dysdiadochokinesia – The breakdown or decomposition of coordination of different single-joint movement components when performing rapidly alternating or fine repetitive movements.
Dysmetria – Inaccuracy in judgment of distance of the trajectory of a body part during active movement, in range, direction, and speed. Hypermetria involves overshooting the target, and hypometria, undershooting the target.
Dyssynergia or asynergia – Often referred to as decomposition of movement, disruption of normal coordination and execution of a voluntary movement, particularly with multijoint movements.
Trinucleotide repeat disorders or polyglutamine disorders – Disorders due to CAG repeat expansions that encode the repeat of the amino acid glutamine in the disease protein; includes SCA1 2, 3, 6, 7, and 17, Huntington disease, spinobulbar muscular atrophy, and dentatorubropallidoluysian atrophy.

Definition and History

Historical Concepts

Early concepts of the cerebellum date back to Galen's time (130–200 CE). Galen proposed that the cerebellum was a valve that controlled the animal spirits flowing from spinal and cranial nerves, and was the site from which cranial nerves and the spinal cord originated. The English physician, Thomas Willis (1621–1675), discussed cerebellar control of involuntary movements as well as cardiac and respiratory functions. Subsequent animal experiments furthered our knowledge of cerebellar function

and pathology. For example, after partial removal of the median lobe of the cerebellum in a goat, Luigi Rolando (1773–1831) observed that the animal swayed and fell to one side or the other. Ablative lesions in the cerebellum in animals demonstrated irregular and clumsy movements, lack of muscular coordination, and changes in gait with functional recovery in some. In the nineteenth century, gait ataxia and tremors were observed in humans and discussed by Charcot and his students in France, Hammond in America, and Gowers in Britain. Much attention was focused on the distinction between cerebellar and sensory (proprioceptive) ataxia with the latter resulting from posterior column sclerosis as in tabes dorsalis. Patients with cerebellar ataxia were noted to have a staggering gait, jerky and irregular movements, but intact sensation and less postural sway with eyes closure than those patients with sensory ataxia. At the turn of the nineteenth century, the French neurologist, Babinski (1857–1932) introduced several terms that are still used today to characterize cerebellar abnormalities. He described asynergia, dysdiachokinesia, hypermetria, and deficits in acceleration and deceleration of movements. Holmes (1876–1965), an Irish neurologist, examined the effects of acute cerebellar injuries and wounds in World War I soldiers and observed hypotonia ipsilateral to the cerebellar lesion, rebound and loss of check. These clinical observations provide a basis for our neuroanatomical and phenomenological understanding of cerebellar disease and ataxia.

Cerebellar Neuroanatomy

This section briefly reviews cerebellar neuroanatomy as related to clinical findings. The cerebellum is located in the posterior fossa and consists of two large hemispheres and a midline structure, the vermis. The hemispheres are involved in motor planning and limb control, whereas the midline structures or vermis control motor execution, balance and gait, and ocular movements. The cerebellum consists of three main parts – the flocculonodular, anterior, and posterior lobes. In addition, the lobes are subdivided into lobules which carry several different names. Based on phylogenetic and embryological studies, the archicerebellum (oldest part) corresponds to the flocculonodular lobe, paleocerebellum consists of the anterior and posterior parts of the vermis except the nodulus, and the neocerebellum (newest part) corresponds to the hemispheres and the middle vermis.

Afferent projections from the vestibulocerebellum (originating from vestibular nerve and nuclei), spinocerebellum (originating from the dorsal and ventral spinocerebellar tracts), and pontocerebellum (originating from the contralateral hemisphere) correspond to the projections areas of the archicerebellum, paleocerebellum, and neocerebellum, respectively. Anatomic designation based on the efferent projections from the cerebellar cortex to the cerebellar nuclei divides the cerebellum into three longitudinal zones – medial (vermis) projecting to the fastigial nucleus, intermediate (paravermal) projecting to the interposed nuclei (globose and emboliform nuclei), and lateral (lateral hemisphere) zone projecting to the dentate nucleus. From the deep cerebellar nuclei, efferent fibers from the fastigial nucleus project to the vestibular nuclei and reticular formation via the inferior cerebellar peduncle, and are concerned with balance and ocular movements. From the interposed nuclei, efferent fibers project to the contralateral thalamus and red nucleus via the superior cerebellar peduncle and are involved in execution of movements and gait. Other efferent fibers travel from the dentate nuclei to the contralateral thalamus and then primary motor and frontal/prefrontal cortex as well as to the contralateral red nucleus and then spinal cord via the superior cerebellar peduncle and are involved in motor planning and limb coordination. Furthermore, the cerebellar cortex is somatotopically organized with two inverted homunculi (leg representation anteriorly in the anterior lobe and posteriorly in the posterior lobe).

The output neuron of the cerebellum, the Purkinje cell, is inhibitory to cerebellar nuclear neurons and uses γ-aminobutyric acid (GABA) as its neurotransmitter, whereas Purkinje cells receive indirect input from many excitatory granule cells via their input from mossy fibers, excitatory climbing fibers (mainly from the inferior olive) connect directly with Purkinje cells. Neurotransmitters in the cerebellum primarily include GABA, glutamate, norepinephrine, serotonin, histamine, and acetylcholine. Disruption of the cerebellar blood supply (posterior inferior cerebellar artery, anterior inferior cerebellar artery, and superior cerebellar artery) leads to distinct neurological deficits and stroke syndromes.

Clinical Definitions

The cerebellum functions primarily to modulate and coordinate movements. Cerebellar disease is often characterized by limb and gait ataxia, clumsy and irregular movements, and decreased coordination and balance. Ataxia means literally, without order from the Greek, *taxi* (order). Abnormalities in the cerebellum lead to interruptions in speed, direction, timing, amplitude, and target accuracy of movements. These disturbances reflect difficulties in initiating and terminating movements, gauging target distances and timing, changing directions, and maintaining postural reflexes.

Clinically, limb or appendicular ataxia is exemplified by dysdiadochokinesis, dysmetria, or dyssynergia (see Glossary entries and Clinical examination section). Movements may appear slowed due to either the underlying cerebellar disorder or attempts by the patient to improve accuracy of movement by slowing his movements. Tone may be reduced, and reflexes may be pendular.

Kinetic or intention tremor is also a feature of cerebellar limb dysfunction, in contrast to the rest tremor of parkinsonism. Titubation and poor truncal control when seated or standing demonstrate axial involvement. Ataxic gait is characterized by a wide-based stance, irregular stride, unsteadiness when walking or turning, and difficulty performing tandem gait.

Cerebellar disease also can affect extraocular movements, speech, and cognition. Abnormalities in eye movements include nystagmus (gaze-evoked, rebound, and sometimes down-beating), square-wave jerks, abnormal saccades (hypo- or hypermetric saccades), jerky or saccadic smooth pursuit, ocular flutter, and opsoclonus. Speech disorders in cerebellar disease often have a 'scanning' quality and are described as dysarthric, hesitant, or slow. Many speech abnormalities have been described including deficits in articulation, phonation, respiration, timing, pitch, volume, and prosody. With bulbar musculature involvement, differences in labial, lingual, and palatal sounds may be seen. Patients with cerebellar disease have been shown to have deficits in motor learning, perception, and cognitive function. In some, systemic and other neurologic signs and symptoms are present and may include gastrointestinal problems, autonomic dysfunction, dizziness, spasticity, neuropathy, dystonia, and parkinsonism.

Pathogenesis/Pathophysiology

The pathogenesis of the ataxias is not surprisingly broad due to the many different types of ataxias recognized under the umbrella term of 'ataxia.' Much of our current understanding about the ataxias is rooted in genetics. As a result, the ataxias have often been classified as congenital, hereditary (autosomal dominant (AD), autosomal recessive (AR), X-linked, mitochondrial), or sporadic. Over the past two decades, researchers have identified specific gene mutations in many of the ataxias which provide insights into the pathogenesis of some of the hereditary ataxias. With increased understanding of the molecular basis of some of the ataxias, organization schemes that focus on disease mechanisms have been proposed, thereby classifying the ataxias as disorders of trinucleotide repeat or polyglutamine expansions, 'gain' or 'loss' of function, channelopathies, defective DNA repair, mitochondrial dysfunction, and metabolic abnormalities. This section will highlight several mechanisms of the ataxias; many of these ataxia disorders are discussed in further detail in separate entries in the encyclopedia.

Abnormal Protein Folding and Degradation: Trinucleotide or Polyglutamine Expansion Disorders

Several autosomal dominant spinocerebellar ataxias (SCAs) are caused by trinucleotide or polyglutamine expansions (CAG repeat expansions that encode the repeat of the amino acid glutamine in the disease protein), particularly in coding regions. The family of polyglutamine repeat disorders includes SCA1, 2, 3, 6, 7, and 17 as well as Huntington disease, spinobulbar muscular atrophy, and dentatorubropallidoluysian atrophy (DRPLA). Clinically, these SCAs share features such as anticipation and an inverse correlation of CAG repeat length to onset age. There may be an earlier age of onset with paternal transmission. These disorders also are thought to share a common toxic gain-of-function mechanism leading to the aggregation and deposition of misfolded proteins and subsequently, neuronal dysfunction and cell death. The polyglutamine aggregates form nuclear or cytoplasmic inclusions that may contain ubiquitin, HSP70, or transcription factors. Although these aggregates constitute neuropathological hallmarks of those SCAs due to repeat expansions, it is not known whether the toxicity results directly from the aggregate or is a byproduct of other ongoing processes.

There are other abnormal repeat expansions in SCA 12, 8, and 10. SCA12 is also caused by a CAG repeat expansion, similar to SCA1, 2, 3, 6, 7, and 17; however, the CAG repeat is located in the untranslated region of the *PPP2R2B* gene on chromosome 5, encoding a brain-specific regulatory subunit of the protein phosphatase PP2A. Since the polyglutamine expansion lies outside of the open reading frame, pathogenesis seems less likely to relate to a toxic gain of function. SCA8 is caused by a CTG repeat expansion in the 3′ untranslated region on chromosome 13. In contrast, SCA8 expansions vary greatly between generations, and correlations between repeat length and disease severity are less. Furthermore, the CTG repeat occurs as part of the natural antisense RNA of the Kelch-like 1 gene which may act in the formation or maintenance of Purkinje cell dendritic function. SCA10 is caused by an unstable ATTCT pentanucleotide repeat expansion in *E46L*, a novel gene of unknown function.

Channelopathies

Several ataxias, such as SCA6 and the episodic ataxias (EAs), are due to mutations in genes involved in calcium or potassium channel function. For example, SCA6 is caused by a CAG repeat expansion on chromosome 19p13 in the *CACNA1A* gene. The *CACNA1A* gene encodes the P/Q type voltage-gated calcium channel complex which is abundantly expressed in the cerebellum and also presynaptic neuromuscular junction. Proposed pathogenetic mechanisms include a toxic 'gain of function' or increased calcium entry into cerebellar cells. Mutations in the *CACNA1A* gene on chromosome 19 are allelic with EA type 2 (EA2) and familial hemiplegic migraine (FHM). EA-2 is caused by a point mutation in the calcium channel

gene *CACNA1A* on chromosome 19p13. Most mutations in EA2 involve point mutations causing truncated proteins, but missense mutations have been reported. In addition, a missense mutation in *CACNB4*, the calcium channel β4 subunit gene, has been identified in a family with EA-2. Episodic ataxia-1, EA-1, is caused by a missense mutation in the potassium channel gene *KCNA1* on chromosome 12p13. This was not only the first known ion channel mutation in the brain but also the first report of a mutation in the human potassium channel gene. The KCNA1 protein is widely expressed in the cerebellum and nodal regions in peripheral nerves. Several different missense mutations in *KCNA1* have been identified. Mutations may alter potassium channel function by reducing channel expression or affecting channel gating.

Mitochondrial Dysfunction

Friedreich's ataxia (FRDA) is often considered a prototype for an ataxia due to abnormal mitochondria oxidative metabolism. FRDA, the most common AR ataxia, is caused by a GAA repeat expansion in the intron of the *frataxin* gene on chromosome 9q13. This expansion accounts for about 96% of patients with FRDA; the remainder (4–5%) is heterozygous and has a point mutation in the *frataxin* gene. Larger repeat expansions are associated with earlier onset of disease and more severe phenotype. However, expansions >50 repeats form sticky DNA and may be pathological. Expanded GAA repeats suppress *frataxin* gene expression. Since the frataxin yeast homologue plays a role in iron, it has been proposed that decreased frataxin leads to abnormal iron accumulation in the mitochondria, increased reactive oxygen species, and disruption in mitochondrial function. Knockout models and yeast experiments suggest that frataxin is involved in iron–sulfur cluster assembly and that the impaired iron–sulfur cluster assembly may precede the iron accumulation in FRDA. Abnormal mitochondrial function forms the basis for therapeutic studies with idebenone and other free-radical scavengers.

Defective DNA Repair

Several recessive ataxias such as ataxia-telangiectasia (AT), xeroderma pigmentosum (XP), Cockayne syndrome, and ataxia with oculomotor apraxia types 1 and 2 (AOA1, AOA2) are thought to relate to defective DNA repair. In AT, truncating mutations occur in the ataxia telangiectasia mutated (*ATM*) gene. The ATM protein carries a region similar to the lipid kinase phosphatidylinositol-3 kinase (PI-3K), a signal transduction mediator, and another region similar to yeast proteins involved in DNA repair. Thus, although exact mechanisms of the *ATM* mutation have not been elucidated, ATM may have a role in DNA damage detection, cell checkpoint control, and intracellular growth factor signaling.

Both XP and Cockayne syndrome involve multiple mutations with defective DNA repair or reduced RNA synthesis after ultraviolet damage. AOA1 is caused by missense and truncating mutations in the *aprataxin* (*APTX*) gene. The *APTX* gene is a member of the histidine family and may affect DNA repair by interacting with repair proteins and affecting cellular response to stress. AOA2, which is due to mutations in the *SETX* gene, which codes for senataxin, a protein with RNA and DNA helicase activities.

Epidemiology/Risk Factors

Since the etiologies of ataxia are heterogeneous, many epidemiological studies focus on specific types of ataxia in the population (e.g., SCA types, FRDA, multiple system atrophy (MSA)). However, with genetic testing, the ability to diagnose patients and recognition of broader clinical phenotypes has increased; therefore, published frequencies may represent conservative estimates. This section will highlight the prevalence rates and geographic distributions for several different types of ataxia.

Prevalence rates reported for the AD SCAs range from 0.9 to 3 per 100 000. Of the SCAs, SCA2, SCA3, and SCA6 appear to be the most common. Differences in geographic region and ethnic origin occur. For example, SCA3 is one of the most common SCAs, ranging from about 20% in the US to 50% in German, Japanese, and Chinese series. SCA2 has been described in Cuban and Indian kindreds. SCA3 is frequently associated with descendants from the Azorean islands or Portuguese missionaries in Asia, from whom the disease was initially identified. SCA10 has been reported in Mexican and Brazilian kindreds, with the combination of ataxia and epilepsy described only in the Mexican families.

FRDA, an AR ataxia, is found predominantly in Caucasian populations (rare in non-Caucasian), with an incidence of 1 in 30–50 000. FRDA accounts for about 50% of the hereditary ataxias and 75% of those before age 25. AT is the second most common recessive ataxia with an incidence of 1 in 80–100 000 live births.

Regarding the sporadic ataxias, the prevalence of MSA has been reported to be 1.9–4.9 cases per 100 000 population in the US, with lower estimates from United Kingdom and France population studies. Diagnostic distinctions between MSA and idiopathic Parkinson's disease, pure autonomic failure or other atypical parkinsonian disorders, however, may be difficult, and these rates may not provide true estimates. About 29–33% of patients with isolated late-onset cerebellar ataxia are thought to develop MSA. Some studies have reported high prevalences of antigliadin antibodies in patients with sporadic and hereditary cerebellar

ataxia, thereby challenging our understanding of gluten ataxia as a distinct disorder. For example, the prevalence of antigliadin antibodies in hereditary ataxias was 14%, sporadic idiopathic ataxia 41%, MSA-C 15%, and normal controls 12% in one study, and in another, prevalent in 37% in AD ataxias and 27% in sporadic ataxias.

Clinical Features and Diagnostic Criteria

AD Ataxias

The autosomal dominant cerebellar ataxias (ADCA) were initially classified according to phenotype and accompanying signs by Harding. ADCA I consisted of cerebellar ataxia along with variable pyramidal, extrapyramidal, and neuropathic signs. ADCA II presented with cerebellar ataxia and retinal degeneration, and ADCA III manifested as a pure cerebellar ataxia (**Table 1**). Genetic advances have led to modification of these criteria as specific genes, and mutations responsible for cerebellar ataxias have been discovered and phenotypic heterogeneity has been observed. This section describes the clinical features of AD ataxias: selected SCAs, dentatorubral-pallidoluysian atrophy (DRPLA), and selected EAs.

Spinocerebellar Ataxias (SCAs)

SCA1

SCA1 is characterized by cerebellar ataxia (gait ataxia, dysarthria, slow saccades, and nystagmus), corticospinal tract signs, and neuropathy, as well as later ophthalmoplegia and bulbar dysfunction (dysphagia, tongue fasciculations). Extrapyramidal signs may be seen, but cognitive deficits are not typically present. The age of onset varies from adolescence to late adulthood with the average age of onset around third to fourth decades. Clinically, nerve conduction studies may reveal sensory axonal neuropathy, and brain magnetic resonance imaging (MRI) reveals atrophy involving the cerebellum, brainstem, and cervical spinal cord. Pathology reveals marked cerebellar atrophy with loss of Purkinje cells in cerebellar cortex and vermis in particular, atrophy of the pons and inferior olives as well as spinal cord spinocerebellar tracts and posterior columns. In addition, neuronal loss in cranial nerves III, X, and XII is seen, and ubiquitin-positive nuclear inclusions can be seen.

Table 1 Classification of autosomal dominant cerebellar ataxias (ADCA), modified from Harding

Type	*Clinical phenotype*	*Common genotypes*
ADCA I	Cerebellar ataxia plus other symptoms: extrapyramidal symptoms, neuropathy	SCA 1, 2, 3, 4, 12, 17, 21, 23, 25, 27, 28
ADCA II	Cerebellar ataxia plus retinal degeneration	SCA 7
ADCA III	Cerebellar ataxia – pure	SCA 5, 6, 8, 10, 11, 14, 15, 16, 22, 26, 30

SCA2

SCA2 clinically appears similar to SCA1, as it was described in a large Cuban kindred that phenotypically resembled SCA1 but lacked the same genetic mutation. However, SCA2 is distinguished by prominent slow saccades. Other clinical symptoms in its wide phenotype include ataxia, dysarthria, neuropathy, initial hyperreflexia followed by hyporeflexia, cerebellar tremor, and ophthalmoplegia. Parkinsonism, with levodopa response in some, has been reported in the literature. In other cases, myoclonus, chorea, corticospinal tract signs, and executive dysfunction have been reported. The age of onset is typically in the third or fourth decade. Sensory axonal neuropathy is present in nerve conduction studies, and neuroimaging reveals more severe cerebellar and brainstem atrophy than in SCA1 and SCA3. Neuropathology includes loss of Purkinje cells and other cerebellar neurons, neuronal loss in the brainstem including inferior olives, degeneration in the substantia nigra, and loss of spinal cord neurons in spinocerebellar tracts, posterior columns, and anterior horn cells though neuronal inclusions are not seen. Clinically, there is no curative treatment, but parkinsonian features may respond to levodopa. Median survival after disease onset is about 25 years.

SCA3/Machado–Joseph disease

SCA3 and Machado–Joseph disease MJD are now known to be synonymous, sharing a genetic mutation on chromosome 14q24.3–q32. Historically, reports in the 1970s described several Azorean kindreds in the United States with dominantly inherited but clinically variable neurodegenerative conditions. Three distinct phenotypes were reported in these kindreds: Type I – early onset (<30 years), rapid progression, symptoms of spasticity, rigidity, myokymia, facial-lingual fasciculations, dystonia; Type II – intermediate onset age (age 30s), ataxia, spasticity, and extrapyramidal features; Type III – later onset (age 40–60s), ataxia, neuropathy, and variable amyotrophy. Another type, Type IV, has been described with older onset, predominantly parkinsonian phenotype with possible levodopa response, and neuropathy.

SCA3/MJD has a broad phenotype with ataxia, neuropathy, parkinsonism, dystonia, spasticity, rigidity, ophthalmoplegia, bulging eyes, facial-lingual fasciculations, amyotrophy, and sleep disturbances, such as restless legs syndrome. Dementia is not typically seen. The average age of onset is in the third to fourth decades but ranges from childhood to 70s. Death usually occurs within 20–25 years after disease onset due to complications of immobility and respiratory dysfunction. Studies reveal axonal neuropathy

on nerve conduction studies and cerebellar and brainstem atrophy on neuroimaging. Marked dilatation of the fourth ventricle may be seen, and atrophy of the frontal and temporal lobes, as well as globus pallidus may be evident. Neuropathology reveals degeneration of the cerebellar tracts, spinocerebellar tracts, substantia nigra, and motor cranial nuclei with sparing of the cerebellar cortex and inferior olives in contrast to other SCAs. Neuronal inclusions, staining for ubiquitin, are widespread in the pons but also present in substantia nigra and brainstem.

SCA4

SCA4 is a rare spinocerebellar ataxia that manifests clinically as cerebellar ataxia, sensory axonal neuropathy, and pyramidal tract signs. Symptoms begin in the fourth to fifth decade with gait ataxia, followed by impaired fine motor function, dysarthria, hypo- or areflexia, and neuropathy (particularly vibratory and joint position sense loss). Limb weakness and extensor plantar responses may be present. Although known previously as Biemond ataxia (initially reported in 1954), genetic linkage to chromosome 16q22.1 was discovered in a large Scandinavian family in Utah with similar symptoms. More recently, a pure cerebellar ataxia syndrome in six Japanese families linked to the SCA 4 gene locus was described and may represent a phenotypic variation of the same disease.

SCA5

SCA5 is largely a pure cerebellar syndrome, consistent with phenotypic ADCA III classification. Onset ranges from 10 to 68 years of age, but typically occurs in the third or fourth decade with symptoms of gait and limb ataxia and dysarthria. Extrapyramidal, corticospinal, and cognitive dysfunction are not seen. One-third of patients report mild sensory deficits. Its course is relatively slowly progressive and mild with normal life span in adult cases. However, in childhood onset, bulbar atrophy and corticospinal tract abnormalities may lead to a more rapid course. Neuroimaging reveals marked cerebellar cortical atrophy but without involvement of the brainstem, basal ganglia, or cerebral hemispheres. Pathological studies are limited but show predominantly cortical cerebellar degeneration.

SCA6

SCA6 has been considered to be a relatively pure cerebellar ataxia with a slowly progressive course, although extracerebellar features may occur. Clinical manifestations include gait and limb ataxia, dysarthria, downbeat or gaze-evoked nystagmus, and oculomotor findings. Unlike SCA1, 2, and 3, saccade velocity is normal. Saccades are dysmetric and smooth pursuit, optokinetic responses, and vestibular suppression, impaired. Later in the course, dysphagia, mild sensory neuropathy, corticospinal tract signs, and occasional parkinsonism or dystonia can occur. The age of onset is typically in the fourth or fifth decade, with slow progression. Brain MRI typically reveals midline cerebellar atrophy. Neuropathology demonstrates cerebellar degeneration with predominant loss of Purkinje cells and presence of cytoplasmic and nuclear polyglutamine aggregates. Based on improvement in EA2, acetazolamide, a carbonic anhydrase inhibitor, has provided modest symptomatic improvement in SCA6.

SCA7

SCA7, classified as ADCA II, is a progressive ataxia distinguished by retinal degeneration. The earliest sign of retinal dysfunction may be blue–yellow dyschromatoptia, followed by central vision loss (predominant macular involvement), and progression to bilateral vision loss and blindness. Other symptoms include cerebellar ataxia, dysarthria, corticospinal tract signs, hyporeflexia, decreased vibration, dysphagia, sphincter dysfunction, and ophthalmoplegia and slow saccades. The age of onset is typically in the third or fourth decade (range from infancy to over age 70). Anticipation and inverse correlation with repeat length and age of onset occur. Early-onset patients may present with visual symptoms preceding or coinciding with ataxia onset. Juvenile cases, marked by larger repeat sizes (>200) due to paternal transmission, may have cardiac involvement and seizures in addition to retinal dysfunction. Clinical tests reveal dyschromatoptia and abnormal fundoscopy with mottling of macula pigment and loss of foveal reflex. Nerve conduction studies may show subclinical sensory neuropathy. Brain MRI demonstrates marked cerebellar atrophy, especially in the superior vermis and brainstem, and moderate cortical atrophy. Neuropathology of the retina reveals degeneration of photoreceptors, bipolar and granule cells in foveal and parafoveal areas, and patchy loss of retinal epithelial cells. Brain pathology includes marked degeneration in the cerebellum (vermis greater than hemispheres) and inferior olives as well as pons, basal ganglia, and spinal cord.

SCA8

Clinically, SCA8 presents as a slowly progressive limb and gait ataxia with dysarthria and abnormal eye movements (impaired smooth pursuit and nystagmus). Neuropathy (reduced vibratory sensation), tremor, spastic dysarthria, and upper motor neuron findings, such as spasticity and hyperreflexia may occur. The age of onset is from infancy to over 60 (mean onset in the fifth and sixth decades). Neuroimaging typically reveals marked cerebellar vermian and hemispheric atrophy with relative sparing of the brainstem. Neuropathological reports are not available to date.

SCA10

SCA10 ataxia has been reported in Mexican and Brazilian families; only the Mexican families, to date, have had epilepsy. Symptoms include limb and truncal ataxia, dysarthria,

dysphagia, abnormal eye movements (saccadic pursuit, ocular dysmetria). About 20–60% have recurrent seizures, mostly generalized motor but also complex partial seizures. Other features have included mild cognitive dysfunction, mild sensory neuropathy, and hepatic dysfunction. The age of onset ranges from 14 to 45 years. Neuroimaging reveals generalized cerebellar atrophy and EEGs, cortical dysfunction, or epileptiform discharges. Neuropathological findings are unknown presently. Although there is no known treatment for the ataxia, seizures can be managed with antiepileptic medications.

SCA11

SCA11 is a relatively mild, cerebellar ataxia mapped to chromosome 15q14. Symptoms include limb and gait ataxia, dysarthria, saccadic pursuit, nystagmus, and hyperreflexia. The mean age of onset in the one British family with linkage to chromosome 15q is 25 years. Life expectancy appears normal.

SCA12

Clinical manifestations of SCA12 include cerebellar ataxia and action tremor. Other features include dysarthria, nystagmus, hyperreflexia, axial dystonia, bradykinesia, neuropathy, psychiatric symptoms, and dementia (in cases with older age onset). The age of onset ranges from 8 to 55 years, typically in the fourth decade. Families described are German-American or Indian. Neuroimaging demonstrates generalized cortical and cerebellar atrophy. Possible treatments address specific symptoms, such as tremor, parkinsonism, and psychiatric features.

SCA13

SCA13 has been reported in French families with cerebellar ataxia and mild mental retardation. Other features include dysarthria, nystagmus, hyperreflexia, urinary urgency (2 cases), and absence seizures (1 case). The age of onset is usually in early childhood but ranges from infancy to 40s. Neuroimaging in two cases revealed cerebellar and pontine atrophy.

SCA14

Clinical presentations of SCA14 as described in Japanese and English-Dutch families and one sporadic case include cerebellar ataxia, nystagmus, dysarthria, possible hyperreflexia, and axial myoclonus especially in earlier onset cases. The age of onset ranges from 10 to 59 years, mean fourth and fifth decades. Brain MRI reveals atrophy in the cerebellum vermis and hemispheres. Neuropathology demonstrates reduced staining for protein kinase C, gamma and ataxin-1 in Purkinje cells.

SCA15

SCA15 has been described in an Australian family with a slowly progressive, pure cerebellar ataxia. Patients are ataxic but remain ambulatory. The age of onset ranges from 10 to 50 years, mean 25 years. Brain MRI reveals superior vermis atrophy and nerve conduction studies are normal.

SCA16

SCA16 has been reported in a Japanese family as predominantly a slowly progressive, pure cerebellar syndrome accompanied by constant gaze-evoked nystagmus, dysarthria, and head tremor in some. The age of onset ranges from 20 to 66 years, mean 40 years. Anticipation was not seen in the Japanese kindred. Brain MRI reveals cerebellar atrophy and sparing of the brainstem.

SCA17

SCA17 is characterized by cerebellar gait ataxia and dementia with development of limb ataxia, bradykinesia, and hyperreflexia over several decades. Eye movements are normal. The age of onset ranges from 19 to 48 years, mean 33 years. SCA17 has been described in Japanese, German, and Italian families. Others have reported similarities to Huntington's disease due to the presence of dementia, psychiatric features, and chorea. Brain MRI reveals marked cerebellar atrophy and mild cortical atrophy. Neuropathology reveals moderate cerebellar degeneration, neuronal intranuclear inclusions, and mild-to-moderate changes in the basal ganglia and cortical regions.

SCA18

SCA18 has been designated sensorimotor neuropathy with ataxia (SMNA) and may not truly represent spinocerebellar ataxia. Features of dysmetria, hyporeflexia, muscle weakness, muscle atrophy, neuropathy with decreased vibration and proprioception, and pes cavus in some were described in a five generation American-Irish kindred. The age of onset was from 13 to 27 years. Progression was slow with normal lifespan and wheelchair use in later years. Brain MRI revealed cerebellar atrophy, electrodiagnostic studies showed sensory axonal neuropathy and denervation, and muscle biopsy revealed neurogenic atrophy.

SCA19

SCA19 has been described in a Dutch kindred with symptoms of mild ataxia, postural tremor, myoclonus, cognitive impairment, variable reflexes, and neuropathy. The age of onset was between 20 and 45 years. SCA19 has been mapped to chromosome 1p21–q21. Since another form of FHM links to this locus, possible disease mechanisms may relate to mutations in ion channels. Brain MRI reveals marked atrophy of cerebellar hemispheres and mild atrophy of the vermis and cerebral cortex.

SCA20

SCA20 has been reported in an Anglo-Celtic family with relatively pure, AD spinocerebellar ataxia. Symptoms

include dysarthria, gait and limb ataxia, hypermetric saccades, mild nystagmus, mild corticospinal tract signs, palatal myoclonus, and had slow progression. The age of onset ranges from 19 to 64 years, mean 45 years. Head CT scans have revealed prominent dentate calcifications in all nine patients imaged.

SCA21

SCA21 has been reported in a French family with slowly progressive gait and limb ataxia, as well as variable parkinsonian signs, hyporeflexia, and cognitive impairment. The age of onset ranges from 6 to 30 years, mean 17 years. Brain MRI reveals cerebellar atrophy without brainstem involvement. More study is likely needed to define and assess parkinsonian features of SCA21 and responses to dopaminergic agents.

SCA22

SCA22 represents a pure AD cerebellar ataxia described in a Chinese Han family. Hyporeflexia was also present and course was slowly progressive. The age of onset ranges from 10 to 46 years. Brain MRI reveals cerebellar atrophy.

SCA23

SCA23 has been described in a Dutch family with a slowly progressive gait and limb ataxia accompanied by abnormal eye movements (slow saccades, ocular dysmetria), neuropathy, and corticospinal tract signs (hyperreflexia, extensor plantar responses). The age of onset was later, ranging from 43 to 56 years. Brain MRI revealed cerebellar atrophy, and pathology demonstrated cerebellar, brainstem, and spinal cord atrophy with cell loss in Purkinje cells, dentate nuclei, and inferior olives.

SCA25

SCA25 involves cerebellar ataxia along with variable nystagmus, hyporeflexia, neuropathy, urinary urgency, and gastrointestinal symptoms. SCA25 has been described in a large Southeastern French family. The age of onset was from 17 months to 39 years. Brain MRI reveals cerebellar atrophy and nerve conduction studies, absent sensory nerve action potentials.

Dentatorubral-pallidoluysian atrophy (DRPLA)

DRPLA is an AD ataxia with phenotypic similarities to progressive myoclonic epilepsy, spinocerebellar ataxia, and Huntington's disease, depending on the age of onset. Ataxia and dementia are present regardless of the age of onset. Inverse correlation between the age of onset and CAG repeat length and anticipation, particularly with paternal transmission, occur. The age of onset is variable, ranging from childhood to late adulthood but on average, age 30. Patients with symptom onset less than age 20 share a phenotype with progressive myoclonic epilepsy with additional seizures and myoclonus. Those patients with symptom onset after age 20 are more likely to resemble either SCAs or Huntington's disease due to chorea and neuropsychiatric symptoms.

DRPLA is relatively common in Japan with a prevalence rate of 0.2–0.7 per 100 000 and is present in the United States as a variant, Haw River syndrome that has been reported in African-American kindreds in North Carolina. DRPLA is caused by a trinucleotide CAG repeat mapped to chromosome 12p, encoding atrophin-1; abnormal alleles range from 49 to 88 repeats, whereas normal alleles typically have less than 30 repeats. Neuropathological examination reveals degeneration in the dentate, red nucleus, subthalamus, and globus pallidus and accumulation of atrophin-1 in neuronal nuclei. Useful laboratory studies include brain MRI, EEG, and genetic testing. Epilepsy requires anticonvulsant treatment, but other therapies are only for symptomatic effects.

Episodic ataxias

The EAs are a group of AD ataxias with intermittent symptoms and different genetic mutations. To date, seven EAs have been described (EA1–EA7), with mutations identified in four genes.

In EA-1, patients have sudden episodes of dysarthria and truncal and gait ataxia with normal eye movements. Episodes are brief, lasting from seconds to a few minutes, and often triggered by startle, emotional factors, or exercise. Preceding auras with weakness, dizziness, and blurred vision may occur. Interictal examination is normal except for myokymia, particularly in periorbital areas and fingers, and seen either clinically or by electromyography (EMG) only. The age of onset ranges from 3 to 20 years. Episodes decrease with age and may remit in teenage years. Families with EA-1 may have different types of epilepsy. Episodes may respond to acetazolamide.

In contrast, EA-2 is characterized by longer episodes of ataxia lasting for hours. Symptoms include ataxia, vertigo, nausea, emesis, and headaches, and examinations reveal cerebellar ataxia, dysarthria, and nystagmus. Episodes can be triggered by stress, exercise, alcohol, and caffeine. Interictal examination may show gaze-evoked nystagmus, downbeat nystagmus, and mild truncal ataxia. The age of onset is similar to EA-1, ranging from 3 to 30 years. Brain MRI often reveals cerebellar atrophy, particularly midline. Acetazolamide may decrease the severity and frequency of episodes by stabilizing the ion channel.

AR Ataxias

Although there are numerous AR ataxias described in the literature, this section will focus on a few selected ataxias. The AR ataxias can be divided into three primary phenotypes: (1) a Friedreich ataxia (FRDA)-like phenotype without cerebellar atrophy (e.g., FRDA, ataxia

with vitamin E deficiency, abetalipoproteinemia, and Refsum's disease), (2) a FRDA-like phenotype with cerebellar atrophy and possibly other neurological findings (e.g., cerebrotendinous xanthomatosis (CTX), late-onset Tay–Sachs disease, mitochondrial ataxia syndromes, and spinocerebellar ataxia with axonal neuropathy), and (3) an early-onset ataxia with cerebellar atrophy phenotype (e.g., AT, ataxia with oculomotor apraxia 1 and 2, AR ataxia of Charlevoix-Saguenay, infantile-onset spinocerebellar ataxia, Cayman ataxia, and Marinesco-Sjogrens syndrome).

Friedreich ataxia

FRDA clinically presents with gait instability and clumsiness or scoliosis diagnosed in adolescence. Neurological features include a mixed sensory and cerebellar ataxia, gait and limb ataxia, dysarthria, dysphagia, ocular fixation difficulty with square-wave jerks, areflexia, proprioceptive sensory loss, weakness, and extensor plantar responses. Cognition remains intact; optic atrophy and sensorineural hearing loss occur in some. On average, patients require a wheelchair 10–15 years after disease onset. Nonneurological abnormalities include musculoskeletal changes of kyphoscoliosis and pes cavus or equinovarus, hypertrophic cardiomyopathy (inverted T waves on electrocardiogram, symptoms of shortness of breath and palpitations), diabetes mellitus or glucose intolerance, and autonomic disturbances. In FRDA, evaluation reveals nerve conduction studies with sensory axonal neuropathy and absent sensory nerve action potentials (SNAPs), abnormal evoked potential studies (visual, brainstem, motor, and somatosensory), and atrophy of the cervical spinal cord rather than cerebellum on neuroimaging. Neuropathology demonstrates degeneration of posterior columns of the spinal cord and spinocerebellar tracts, the sensory tracts projecting to the brain and cerebellum; loss of large primary sensory neurons in the dorsal root ganglia; and mild cortical cerebellar atrophy late in the course.

Although onset is usually in adolescence, before age 20, late onset variants can occur. Late-onset FRDA (LOFA) can occur even after age 50–60; it is associated with shorter repeat lengths, and clinically may have intact reflexes, fewer skeletal deformities, and a more benign, slower progression. Another variant is FRDA with retained reflexes (FARR) which also may be milder in phenotype, and as its name suggests, patients have intact reflexes.

Ataxia with isolated vitamin E deficiency

Ataxia with isolated vitamin E deficiency (AVED) shares a phenotype with FRDA – progressive cerebellar ataxia, areflexia, proprioceptive sensory loss, and corticospinal tract signs with spastic gait and extensor plantar responses. Symptoms occur in the absence of fat malabsorption or gastrointestinal syndromes. Affected individuals may have retinal pigmentary changes but rare oculomotor signs, skeletal deformities such as pes cavus and possibly scoliosis, and hypertrophic cardiomyopathy only in about 19%. Patients become wheelchair bound after an average of 11 years. The age of onset typically is before 20 years but has been reported in the fifth decade. AVED, due to a mutation in the α-tocopherol transfer protein (αTTP) on chromosome 8q13.1–q13.3, is a relatively rare AR ataxia with the largest group of patients found in North Africa sharing a common mutation. Since α-TTP is involved in the transfer of vitamin E into circulating lipoproteins, the mutation results in the failure of incorporation of vitamin E into very low density lipoproteins in the liver. Diagnostic tests include vitamin E levels (typically $<2\,\mathrm{mg\,l^{-1}}$) and confirmatory genetic testing; other tests, such as complete blood count, creatine kinase, hepatic enzymes, copper studies, lipoproteins electrophoresis, peripheral smear for acanthocytes, and tests for steatorrhea are normal. Treatment with vitamin E at doses of $800\,\mathrm{mg\,day^{-1}}$ can reverse or slow down the ataxia.

Abetalipoproteinemia

Abetalipoproteinemia (also known as Bassen–Kornzweig disease) is a rare condition whose neurological manifestations are due to underlying vitamin E deficiency. As a result, abetalipoproteinemia clinically resembles AVED in the setting of a gastrointestinal malabsorption syndrome. Clinical features include cerebellar ataxia, proprioceptive sensory loss, areflexia, weakness, retinal degeneration, as well as steatorrhea, fat malabsorption, celiac syndrome, and acanthocytosis. Onset typically occurs in adolescence. Abetalipoproteinemia is caused by mutations in the gene coding a subunit of the microsomal triglyceride transfer protein (MTP) on chromosome 4q22–q24. Since MTP is necessary for lipoprotein assembly, the mutation impairs synthesis of apoB peptide of low density lipoprotein and very low density lipoprotein; this leads to impaired fat absorption and in turn, vitamin E deficiency. Levels of cholesterol and triglycerides are extremely low and apolipoprotein B-containing lipoproteins are absent. Treatment involves supplementation of fat soluble vitamins including vitamin E.

Refsum disease

Refsum disease, in its classic form, manifests as cerebellar ataxia, demyelinating sensori-motor polyneuropathy, and retinitis pigmentosa. Non-neurologic features include icthyosis, deafness, multiple epiphyseal dysplasia, and cardiac arrhythmias. Onset typically occurs before the age of 20. Diagnostic studies include elevated serum phytanic acid, reduced oxidation of phytanic acid in fibroblasts, demyelinating neuropathy on nerve conduction studies, and elevated cerebrospinal fluid protein. Neuropathology demonstrates large onion bulbs and decreased myelinated axons on nerves and decreased Purkinje cells in cerebellum and neurons in inferior olive and vestibulocochlear nuclei. Refsum

disease is a peroxisomal disorder due to an inability to degrade phytanic acid, a branched-chain fatty acid, with mutations in the gene coding phytanoyl-CoA hydroxylase on chromosome 10pter–p11.2. As a result, phytanic acid accumulates in body tissues. Treatment involves dietary restriction of phytanic acid to less than 10 mg day^{-1}. Dietary measures may improve ataxia and neuropathy but not vision and hearing loss.

Cerebrotendinous xanthomatosis

CTX is a rare AR ataxia that involves both neurologic and systemic features. CTX typically presents after puberty with progressive cerebellar ataxia, neuropathy, pseudobulbar dysfunction, parapesis, and myoclonus and dementia, in some. Systemically, premature atherosclerosis, cataracts, and xanthelasma with thickened tendons (cholesterol deposition) occur. Nerve conduction studies reveal axonal loss and biopsies demonstrate axonal loss with demyelination in some patients. Laboratory testing is diagnostic, revealing increased serum cholestanol and increased urinary bile alcohol. Plasma cholesterol concentrations are low normal in CTX. The defect in CTX is due to mutations in the *CYP27A1* gene on chromosome 2q33–qter, which is involved in bile acid synthesis pathway. Treatment involves administration of chenodeoxycholic acid to compensate for the pronounced deficiency of chenodeoxycholic acid in the intrahepatic pool. Some series of CTX patients have revealed improvement in neurological features (ataxia, neuropathy, dementia) in patients after at least 1 year of treatment. Management of atherosclerosis with HMG-CoA reductase inhibitors may also be necessary.

Ataxia-telangiectasia

AT, caused by a mutation in the *ATM* gene on chromosome 11q22–23, manifests itself as a progressive cerebellar ataxia, also complicated by systemic features. Neurologic signs and symptoms include limb and gait ataxia, oculomotor apraxia, choreoathetosis, dystonia, dysarthria, hyporeflexia, sensory loss, distal muscular atrophy, and impaired cognition. Nonneurologic features include oculocutaneous telangiectasias (occur after neurologic symptoms), impaired humoral and cellular immunity resulting in sinopulmonary infections, high incidence of malignancy, such as leukemia and lymphoma, radiosensitivity, infertility, and diabetes mellitus. Onset begins around age 1–2 years with truncal ataxia and oculomotor problems. Children may be wheelchair bound by age 10 and death occurs between 20 and 30 years of age. Adjunctive diagnostic studies include elevated serum α-fetoprotein and carcinoembryonic antigen, abnormalities in immunoglobulins (particularly absence or low level of serum IgA), neuroimaging revealing cerebellar atrophy, and genetic testing. No specific pharmacologic treatment for neurologic symptoms exists, but ongoing trials are assessing α-lipoic acid and PARP-1 inhibitor. Patients should be monitored for infections and malignancy; antibiotics should be used for sinopulmonary infections but treatment of malignancies with radiation may be problematic due to radiosensitivity.

Ataxia-ocular apraxia (AOA) types 1 and 2

Ataxia-ocular apraxia Type 1 (AOA1), caused by mutations in the APTX protein located on chromosome 9p13, is a slowly progressive, childhood disorder with limb and gait ataxia, oculomotor apraxia, motor and sensory neuropathy, and extrapyramidal features, such as dystonia and hypomimia. In addition, hypoalbuminemia and hypercholesterolemia may occur. The mean age of onset is 5 years. Epidemiology reveals a Portuguese and Japanese predominance. Laboratory studies support axonal neuropathy on nerve conduction studies, mild loss of myelinated axons on nerve biopsy, and cerebellar atrophy with possible brainstem involvement on neuroimaging.

Ataxia-ocular apraxia Type 2 (AOA2), caused by a mutation in the senataxin protein on chromosome 9q34, presents later than AOA1 with the age of onset from10 to 22 years and with severe gait ataxia, variably present oculomotor apraxia, slow saccades, choreoathetosis and dystonia, sensory-motor neuropathy, areflexia, and extensor plantar responses. Serum α-fetoprotein and creatine kinase may be elevated, but chromosomal instability and radiosensitivity are absent.

Spastic ataxia of Charlevoix-Saguenay (ARSACS)

ARSACS, caused by mutations on chromosome 13q12 in the *sacsin* gene, is characterized by cerebellar ataxia, spasticity, and prominent retinal myelinated fibers. Onset is typically around age 1–2 years with gait ataxia and lower limb spasticity, increased cerebellar signs around adolescence, motor axonal polyneuropathy in the third decade, and loss of ambulation around age 40. Other features include pes cavus or equinovarus, saccadic smooth pursuit, and distal amyotrophy, but absence of cardiac disease as in FRDA. ARSACS is prevalent in Charlevoix-Saguenay, a region in Northeastern Quebec. Diagnostic studies reveal abnormal fundoscopy, early demyelination and axonal neuropathy on nerve conduction studies, neurogenic atrophy of muscle biopsy, loss of large myelinated axons on nerve biopsy, and cerebellar atrophy of the superior vermis and later hemispheres on neuroimaging. No specific treatment is available for the ataxia but antispasticity medications may be considered.

X-Linked Ataxias

Fragile X-associated tremor-ataxia syndrome

The clinical syndrome of fragile X-associated tremor-ataxia syndrome (FXTAS) includes progressive gait

ataxia, action tremor, parkinsonism, cognitive decline/executive dysfunction, polyneuropathy, and autonomic dysfunction. The features typically occur in males over age 50, who are often the male grandparents of patients with FMR syndrome. Many patients have been previously diagnosed as having essential tremor, parkinsonism, or MSA. Neuroimaging reveals increased T2 signal in middle cerebellar peduncles and adjacent white matter. Neuropathology in mice and humans demonstrates eosinophilic, ubiquitin-staining, intranuclear inclusions in neurons and astrocytes throughout the brain and hippocampus. Treatments so far include symptomatic therapies for tremor, parkinsonism, and cognitive dysfunction.

Fragile X is caused by a CGG repeat expansion in the 5′ untranslated region of the fragile X mental retardation 1 (*FMR1*) gene with full mutation expansion lengths >200 CGG repeats. Instead, FXTAS is due to premutations in the *FMR1* gene with CGG repeat lengths of 55–200. The frequency of the premutation is 1/259 in females and 1/813 males in the general population. In FMR, the CGG repeat expansion leads to methylation and transcriptional silencing of the *FMR1* gene. In premutation carriers, however, levels of *FMR1* mRNA are elevated thereby, suggesting a possible toxic 'gain of function' mechanism. FMR protein production is reduced due to reduced translational efficiency of *FMR1* mRNA. CGG repeat length appears to influence FMR1 mRNA levels (elevated in premutation carriers) and position of transcription start (farther upstream with increasing repeats).

Sporadic or Nonhereditary Ataxias

Sporadic ataxias may be diverse in etiology. Differential diagnosis is influenced by the tempo of the ataxia and presence of systemic or neurologic abnormalities. Causes for sporadic ataxia include MSA, autoimmune disorders such as glutamic decarboxylase (GAD) antibodies, infections such as viral or prion disease, endocrine dysfunction such as hypothyroidism or hypoparathyroidism, gastrointestinal disorders such as celiac ataxia or Whipple's disease, paraneoplastic syndromes, toxins, trauma, neoplastic, and vascular events, among others.

Multiple system atrophy

MSA is a progressive neurodegenerative disorder with elements of parkinsonism, cerebellar ataxia, and autonomic dysfunction. Although previously classified as striatonigral degeneration, Shy-Drager syndrome, and olivopontocerebellar atrophy (OPCA, sporadic), MSA is currently defined by the predominant clinical presentation with parkinsonism (MSA-P) in 80% or cerebellar ataxia (MSA-C) in 20% of patients. Clinical features of MSA-P include: parkinsonism with tremor (more commonly action or postural than rest tremor), akinesia, and rigidity, often symmetrical; autonomic disorders with lightheadedness, recurrent syncope, urinary incontinence or incomplete emptying, and impotence; and cerebellar dysfunction with limb and gait ataxia, nystagmus, and tremor. Other manifestations include corticospinal tract signs with hyperreflexia and extensor plantar responses, inspiratory stridor, antecollis, myoclonus, rapid eye movement (REM) behavior disorder, facial dystonia, and cold or dusky hands. Clinical features of MSA-C include: impaired balance with ataxia, nystagmus, tremor, dysarthria; autonomic dysfunction with lightheadedness and syncope, bladder dysregulation and impotence; parkinsonism, and corticospinal tract signs. Patients typically have a poor and nonsustained response to levodopa although some benefit initially. Late-onset cerebellar ataxia and sporadic OPCA both may represent forms of MSA-C. Of patients diagnosed with OPCA followed longitudinally, about 25% developed MSA. The mean age of onset for MSA-P and MSA-C is around 50 years of age and survival, about 10 years. Average incidence rate for MSA is 3 new cases/100 000 person-years.

Diagnostic criteria for MSA have been established by Quinn et al., Gilman et al., and recently revised by Gilman et al. with possible, probable, or definite MSA designations. Definite MSA requires neuropathological demonstration of α-synuclein-positive glial cytoplasmic inclusions in the central nervous system with neurodegenerative changes in striatonigral or olivopontocerebellar structures. Probable MSA requires a sporadic, progressive, adult-onset disorder meeting criteria for autonomic failure and poorly levodopa-responsive parkinsonism or cerebellar ataxia. Possible MSA also requires a sporadic, progressive, adult-onset disorder with parkinsonism or cerebellar ataxia but at least one feature suggesting autonomic dysfunction plus either a clinical or neuroimaging abnormality. Neuroimaging with MRI may be helpful when characteristic findings are present. In MSA-P, putaminal hypointensity with a lateral hyperintense rim on T2 weighted images may occur. In MSA-C, the 'hot cross bun' sign with cerebellar atrophy and increased T2 signal in the pons may be seen. Variable sensitivity and specificity has been reported. PET imaging reveals decreased cerebral glucose metabolic rates in the striatum in MSA-P and brainstem and in the cerebellum in MSA-C. Studies related to autonomic failure indicate a preganglionic defect in MSA; cardiac SPECT imaging with [^{123}I] metaiodobenylguanidine (MIBG) which labels postganglionic adrenergic neurons may reveal significant decreases of uptake in PD but not in MSA due to its preganglionic deficit. Rectal sphincter EMG is a sensitive measure for denervation but may be abnormal in PD. Neuropathology of MSA includes degeneration of the striatum, substantia nigra, locus ceruleus, inferior olives, brainstem, cerebellum, interomedial cell columns, and Onuf's nucleus. The pathological hallmark is the glial cytoplasmic inclusion, an α-synuclein and ubiquitin staining inclusion found in oligodendrocytes in the cortex, striatum, brainstem, and interomedial cell column.

Gluten ataxia

Neurological features of celiac disease or sprue, a gluten-sensitive enteropathy due to T cell mediated immune responses to ingested gluten in genetically susceptible populations, including ataxia, peripheral neuropathy, myopathy, and headaches. White matter changes on MRI have been reported. Cerebellar dysfunction manifests as truncal or gait ataxia, dysarthria, and oculomotor signs with a mean age of onset of about 50–60 years. Gluten sensitivity may present with neurological dysfunction in the absence of gastrointestinal or systemic symptoms. Diagnostics tests include IgG and IgA antibodies to gliadin, but antiendomysial, and tissue transglutaminase antibodies may offer greater specificity despite being less common in neurological dysfunction alone. Duodenal biopsy typically reveals absent villi with hyperplastic crypts and inflammatory and lymphocytic infiltration. Cerebellar atrophy may be present on brain MRI. Treatment involves a gluten-free diet; however, unlike gastrointestinal symptoms, improvement in ataxia may not be as robust.

Cerebellar syndrome with anti-GAD antibodies

Cerebellar ataxia with anti-GAD antibodies is a variant of stiffperson syndrome (SPS) which presents as a slowly or subacutely progressive cerebellar ataxia involving the limbs and trunk, nystagmus, and dysarthria. Stiffness is less prominent than in SPS, occurring in about 15%, and the brainstem is unaffected. Similar to SPS, autoimmune diseases, such as diabetes mellitus, thyroiditis, and polyendocrine syndrome may be present. Paraneoplastic syndromes should be excluded. The age of onset ranges from 20 to 75 years with a female predominance. Laboratory tests reveal high titers of anti-GAD antibodies and also anti-parietal cell antibodies. Neuroimaging may be normal or exhibit cerebellar atrophy. There are no specific treatments for the cerebellar syndrome but case reports or series cite some response to steroids and intravenous immunoglobulin.

Paraneoplastic syndromes

Ataxia may be a presenting feature of a paraneoplastic cerebellar degeneration syndrome (PCD). Paraneoplastic antibodies are thought to react with antigens in the cancer and nervous system, targeting antigens on Purkinje cells in cases with cerebellar ataxia. Onset typically precedes the neoplasm by months to even years. Symptoms of limb and gait ataxia, dysarthria, nystagmus, and oculomotor dysfunction may progress rapidly over weeks to months and then plateau.

PCD has been described most often with cancers of the lungs (small cell), ovaries, breast, and lymphoma, but other cancers have been reported. Specific paraneoplastic antibodies associated with PCD include: Hu – small cell lung cancer, Yo – ovarian or breast cancer, Ri – breast cancer, Tr and metabotropic glutamate receptor R1 (mGluR1) – Hodgkin's lymphoma, Ma – breast, colon, or large cell lung cancer, Ma2 – testicular cancer, CV2 (CRMP5) – small cell lung cancer or thymoma, voltage gated calcium channels (VGCC) – small cell lung cancer, and Zic4 – small cell lung cancer. Diagnostic studies focus on serum antibodies and detection of underlying cancer. Increased protein, IgG synthesis, oligoclonal bands, and paraneoplastic antibodies may be found in cerebrospinal fluid. MRI, however, may not demonstrate cerebellar atrophy initially. Pathology reveals degeneration of cerebellar Purkinje cells, inflammatory infiltrates, and Purkinje cells that stain for specific paraneoplastic antibodies. Treatment usually involves cancer management but responses to intravenous immunoglobulins or plasmapheresis have been reported, particularly with Lambert–Eaton myasthenic syndrome, paraneoplastic encephalomyelitis or sensory syndromes, and in cerebellar degeneration. However, despite decreased titers of paraneoplastic antibodies with cancer resection and treatment, improvement of ataxia may be disappointing due to neuronal destruction.

Prion disease

Cerebellar ataxia may be a component of prion diseases and has been described in familial and sporadic Creutzfeldt–Jacob disease (CJD), Kuru, and familial Gerstmann–Straussler–Sheinker disease (GSS). Clinical features associated with CJD include progressive cerebellar ataxia, myoclonus, corticospinal tract and extrapyramidal signs, visual disturbances and oculomotor dysfunction, as well as dementia and behavioral problems. Patients with sporadic CJD carrying the valine–valine (VV) or methionine–valine (MV) polymorphism at codon 129 of the prion protein gene (*PRNP*) and PrP^{Sc} type 2 may present with a cerebellar form of CJD. In addition, sporadic CJD patients with MV polymorphism and type 1 PrP^{Sc} may demonstrate ataxia and sensory deficits before cognitive decline. Point mutations on chromosome 20 in familial CJD (P102L) and GSS (G131V or H187R) may present as a classical ataxic forms. Diagnostic tests include detection of 14–3–3 protein in cerebrospinal fluid, periodic sharp wave activity on EEG, hyperintense signal in the basal ganglia on MRI, and possible biopsies of tonsils and brain, although these tests vary in sensitivity and specificity for prion disease. More recently, genotype–phenotype correlations can be made by evaluating different polymorphisms at codon 129 in the PRNP and different types of PrP^{Sc}. Neuropathology of prion diseases reveals spongiform encephalopathy but specific patterns of spongiform degeneration, astrogliosis, and neuronal loss depends on the subtype of CJD.

Differential Diagnosis

See **Table 2** for salient SCA features.

Diagnostic Work-Up/Tests

When approaching a patient with ataxia, an organized, stepwise process is important (see **Figure 1**). There are several key components in addition to a comprehensive neurological examination that will aid in developing a differential diagnosis and in some cases, deciding on acute medical intervention. The clinician must first 'localize the lesion' and determine whether the ataxia is due to cerebellar disease or to other neurologic problems such as in the vestibular or sensory/proprioceptive systems. If the deficits result from cerebellar dysfunction, one should then assess whether the syndrome is purely cerebellar or has other associated neurologic or systemic features ('cerebellar-plus'). A detailed family history is necessary. Further investigation may require supplemental neuroimaging, electrophysiological studies, laboratory tests, and genetic tests.

Table 2 ADCAs classified by presence of neurologic signs and symptoms

Pure cerebellar ataxia	SCA 5, 6 (see ***Table 1***)
Peripheral neuropathy	SCA 1, 2, 3, 4, 18, 25
Corticospinal tract signs	SCA 1, 3, 6, 7, 8, 12
Parkinsonism	SCA 2, 3, 12, 21
Dystonia	SCA 3, 12, 17
Chorea	SCA 1, 17; DRPLA
Myoclonus	SCA 2, 14, 19; DRPLA
Ophthalmoplegia	SCA 1, 2, 3
Slow saccades	SCA 1, 2, 3, 7
Nystagmus (downbeat)	SCA 6
Pigmentary retinopathy	SCA 7
Cognitive impairment/ dementia	SCA 2, 13, 17, 19, 21; DRPLA
Seizures	SCA 10, 17; DRPLA
Dentate calcifications on CT	SCA 20

Clinical History

Key features in the history of a patient with ataxia include: the onset age, time course and progression, and medical, social, and family history. In children, congenital ataxias, metabolic disorders, infectious/acute cerebellitis, posterior fossa tumors, and hereditary ataxias are often part of the differential diagnosis, whereas in adults, the sporadic and hereditary ataxias predominate. The time course of the ataxia is important. Acute ataxias are more likely to be vascular, metabolic/toxic, infectious, inflammatory, or traumatic in origin. Subacute causes may include metabolic/toxic, infectious, inflammatory, or paraneoplastic, tumor processes. Chronic ataxias are more likely genetic or degenerative. Accompanying symptoms such as headache, nausea, or vomiting may signify an acute cerebellar hemorrhage or increased intracranial pressure as in childhood posterior fossa tumors. Systemic signs such as weight loss, gastrointestinal symptoms, autonomic dysfunction, skin changes or other neurological signs, such as parkinsonism, dystonia, spasticity, neuropathy may be present. The course of the ataxia may be stable, progressive, or episodic. Medications such as anticonvulsants (phenytoin, barbiturates), lithium, immunosuppressants (methotrexate, cyclosporine), or antineoplastic agents (fluorouracil, cytarabine) may contribute to ataxia symptoms. Other medical problems such as cancer, infections,

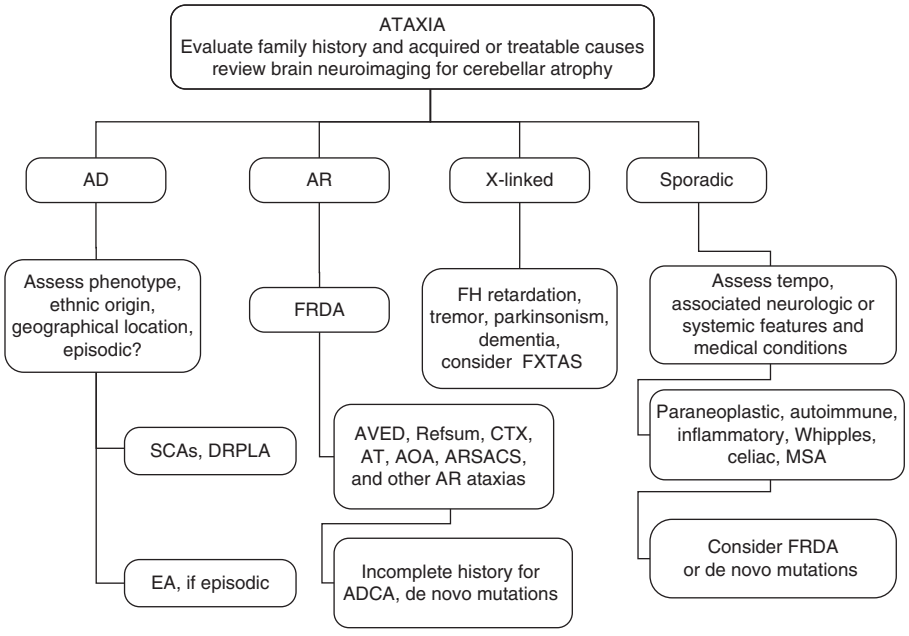

Figure 1 Proposed diagnostic algorithm for evaluating ataxia patients.

HIV, thyroid disease, gastrointestinal disease (malabsorption, celiac), or multiple sclerosis may be the cause of ataxia. Ascertaining the patient's history of alcohol or substance use and toxin exposures (heavy metals, solvents, thallium) is important. Lastly, obtaining a detailed family history is imperative. The presence of ataxia, similar symptoms, or other neurologic disease should be recorded for at least three generations to best determine the mode of inheritance and identify phenotypic heterogeneity.

Clinical Examination

In addition to the general physical and neurological examination, one should pay attention to several specific elements of cerebellar function: speech, ocular movements (nystagmus, smooth pursuit, hypo or hypermetric saccades), limb coordination, tremor, stance, and gait. Cerebellar function, especially appendicular function, can be tested at the bedside with the following maneuvers: for dysmetria (finger–nose–finger, heel–knee–shin), dysdiadochokinesia (rapid alternating movements of tapping the palmar and dorsal surfaces of the hands), dyssynergia (tapping of hands, fingers, feet, and other multijoint movements), rebound (application of a downward tap on the patient's outstretched arm which produces a rapid, excessive upward displacement), and impaired check (sudden release of the patient's flexed arm which leads to the inability of the patient to stop the movement). Tremor is more typically present with action and increases as the limb approaches the end-point or target (intention tremor). Tremor may be slow (2–5 Hz) and more proximal with wide amplitude. One should assess the patient's sitting position for titubation, stance (typically wide based), and ability to perform tandem gait, single leg stance, and stand with and without eye closure. Furthermore, the comprehensive neurological examination should include evaluation of mental status, cranial nerves (vision, bulbar involvement, asymmetry), tone (hypotonia, rigidity, spasticity), strength, reflexes, sensation (presence of neuropathy), and movement disorders (parkinsonism, dystonia, myoclonus, chorea, tremor). Abnormalities in these other neurological systems may provide diagnostic clues (vision loss in SCA7, ophthalmoplegia and/or parkinsonism and/or dystonia in SCA3, arreflexia and neuropathy in FRDA, etc.). General physical examination should include assessment of blood pressure for orthostatic hypotension (MSA), thyroid, eyes, cardiac (FRDA), endocrine, skin (AT), nail changes, and skeletal system.

Rating Scales

Specific ataxia rating scales can be used to monitor ataxia for both clinical management and research studies. The International Cooperative Ataxia Rating Scale (ICARS) rates gait, kinetic functions (limb ataxia), speech/dysarthria, and oculomotor findings, with scores ranging from 0 to 100; the ICARS demonstrates high-reliability as well as high test–retest reliability and internal consistency but has several overlapping, interdependent items that may affect its practicability. The Scale for the assessment and rating of ataxia (SARA) is a short, quick, semiquantitative scale that evaluates gait, stance, sitting, speech, and limb kinetic functions, but not oculomotor function; scores range from 0 to 40. The Unified Multiple System Atrophy Rating Scale (UMSARS) is a longer scale validated for MSA; it includes a historical interview, motor and autonomic examination, and global disability scale. Scales proposed for FRDA including the Friedreich Ataxia Rating Scale (FARS) which combines scores for ataxia, activities of daily living, and neurological examination. Other scales for tremor and parkinsonism (e.g., Unified Parkinson's Disease Rating Scale) may be useful. Details and clinimetric properties of these scales are discussed in other encyclopedia entries.

Studies of Potential Utility in Patients With Ataxia

This section describes tests that may be useful in the evaluation of a patient with ataxia. However, pursuit of these tests should be guided by the patient's history, family history for inheritance patterns, and examination, among other factors, particularly since many of the specialized tests are very expensive.

Laboratory studies to be considered (depending on clinical situation) include: thyroid function, vitamin B12, vitamin E, vitamin B1, heavy metal screen, antigliadin antibodies, GAD antibodies, serum cholesterol and plasma lipoprotein profile, peripheral blood smear for acanthocytes, serum lactate and pyruvate, very long chain fatty acids, hexosaminidase A or B, paraneoplastic antibodies, toxicology screen, α-fetoprotein and immunoglobulins, serum ceruloplasmin and 24 h urinary copper, and phytanic acid. Cerebrospinal fluid analysis may be used to assess protein, oligoclonal bands, 14–3–3 protein, GAD antibodies, or paraneoplastic antibodies. Many genetic tests are now commercially available, and some are available on a research basis. To date, genetic tests include SCA1, 2, 3, 5, 6, 7, 8, 10, 13, 14, 17, 27 (for SCA5, 13, 14, and 27, the analysis is of the entire coding region: sequence analysis, whereas the other SCAs have targeted mutation analysis); DRPLA; FRDA; Ataxia with oculomotor apraxia types 1 and 2 (APTX and senataxin); Fragile X DNA; Rett syndrome; X-linked sideroblastic anemia and ataxia; ataxia telangiectasia; ARSACS (targeted mutation analysis); *TTPA* gene for ataxia with vitamin E deficiency; SIL1 for Marinesco–Sjogren syndrome; mitochondrial recessive ataxia syndrome (MIRAS)-specific POLG1; and EAs type 1 and 2 (sequence

analysis). Tissue biopsies of muscle, skin, rectum, bone marrow, tonsil, or brain may be considered in appropriate circumstances.

Neuroimaging with MRI of the brain and possibly, cervical spine may be useful in excluding structural causes, multiple sclerosis, or assessing regional atrophy (i.e., in the cerebellum, brainstem, or cervical cord). In some cases, magnetic resonance spectroscopy may be helpful. Electrodiagnostic tests such as nerve conduction studies and EMG may be used to evaluate neuropathy which is often associated with the ataxias or other neuromuscular abnormalities; electoencephalography, evoked potentials, electronystagmography, or electroretinography may be considered in selected circumstances. Tests of autonomic dysfunction for tilt-table tests, sympathetic skin responses, cardiac I^{123}-MIBG-SPECT scans, or anal sphincter EMG, particularly in MSA. Ophthalmologic examination may be targeted for pigmentary retinopathy, macular degeneration, cataracts, Kayser–Fleischer rings.

Management

Treatment of cerebellar ataxias encompasses both pharmacologic and nonpharmacologic strategies and in some cases, depends on the specific etiology of the ataxia. Some of the management issues have been previously discussed in the individual ataxia sections and where available, specific trials will be noted. In addition to management of neurologic systems, one must pay attention to systemic disorders affecting cardiac, endocrine, gastrointestinal, and skeletal systems as well as underlying neoplasms. Trials of medications for cerebellar ataxia mainly consist of open label studies or case reports, and better therapeutics and double-blind, placebo-controlled trials are needed. Lastly, genetic counseling is an important aspect of the management of hereditary ataxias.

Pharmacologic Strategies

First, treatable causes of ataxia will be mentioned. Although not curative, high doses of vitamin E can improve neurologic symptoms in ataxia with vitamin E deficiency (AVED) and Abetalipoproteinemia. Phytanic acid should be restricted to less than 10 mg day^{-1} in Refsum disease. Gluten ataxia may improve with restriction of wheat and products containing gluten. Ataxia due to CTX should be treated with chenodeoxycholic acid and possibly other cholesterol medications. Of course, ataxia due to infectious (including Whipple's disease) or vascular etiologies may have disease-specific treatments. Paraneoplastic cerebellar syndromes may respond to treatment of underlying cancer and immunotherapies, such as intravenous immunoglobulin, plasmapheresis, and steroids. However, due to cerebellar neuronal damage, the ataxia symptoms may have modest response to these treatments. Cerebellar ataxia with GAD antibodies has been reported to respond to immunotherapies. EAs, particularly EA-1, 2, and 4, are acetazolamide-responsive. A recent open label trial of the potassium channel blocker 4-aminopyridine (4-AP) in three EA-2 patients reported prevention or decreased attacks during treatment and recurrence when 4-AP was stopped.

For FRDA, treatment focuses on rehabilitation and orthopedic interventions for gait and limb difficulty and skeletal deformities and cardiac and endocrine monitoring. Idebenone, a free radical scavenger, as other antioxidants such as vitamin E, coenzyme q10, and selenium have been studied in FRDA. Most trials with idebenone have been open label although a recent randomized, placebo-controlled study has been reported. Unfortunately, despite reduction of oxidative stress markers and decreased cardiac hypertrophy in some studies with idebenone, significant improvement in ataxia largely has been lacking.

Management for MSA is generally tailored to specific symptoms. Dopaminergic medications may provide some improvement in parkinsonian features (bradykinesia, rigidity, or rest tremor), particularly early in the course. Improvement, however, is not as dramatic or sustained as in idiopathic Parkinson's disease. Orthostatic hypotension can be managed with increased salt and caffeine intake, pressurized stockings, and elevation of the head of the bed. Several trials including double-blind studies have assessed fludrocortisone and midodrine in orthostatic hypotension, but the use of these medications is limited by supine hypertension. A prospective open label trial by Singer et al. evaluating the acetylcholinesterase inhibitor, pyridostigmine, in the treatment of neurogenic orthostatic hypotension in patients with MSA, PD, and diabetic, amyloid, or idiopathic autonomic neuropathy demonstrated significant improvement in orthostatic blood pressure, peripheral resistance index, and orthostatic symptoms with only a moderate and nonsignificant increase in supine blood pressure. Bladder frequency and urgency may be treated with agents, such as oxybutynin and tolterodine. REM behavior disorder responds well to clonazepam.

The neurochemistry of the cerebellum has led to investigations of serotonergic, dopaminergic, GABAergic, and cholinergic treatments in cerebellar ataxias, although symptomatic benefits have been modest. Several studies have examined buspirone, a 5HT1A serotonin agonist with weak dopaminergic properties, in the cerebellar ataxias. An open label trial by Lou et al. with 20 patients with mixed cortical or OPCA received buspirone 60 mg day^{-1} for 8 weeks followed by a washout period; nine patients with mild or moderate symptoms had significant improvement in clinical and subjective ratings but not in motor function or posturography and few patients with severe symptoms showed improvement. Trouillas et al. performed a double-blind, placebo controlled study with buspirone in 19 patients with cortical cerebellar atrophy for 4 months found improvement only in subscores such

as intensity of body sway and time of standing and kinetic score. A double-blind, placebo-controlled study by Botez et al. with amantadine (200 mg day^{-1}), an NMDA antagonist with some dopaminergic properties, was performed with 27 patients with FRDA and 39 patients with olivopontocerebellar ataxias for 3–4 months. Improvement was greater in the olivopontocerebellar ataxia group with improvement in visual and auditory reaction time and movement time. Other studies with amantadine have shown less positive results. An open label trial by Gazzula et al. with gabapentin, a GABAergic medication, in 10 patients (seven with sporadic cortical cerebellar atrophy and three with an unknown ADCA) reported a significant improvement in ataxia scores after single doses of 400 mg day^{-1} and 4 week treatment with 900–1600 mg day^{-1}. Double-blind, placebo-controlled, crossover studies have investigated the cholinergic system with physostigmine, an acetylcholinesterase inhibitor, and L-acetylcarnitine, a cholinomimetic agent, in mixed ataxia populations without any effect on ataxia in the former and significant improvement in coordination but not total ARS score in the latter trial.

Several trials have addressed specific pharmacologic treatments in the SCAs, using a variety of agents but with mixed results. These reports include: zolpidem in five SCA2 patients; buspirone, a 5HT1A serotonin agonist with weak dopaminergic properties, in a single SCA3 patient; tandospirone, also a 5HT1A agonist, in case reports and open label studies in SCA3; fluoxetine in open label study of 13 SCA3 patients; trimethoprim–sulfamethoxazole in a double-blind, placebo-controlled crossover trial in 22 genetically confirmed SCA3 (no effect); acetazolamide in open label studies in small numbers of SCA6 (mixed results in clinical measures and posturography sway); and intravenous lidocaine in a case report of SCA6. More recently, Zesiewicz and Sullivan reported three patients with SCA3 and SCA14 who had improvement in ataxia symptoms with varenicline, a partial agonist selective for $\alpha4(\beta2$ nicotinic acetylcholine receptors and prescribed for smoking cessation. Based on a recent SCA1 knockout mice study in which lithium improved motor function and learning, a safety trial with lithium in SCA1 is currently underway.

Nonppharmacologic Strategies

Although clinical studies are lacking for nonpharmacologic treatments of ataxias, these modalities can be helpful. Physical and occupational therapy may be useful in gait and balance training, safety mechanisms, decreasing spasticity or rigidity, and reducing musculoskeletal problems such as contractures. Occupational therapists may help patients find adaptive devices to improve functional use of upper extremities. Speech therapists can evaluate dysphagia with bedside tests or more formal radiographic studies and teach swallowing techniques, modify diets, and work on dysarthria. Social services and supportive care also are important aspects.

Genetic Counseling

Genetic counseling is extremely important in the management of hereditary ataxias. Patients and families need to be counseled on underlying inheritance and risks of developing disease. Genetic counselors are valuable allies when discussing genetic testing; ethical concerns; potential social, medical, or insurance issues; and family planning with patients and families. Presymptomatic testing in adults, in general, is not routinely performed. In a study on the impact of presymptomatic genetic testing in 50 subjects with hereditary ataxias and neuromuscular disease, testing was reported as helpful in 84%, but increased anxiety at some point in the study occurred in 18 subjects with persistence at follow up and depression occurred in three (of whom two had negative results) in post-test period. Reasons for genetic testing included explanation for symptoms, emotional relief, and family planning.

See also: Aprataxin; Ataxia-Telangiectasia; Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS); Friedreich's Ataxia and Variants; Friedreich's Ataxia Rating Scale (FARS); Idebenone and Friedreich Ataxia; International Cooperative Ataxia Rating Scale (ICARS); Multiple System Atrophy; Paraneoplastic Movement Disorders; Refsum Disease- a Disorder of Peroxisomal Alpha-oxidation; SCA1; SCA2; SCA3, Machado–Joseph Disease; SCA4; SCA5; SCA6; SCA7, Spinocerebellar Ataxia with Macular Dystrophy; SCA8; SCA10; SCA11; SCA12; SCA13, 14, 15, and 16; SCA17; SCA27; Scale for the Assessment and Rating of Ataxia (SARA); Senataxin; Spinocerebellar Ataxia Type 19, 20, 21, 22, 23, 26; Spinocerebellar Ataxias Genetics; Tocopherol Transfer Protein and Ataxia with Vitamin E Deficiency.

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Ataxia (Familial Cerebellar) with Muscle CoQ_{10} Deficiency

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Glossary

Coenzyme Q_{10} – Abbreviated CoQ_{10}, a lipophillic molecule present in cell membranes which transports reducing equivalents (electrons) in the inner membrane of mitochondria.
Primary CoQ_{10} deficiency – Deficiency of CoQ_{10} due to mutations of a gene required for CoQ_{10} biosynthesis.
Respiratory chain – A set of four multisubunit enzymes (complexes I–IV) embedded in the mitochondrial inner membrane that transfers reducing equivalents (electrons) to generate a transmembrane proton gradient.
Secondary CoQ_{10} deficiency – Deficiency of CoQ_{10} that is not due to mutations in a CoQ_{10} biosynthesis gene.

Definition and History

Coenzyme Q_{10} (CoQ_{10}) is comprised of a benzoquinone ring and a tail comprised of 10 isoprenyl units and is synthesized within mitochondria. A major function of CoQ_{10} is to transport electrons from complexes I and II to complex III in the respiratory chain, which reside in the mitochondrial inner membrane (**Figure 1**). In addition, CoQ_{10} is an antioxidant, a cofactor for de novo pyrimidine synthesis, electron transporter of plasma membranes and lysosomes, and modulator of apoptosis.

Deficiency of CoQ_{10} (MIM 607426) was originally described by Ogasahara and colleagues who reported two sisters with an encephalomyopathy characterized by a triad of recurrent myoglobinuria, brain involvement, and ragged-red fibers. Three other major clinical phenotypes have been associated with primary CoQ_{10} deficiency: (1) infantile multisystemic disease typically with prominent nephropathy and encephalopathy; (2) cerebellar ataxia with marked cerebellar atrophy; and (3) pure myopathy. Primary CoQ_{10} deficiencies are due to mutations in ubiquinone biosynthetic genes while secondary CoQ_{10} deficiencies are caused by mutations in genes not directly related to ubiquinone biosynthesis.

Pathogenesis and Pathophysiology

Primary CoQ_{10} deficiency has been molecularly proven by the identification of CoQ_{10} biosynthetic genes in

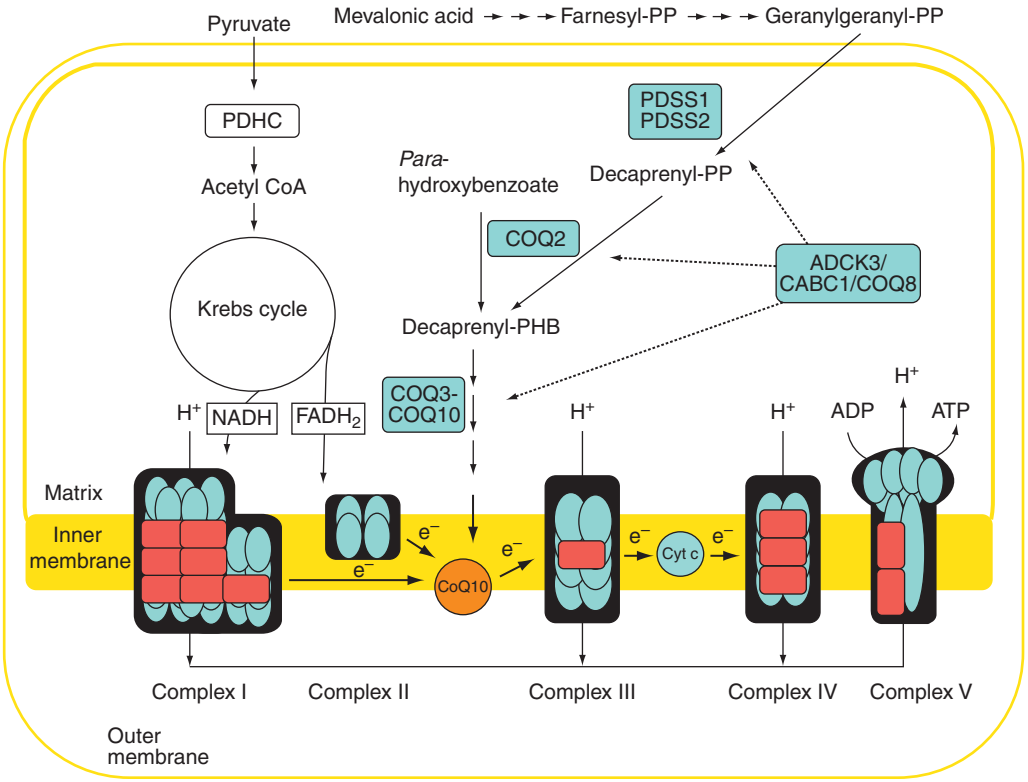

Figure 1 Mitochondrion showing the human CoQ_{10} biosynthetic pathway and the respiratory chain enzyme complexes.

8 patients (6 families) with infantile-onset diseases and in 11 patients (7 families) with cerebellar ataxia. In 2006, Quinzii and colleagues identified the first missense mutation in the *COQ2* gene (p.297Y>C), encoding *p*-hydroxybenzoate-polyprenyl transferase (**Figure 1**), in two siblings of consanguineous parents with infantile steroid-resistant nephropathy, encephalomyopathy in the older child, and deficiency of CoQ_{10} in muscle and fibroblasts in the younger child. Subsequently, *COQ2* mutations were identified in an additional patient with infantile multisystemic disease and two children with early-onset nephrotic syndrome. In addition, mutations in both subunits of decaprenyl diphosphate synthase (**Figure 1**) were identified in three patients with infantile-onset multisystemic diseases; one with fatal Leigh syndrome and nephrotic syndrome due to compound heterozygous *PDSS2* mutations and two siblings with early-onset deafness, encephaloneuropathy, obesity, livedo reticularis, and valvulopathy due to a homozygous missense mutation in *PDSS1*. In all of the infantile multisystemic syndromes, levels of CoQ_{10} were decreased in muscle and fibroblasts.

Finally, mutations in *ADCK3* (also called *CABC1*), a mitochondrial kinase involved in ubiquinone biosynthesis, have been described in 11 patients from 7 families with a cerebellar phenotype. All patients presented with childhood-onset cerebellar ataxia, variably associated with exercise intolerance that improved with years, mild psychomotor delay, and neuropathy. None had kidney disease. Partial CoQ_{10} deficiency was documented in muscle and in some patients' fibroblasts.

Secondary CoQ_{10} deficiency has been genetically proven in the cerebellar and myopathic phenotypes. In 2001, Musumeci and colleagues reported for the first time six patients presenting with cerebellar ataxia, pyramidal signs and seizures, and low level of CoQ_{10} in muscle and fibroblasts. In the three of those patients who were siblings, we found a homozygous W279X mutation in the *APTX* gene, encoding aprataxin, a protein involved in DNA single-strand break repair and known to be the cause of ataxia-oculomotor-apraxia 1 (AOA1). Le Ber and colleagues confirmed that aprataxin gene mutations are associated with decreased CoQ_{10} levels in muscle and that the decrease correlates with the genotype. They noted low levels of CoQ_{10} in muscle from five unrelated patients with AOA1 and the lowest levels of CoQ_{10} were seen in the patients with the homozygous W279X mutation. The CoQ_{10} deficiency was not correlated with duration, severity, and/or progression of the disease or with biological measures, indicating that CoQ_{10} deficiency is not the primary or the only cause of neurological decline in AOA1; nevertheless, patients improved considerately after CoQ_{10} supplementation.

In addition, secondary CoQ_{10} deficiency has been associated with pure myopathy due to mutations in the *ETFDH* (electron-transferring-flavoprotein dehydrogenase) gene, previously associated with glutaric aciduria

type II. A single patient with cardiofaciocutaneous syndrome due to a *BRAF* gene mutation also had CoQ_{10} deficiency and improvement with CoQ_{10} supplementation. All of the patients showed dramatic improvements after CoQ_{10} supplementation.

Despite the aforementioned advances, primary and secondary CoQ_{10} deficiencies have been defined biochemically and genetically in less than half of the reported patients, and their pathogenic mechanisms remain unclear. In skeletal muscle of patients, CoQ_{10} deficiency has been associated with variable defects of the mitochondrial respiratory chain, increased apoptosis, and upregulation of antioxidant defenses.

CoQ_{10} deficiency has variable effects on bioenergetics, oxidative stress, and antioxidant defenses. *PDSS2* mutant fibroblasts with severe CoQ_{10} deficiency (12% of normal) and decreased complex II+III activity showed reduced ATP synthesis without reactive oxygen species (ROS) production, signs of oxidative stress, or increased antioxidant defense markers. In contrast, *COQ2* mutant fibroblasts have milder reductions of CoQ_{10} (30% of normal) and complex II+III activity with moderate defects in ATP synthesis, but significantly increased ROS production and oxidation of lipids and proteins. In addition, *COQ2* mutant cells required uridine to maintain growth and proposed that deficiency of CoQ_{10} caused a defect of pyrimidines biosynthesis because of the dependence of dihydro-orotate dehydrogenase on ubiquinol. Thus, lack of CoQ_{10} may cause human diseases by one or multiple processes including reduced respiratory chain activity; enhanced ROS production, increased ROS susceptibility, or both; or impairment of de novo pyrimidines synthesis.

Epidemiology/Risk Factors

CoQ_{10} deficiencies are rare conditions due to autosomal recessive mutations.

Clinical Features and Diagnostic Criteria

CoQ_{10} deficiency has been associated with four major clinical phenotypes: (1) an encephalomyopathic form characterized by mitochondrial myopathy, recurrent myoglobinuria and central nervous system signs, associated with decrease of complex I+III and complex II+III activity and CoQ_{10} in muscle; (2) a pure myopathic form, with lipid storage myopathy and respiratory chain dysfunction; (3) a cerebellar form, with cerebellar ataxia and atrophy variably associated with other manifestations as neuropathy, seizures, mental retardation, muscle weakness, hypogonadism; and (4) a multisystemic infantile form. Moreover, CoQ_{10} deficiency has been reported in two adult sisters with Leigh syndrome, encephalopathy, growth retardation, infantilism, ataxia, deafness and lactic acidosis, and with cardiofaciocutaneous syndrome. In most of these phenotypes, family history suggests an autosomal recessive mode of inheritance because siblings are often affected while parents are typically unaffected; parents are sometimes consanguineous.

Cerebellar ataxia and atrophy is the most frequent phenotype associated with CoQ_{10} deficiency and is not rare. In a study of 135 patient with genetically undefined cerebellar ataxia (i.e., without spinocerebellar ataxia or Friedreich ataxia gene mutations), about 10% had CoQ_{10} deficiency in muscle.

Differential Diagnosis

The differential diagnosis of cerebellar ataxia due to CoQ_{10} deficiency includes other genetic forms of cerebellar ataxia including Friedreich ataxia, spinocerebellar ataxia, and other mitochondrial diseases such as myoclonus epilepsy with ragged-red fibers (MERRF), neuropathy ataxia retinitis pigmentosa (NARP), and ataxias due to mitochondrial polymerase γ mutations.

Diagnostic Work-up/Tests

Screening patients for cerebellar ataxia due to CoQ_{10} deficiency should begin with routine blood tests including complete blood count, serum electrolytes, liver function tests, blood urea nitrogen, creatinine, lactate, and pyruvate. Nevertheless, blood lactate and pyruvate are often normal in patients with cerebellar ataxia and CoQ_{10} deficiency. Screening for proteinuria may reveal signs of nephrotic syndrome, particularly in infants with the multisystemic disease due to CoQ_{10} deficiency.

In most cases, CoQ_{10} deficiency has been diagnosed by muscle biopsy. In patients with the myopathic forms, elevated serum creatine kinase, and the coexistence of ragged-red fibers and increased lipid in muscle are clues to the diagnosis of CoQ_{10} deficiency, whereas in patients with the ataxic form, muscle morphology is minimally affected. Skin fibroblasts may show CoQ_{10} deficiency, particularly in the ataxic and infantile-onset forms, whereas serum or plasma measurements of CoQ_{10} are not reliable to diagnose CoQ_{10} deficiency.

Management

No treatment for the genetic defect is currently available. Patients often show dramatic clinical improvements or stabilization with high-dose oral coenzyme Q_{10} supplementation (up to 3000 mg daily in adults and 30 mg kg^{-1} day^{-1} in children).

Prognosis

Because ataxia with CoQ_{10} deficiency is a relatively novel syndrome, the long-term prognosis of patients is unknown; however, CoQ_{10} supplementation often produces clinical improvements suggesting that treatment may improve outcome.

See also: Ataxia; Co-enzyme Q_{10}; Friedreich's Ataxia and Variants; Myoclonic Epilepsy with Ragged Red Fibers (MERRF); Neurogenic Muscle Weakness, Ataxia, and Retinitis Pigmentosa (NARP).

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Ataxia with Isolated Vitamin E Deficiency

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Glossary

Ataxia – An inability to coordinate voluntary muscle movements.

Autosomal Recessive – Describes a trait or disorder requiring the presence of two copies of a gene mutation (one inherited from the mother and the other from the father) at a particular locus in order to express observable phenotype. The parents are usually asymptomatic.

Gene – The functional and physical unit of heredity passed from parent to offspring. Genes are pieces of DNA, and most genes contain the information for making a specific protein.

Gene mutation – Any alteration of a gene from its natural state.

Retinitis pigmentosa – Progressive degeneration of the neuroepithelium of the retina characterized by night blindness and progressive contraction of the visual field.

Vitamin – A general term for a number of unrelated organic substances that occur in many foods in small amounts and that are necessary in trace amounts for the normal metabolic functioning of the body. They may be water-soluble or fat-soluble.

Ataxia with Isolated Vitamin E Deficiency

Clinical Characteristics

Ataxia with vitamin E deficiency (AVED, OMIM 277460) is a very rare genetic neurodegenerative disorder, mostly detected in the Mediterranean populations. The disease is transmitted as an autosomal recessive trait. Clinical

features closely resemble those of Friedreich ataxia (FRDA) patients. However, the concomitant presence of specific neurological symptoms and very low levels of plasma vitamin E, in the absence of other clinical conditions commonly associated with fat malabsorption, can guide differential diagnosis. The neurological features include progressive gait and limb ataxia, dysarthria, lower-limb areflexia, loss of proprioceptive and vibration sense, and extensor plantar response. Frequently, the patients have head titubation (44%) and retinopathy (12%). The majority of the patients present the first neurological symptoms between 4 and 18 years of age. AVED patients rarely have cardiac involvement.

Electrophysiological examination shows normal motor and sensory conduction velocity (MCV–SCV) and normal muscle action potential (MAP) amplitude, while the sensory action potential is usually markedly decreased particularly in the lower limbs. Somatosensory evoked potentials demonstrate increased central conduction time and increased latencies at median and tibial nerves. Brain MRI findings include cerebellar atrophy and dilatation of the cisterna magna. Pathology studies demonstrated mild loss of Purkinje cells, atrophy of spinal sensory neurons, dying back-type degeneration of the posterior columns, neuronal lipofuscin accumulation in the third cortical layer of the cerebral cortex, thalamus, lateral geniculate body, spinal horns and posterior root ganglia, and retinal atrophy.

Biochemical Findings

The biochemical hallmark of the disease is a very low level of vitamin E in plasma, in the absence of intestinal fat malabsorption and abetalipoproteinemia. In fact, AVED patients have normal intestinal absorption of α-tocopherol (vitamin E) and normal incorporation into chylomicrons, but they have an impairment of the α-tocopherol incorporation into very low density lipoproteins (VLDL). In 1995, Ouahchi et al. demonstrated that AVED is caused by mutations in the gene coding for the α-tocopherol-transfer protein (*TTPA*). This cytosolic liver protein is able to select among the eight different dietary-derived vitamin E isomers (α,β,γ,δ tocopherols and α,β,γ,δ tocotrienols) and preferentially binds the RRR-α-tocopherol to VLDL proteins, which are then released into the circulation. Thus, the *TTPA* is responsible for the maintenance of normal vitamin E plasma concentrations. No universal normal range of plasma vitamin E concentration can be given, since it depends on the specific method used and varies between laboratories. In individuals with AVED, the plasma α-tocopherol concentrations are generally $<4\,\mathrm{mmol\,l^{-1}}$ ($<1.7\,\mathrm{mg\,l^{-1}}$). Since oxidation of α-tocopherol by air might invalidate test results, precautions should be taken soon after venipuncture to protect the blood sample from air and light. Levels of vitamin E in plasma of heterozygotes are generally within the normal range.

Molecular Genetics

The disease is caused by mutations in the *TTPA*, the gene encoding α-tocopherol transfer protein. Since 1995, when the genetic basis of the disease was elucidated, more than 50 AVED families and ~18 different mutations in the *TTPA* gene have been described. In North-African populations, the mutation most frequently responsible for the disease is the 744delA mutation, while in AVED families of North European origin, the 513insTT mutation has been often identified.

Sequencing the five exons and flanking intron sequences of *TTPA* genomic DNA detect mutations in more than 90% of individuals with AVED. Sometimes, mutations in intron sequences create a cryptic splice site that can cause abnormal splicing, leading to abnormal RNA transcripts and thus to abnormal proteins. These kinds of splice site mutations might be overlooked if sequencing is only done on the exon and flanking intron sequences, on the genomic DNA level. Most individuals are homozygous or compound heterozygous for one of the known mutations. For mutational screening, genomic DNA is extracted from blood samples using standard procedures. The DNA region corresponding to the five exons and to intron–exon boundaries of the *TTPA* gene is amplified by PCR, and direct sequence analysis of the PCR products is performed by automated sequencing system.

Natural History

The phenotype and disease severity vary widely between families with different mutations. Although age of onset and disease course tend to be more uniform within a given family, symptoms and disease severity can vary between siblings. AVED generally manifests in late childhood or early teens between 5 and 15 years of age. Individuals of Japanese descent with the H101Q mutation tend to manifest later between ~20 and 50 years of age. Initial symptoms include progressive ataxia, clumsiness of the hands, and loss of proprioception, especially of vibration and joint position sense. Handwriting deteriorates, and equilibrium in walking is impaired. In many individuals, cerebellar signs such as dysdiadochokinesia and dysarthria with a scanning speech pattern are present. One third of the individuals have a characteristic head tremor (head titubation). In some persons, psychotic episodes, intellectual decline, and dystonic episodes have been described. Most individuals become wheelchair bound because of ataxia and/or leg weakness between 11 and 50 years of age.

No clear genotype–phenotype correlations have been identified, except for two mutations: the 303T >G mutation that is associated with late onset (>30 years of age), mild course, and increased risk for pigmentary retinopathy (mainly described in individuals of Japanese descent); and the 744delA, associated with early onset, severe course,

and increased risk for cardiomyopathy (mainly observed in individuals of the Mediterranean or North African descent).

Management

The treatment of choice for AVED is lifelong high-dose oral vitamin E supplementation. Some symptoms (e.g., ataxia, mental deterioration) can be reversed if treatment is initiated early in the disease process. In older individuals, disease progression can be stopped, but deficits in proprioception and gait unsteadiness generally remain. With treatment, plasma vitamin E concentrations can become normal. Daily doses range from 800 to 1500 mg (or 40 mg kg^{-1} body weight in children).

The vitamin E preparations used are either the chemically manufactured racemic form (*all-rac*-α-tocopherol acetate) or the naturally occurring form (RRR-α-tocopherol). During vitamin E therapy, plasma vitamin E concentration should be checked at regular intervals (e.g., every 6 months), especially in children. Ideally, the plasma concentration of vitamin E should be in the high normal range. Vitamin E treatment should also be initiated in presymptomatic individuals (e.g., younger siblings of an index case), to prevent the onset of neurological deficits.

Genetic Counseling

Ataxia with vitamin E deficiency is an autosomal recessive disorder. The parents of an affected child are obligate asymptomatic heterozygotes and therefore carry one mutant allele. All children of heterozygotes parents have a 25% chance of being affected, a 50% chance of being asymptomatic carriers, and a 25% chance of being unaffected and not carriers. Carrier testing for at-risk family members is available on a clinical basis once the mutations have been identified in the proband.

The moderately lowered plasma vitamin E concentrations in heterozygotes are not sensitive enough to distinguish between heterozygous carriers and noncarriers. Because vitamin E treatment initiated in presymptomatic individuals can prevent the findings of AVED, testing of at-risk family members (particularly younger siblings of the proband) is appropriate.

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of the DNA extracted from fetal cells obtained by amniocentesis or chorionic villus sampling. Mutations in the affected family member must be identified before prenatal testing can be performed.

See also: Ataxia; Friedreich's Ataxia and Variants; Tocopherol Transfer Protein and Ataxia with Vitamin E Deficiency.

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Ataxia-Telangiectasia

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Glossary

ATM gene – Ataxia-telangiectasia mutated (ATM) gene, located on chromosome 11q23 and associated with AT. Functions to sense double-stranded DNA breaks and coordinates cell cycle checkpoints involved in DNA repair.

Choreoathetosis – Involuntary movements of the body characterized by a combination of chorea

(irregular, random, flowing movements) and athetosis (slower, writhing movements).
DNA cycle and repair – Processes which occur in a cell that lead to the replication and repair of damaged DNA.
Oculomotor Apraxia – Difficulty in the initiation of voluntary eye movements.
Purkinje Cells – Neurons in the cortex of the cerebellum which are GABAergic in nature.
Telangiectasias – Dilated blood vessels which appear as tiny, red 'spider veins' on the surface of the skin and in the corners of the eyes.

Definition and History

Ataxia-telangiectasia (AT), first described in 1926 by Syllaba and Henner, is a genetic, degenerative disorder that is characterized by progressive cerebellar ataxia, oculomotor apraxia, telangiectasias, immune dysfunction, and a predisposition to malignancies. Individuals are also abnormally sensitive to ionizing radiation such as X-rays and γ-rays. The gene responsible for the disorder is the ataxia-telangiectasia mutated (ATM) gene, and it is located on chromosome 11q23. Mutations in the gene lead to abnormalities in DNA function and stability. Inheritance is autosomal recessive. Although there is no current cure for the disorder, survival has greatly improved over the last 10–20 years.

Pathogenesis

There are a number of factors that contribute to the AT phenotype. The ATM gene encodes a protein that helps control cell division and DNA repair. Lack of this protein product causes cell instability, leading to increased DNA breakage and death. Previous studies have shown that chromosomal recombination rates in skin fibroblasts from patients with AT are higher than those from controls. Regulation abnormalities of the cell cycle have been found which interfere with DNA repair and proper downstream signaling pathways. Specifically, the G1-S checkpoint of the cell cycle has been found to be absent in AT cells, leading to aberrant DNA formation. In the central nervous system, loss of Purkinje and granule cells in the cerebellum leads to progressive ataxia.

Epidemiology/Risk Factors

AT is an inherited autosomal recessive disorder. The prevalence is 1 in 40 000 to 1 in 100 000 people worldwide. There is no specific cultural predisposition, and males and females are affected equally. Approximately 1% of the population in the United States is felt to be a carrier for AT. Carriers have been found to be at increased risk of developing cancer, particularly breast cancer, as compared to the general population. Carriers also may be at increased risk of developing heart disease and diabetes.

Clinical Features

Clinical signs of AT usually begin in early childhood (typically between ages 1 and 4 years) with delays in motor milestones, progressive ataxia, oculomotor apraxia, and the appearance of telangiectasias. Truncal ataxia tends to occur before appendicular ataxia. Oculomotor apraxia may precede the appearance of telangiectasias and is progressive in nature. The telangiectasias or 'spider veins' can appear in the corner of the eyes as well as on the surface of the ears and cheeks, and appear between 3 and 5 years of age. Although they are characteristic of the disorder, they may not be present. Diagnosis is based on clinical features including the progressive ataxia and oculomotor apraxia with supportive laboratory tests.

Progression of the ataxia usually leads to an inability to ambulate independently and the need for a wheelchair in late childhood or early teen years. Choreoathetosis, myoclonus, dystonia, and intention tremors can be seen in addition to the ataxia. The choreoathetosis is seen in the majority of individuals, while myoclonus and intention tremors are present in approximately 25% of individuals. Deterioration in muscle strength and development of contractures, particularly in distal musculature, occur as the disease progresses. Deep tendon reflexes may initially be present but are diminished or absent by late childhood. Overall, cognitive function is intact, although some report slowed motor and verbal responses or mild learning difficulties.

In addition to the progressive neurological and skin manifestations, individuals with AT are predisposed to infections and the development of malignancies. The immune system is weak, and recurrent sinopulmonary infections may occur. Approximately 38% of individuals also develop cancer. The most common types are leukemias and lymphomas. Acute lymphocytic leukemia is often seen in younger children with AT. Other types of cancers which have been reported include breast, ovarian, gastric, and skin. Individuals with AT are also more sensitive to ionizing radiation such as medical X-rays and γ-rays.

Differential Diagnosis

A thorough history, including family history, physical examination, neuroimaging, and laboratory studies are

all part of the evaluation of a child with ataxia. The early onset of AT and lack of features such as oculomotor apraxia and telangiectasias at initial presentation can make the diagnosis challenging. A diagnosis of cerebral palsy is often made in cases in which ataxia and dysarthria may be part of the clinical picture. Other diagnoses to consider include structural lesions, particularly of the cerebellum, vitamin, and metabolic deficiencies such as B12 and biotinidase, and genetic forms of ataxia. Included in the long list of inherited ataxias would be Friedreich's ataxia, ataxia with vitamin E deficiency (AVED), ataxia with oculomotor apraxia type I (AOA1), ataxia with oculomotor apraxia type 2 (AOA2), and infantile onset SCA (IOSCA). Lysosomal enzyme deficiencies and mitochondrial disorders would also be considered in the differential. An AT variant known as Nijmegen Breakage syndrome is not characterized by ataxia but it is associated with cell radiosensitivity and increased risk of infections. Important findings that would make AT less likely include a nonprogressive ataxia and severe mental retardation.

Diagnostic Studies

A number of supportive tests are available in the evaluation of a child with AT. Neuroimaging, laboratory and chromosomal studies, protein assays, cell stability assays, and gene testing can all be used to confirm the clinical diagnosis of AT. Brain magnetic resonance imaging (MRI) may be utilized to look for evidence of cerebellar atrophy and to rule out other structural lesions or processes. The α-fetoprotein level is elevated in over 95% of individuals with AT. Immunoglobulin levels may show a decrease in IgA levels as well as other immunoglobulins. Karyotyping should be done to evaluate for translocations, particularly 7;14, which are seen in AT. Lymphoblastoid cell lines may be established for immunoblotting to determine whether ATM protein is present or absent. Approximately 90% of individuals with AT have no detectable ATM protein, 10% have trace amounts, and 1% have normal levels but lack ATM protein kinase activity. Colony Survival Assay is an in vitro assay that determines survival of lymphoblastoid cells following irradiation. The test usually takes several months to complete. Sequencing of the ATM gene is clinically available and detects 90% of alterations of the gene.

Management

Although there is no cure, treatment of neurologic and other manifestations is possible to optimize survival and quality of life. Physical, occupational, and speech therapy are important in addressing the functional needs of the individual with ataxia, dysarthria, dysphagia, and progressive weakness.

Although there is a lack of formal clinical trials and data to support their use, agents which have been tried include vitamins and antioxidants. Specifically, vitamin E and α-lipoic acid have been used. Intravenous immunoglobulin (IVIG) also has been utilized in individuals with frequent infections. Proper nutrition is important in maintaining health and decreasing risk of infections.

Given the increased risk for developing malignancies, regular surveillance is important for early detection. Use of radiation should also be minimized and monitored, as standard doses may be deleterious or even lethal to patients with AT.

Prognosis

AT is a progressive disorder for which there is no cure at this time. However, survival continues to improve with better supportive therapy and management. Life expectancy is now past 25 years of age for many patients. There have been reports of individuals in their forties and fifties with AT as well. In older individuals, pulmonary failure seems to be a major source of morbidity and mortality.

See also: Ataxia; Athetosis; ATM Gene; Friedreich's Ataxia and Variants; Tocopherol Transfer Protein and Ataxia with Vitamin E Deficiency.

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www.atcp.org

Ataxin

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Glossary

Ataxin-1 – The protein involved in spinocerebellar ataxia type 1 (SCA1).
High-throughput yeast two-hybrid screen – A molecular biology technique used to discover protein–protein interactions in yeast.
PODs – PML oncogenic domains – nuclear domains, associated with the nuclear matrix, disrupted in human acute promyelocytic leukemia cells.
Polyglutamine disorders – A group of genetic disorders in which the mutation results in the expansion of a triplet sequence (CAG) that codes for the amino acid, glutamine; includes several of the SCAs as well as Huntington's disease among others.
Spinocerebellar ataxia – A term often used to describe a group of autosomal dominant neurodegenerative diseases characterized by progressive motor incoordination typically starting in mid-life.

Ataxin-1 Protein (*ATAXIN-1* Gene)

Ataxin-1 is the protein mutated in the autosomal dominant disease spinocerebellar ataxia type 1 (SCA1; OMIM 164400). *ATAXIN-1* is the gene encoding this protein situated on the chromosome 6p23. The specific mutation in SCA1 is a CAG trinucleotide repeat expansion within exon 8 of the *ATAXIN-1* gene. Because the repeat expansion occurs in the coding region of the gene and because CAG encodes for glutamines, the mutation results in a glutamine repeat expansion in the protein product. As such, SCA1 belongs to the family of polyglutamine repeat disorders. As in other polyglutamine diseases, a longer expansion results in earlier disease onset in patients (i.e., anticipation) and a worse severity of the disease.

Ataxin-1 is ubiquitously expressed. At a subcellular level, ataxin-1 is primarily localized to the nucleus in neurons including Purkinje cells, those neurons most affected by SCA1 toxicity. In peripheral tissue, ataxin-1 has been reported as being mainly cytoplasmic. Ataxin-1 demonstrates a molecular weight of ~100 kDa (with ~800 amino acids). The exact size is determined by the length of the glutamine repeat. In patients, the repeat length varies between 39 and 82 residues, with a tendency for the repeats to expand over generations. The instability of the repeat is especially pronounced with paternal transmission of the expanded allele. Even in normal individuals, the glutamine repeat shows variability in length (6–44 repeats). When the CAG repeat is long in asymptomatic individuals, it is usually interrupted by 1–3 CAT residues (trinucleotides that encode histidine), that presumably stabilizes these long alleles from expanding. The role of the normal polyglutamine tract is still a puzzle, given that the tract can be virtually nonexistent in other mammalian species (e.g., mouse ataxin-1 has only two glutamines).

The function of wild-type ataxin-1 is largely unknown. Because ataxin-1 is developmentally regulated (peaking in expression at postnatal day 14 in the mouse), ataxin-1 likely plays a developmental role, particularly as a transcriptional regulator. Despite the dearth of knowledge of ataxin-1's normal function, studies in genetically engineered mice suggest that SCA1 is predominantly a gain of function disease. This inference can best be summed up by the findings that transgenic or knockin mice with expanded ataxin-1 recapitulate the key features of this disease, while mice lacking SCA1 do not demonstrate ataxia or Purkinje cell degeneration. Indeed, ataxin-1 null mice are essentially indistinguishable from wild-type littermates by home-cage behavior. They do, however, display subtle defects on electrophysiological, behavioral, and locomotor assays. Some of these defects are presumed to occur because ataxin-1 serves a transcriptional role, modulating transcription affecting the dopaminergic pathway.

SCA1 transgenic and knockin mouse models have led to a better understanding of the pathology. They have revealed, for instance, the dual contributions of the expanded glutamine tract and mutant protein expression levels to toxicity. For example, knockin mice that express mutant ataxin-1 with 78 glutamines develop a mild phenotype – most likely because the life-span of the mouse is too short to allow for an accumulation of damage required for overt toxicity. However, knockin mice with a single copy of the *ataxin-1* gene expanded to encode 154 glutamine repeats ($SCA1^{154Q/2Q}$; Q = glutamine) display a robust, early-onset ataxic phenotype. In transgenic mouse and drosophila models, high expression of ataxin-1 with even a wild-type human CAG repeat length produces a mild version of SCA1.

SCA1 mouse models have also led to a detailed analysis of the pathology, which has been confirmed in the limited tissue available from human patients. For instance,

immunohistochemical studies on Purkinje cells show that ataxin-1, a protein that normally displays a diffuse nuclear staining pattern, relocates into a single ~2-μm structure called the nuclear inclusion that is thought to be a fibrillar proteinaceous aggregate. Recent studies suggest that inclusions form because ataxin-1 is misfolded and is poorly cleared by the ubiquitin–proteasomal proteolytic (UPP) system acting in concert with cellular chaperones. In fact, the evidence that the inclusions contain cellular components such as ubiquitin, proteasomal components of the proteasome, and chaperones suggested the role of misfolding and protein-clearance in the disease. In addition, the inclusions sequester ataxin-1 binding proteins. Although the role of inclusions is still debated, several studies suggest that it is the accumulation of soluble, misfolded ataxin, and not the inclusions per se, that causes toxicity. Inclusion formation and recruitment of chaperones have also been demonstrated in transfected cells. These inclusions can even form if wild-type ataxin-1 is overexpressed. The ataxin-1 inclusions are typically incorporated into the nuclear matrix associated with the PML oncogenic domains (PODs).

Ataxin-1 has several important domains or amino acid residues. It has a nuclear localization sequence on the C terminal domain that appears essential for toxicity; a self-aggregation domain – a region spanning residues 495–605 – that is important for dimerization (and aggregate formation); and a domain called the AXH (ataxin-1 and HMG-box protein 1). This domain (spanning amino acids 570–689) encompasses the self-association region, made up of several charged residues well-designed for protein–protein interactions and appears crucial for toxicity. This domain also has an oligonucleotide binding fold motif that might explain why ataxin-1 has a tendency to bind RNA. The binding to RNA has been shown to be inversely related to the length of the polyglutamine tract.

Ataxin-1 interacts with several proteins including LANP, 14–3–3, coilin, PQBP-1, SMRT, BOAT, capicua, RBM17, Gfi-1/senseless, Tip-60, and Sp1. Yet, other interactors have been identified by high-throughput yeast two-hybrid screening, but many of these are still largely poorly characterized. There is evidence to suggest that a significant amount of endogenous ataxin-1 is complexed to other proteins. There are at least two biochemically and functionally distinct complexes of ataxin-1. In the normal state, ataxin-1 is shared between these complexes. In the mutant state, expanded ataxin-1 drives the formation of one (defined by RBM17) at the expense of another (defined by capicua). The RBM17 complex appears to be toxic, given that excess RBM17 in SCA1 mouse models is toxic. The Capicua complex appears to be protective, given that overexpressing capicua thwarts degeneration. These interactions lead to the dissection of both the normal functions of ataxin-1 and a delineation of pathological intracellular pathways. Remarkably, many of these interactors appear to regulate gene expression. Thus, these interactions might help explain why transcriptional abnormalities are among the first phenotypic derangements to be noticed in mouse models of SCA1. In addition to these interactors, ataxin-1 also interacts with itself and a close homologue (ataxin-1-like; or atxnl-1). Indeed, wild-type ataxin-1 and atxn1-l protect against toxicity in the context of modulating the levels of these proteins genetically, presumably by competing with ataxin-1 for components of the complexes.

Ataxin-1 also undergoes several posttranslational modifications. As noted earlier, ataxin-1 is ubiquitinated, a modification involved in clearance. Ataxin-1 is sumoylated at multiple residues, although the precise role of this modification is still unclear. In addition, ataxin-1 undergoes phosphorylation. Phosphorylation at serine 776, appears to modulate binding to the protein 14-3-3, and regulates the stability of ataxin-1. In fact, ablating this phosphorylation renders expanded ataxin-1 incapable of causing toxicity. Intriguingly, RBM17 – the protein that defines the toxic ataxin-1 binding complex – has been shown to bind to ataxin-1 in a glutamine repeat dependent and phosphorylation dependent manner, suggesting that phosphorylation may act along with the glutamine expansion as an important mediator of toxicity. More recently, another phosphorylation site has been identified on serine 239. The significance of this phosphorylation and the kinase involved is unclear.

See also: Ataxia with Isolated Vitamin E Deficiency; SCA10; SCA11; Spinocerebellar Ataxias Genetics.

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Athetosis

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Glossary

Athetosis – Sinuous, slow, irregular, and involuntary movements affecting distal limbs.
Proprioception – Sense of position of joints.
Pseudoathetosis – Writhing finger and/or toe movements due to loss of proprioception.

Definition and History

The term athetosis ('without fixed posture') describes sinuous, slow, irregular and involuntary movements affecting distal limbs, particularly the arms. The term was coined by Hammond in the late nineteenth century, when describing a movement disorder in an alcoholic patient with onset following an episode of *delirium tremens*. Shortly afterward, Shaw also used the word athetosis to describe a similar sinuous movement disorder in a patient with cerebral palsy. The term has also been applied to movements seen in subjects with dysfunction of proprioception, but because the movements are a consequence of sensory abnormalities, this syndrome is called 'pseudoathetosis.' This latter term remains in the current medical literature, despite the sharp decline of the use of the term 'athetosis' in the last decades. The reason behind this decline is the realization that athetosis is better defined as dystonia occasionally associated with some degree of chorea. There are authors, however, who continue to advocate the usefulness of athetosis as a distinct type of hyperkinesia.

Etiology and Pathogenesis

Athetosis is usually associated with cerebral palsy caused by kernicterus, that is, lesions of the central nervous system due to severe jaundice in the new born. However, cerebral palsy of any etiology may cause this movement disorder. In the few patients who came to autopsy, there are reports of lesions in the putamen or caudate. (Please refer to the entry on Dystonia in this Encyclopedia for further details on the pathogenesis of athetosis).

In pseudoathetosis, the movements are thought to result from the inability of the fingers or toes to remain still because of the loss of proprioception. Traditionally, this movement disorder is associated with peripheral neuropathy. However, it may also result from central nervous system lesions causing impairment of sense of position. There are many reports of pseudoathetosis caused by lesions of spinal cord and, less commonly, thalamus. The causes listed in these reports are vascular lesions, B12 vitamin deficiency, and syringomyelia.

Epidemiology

There are no epidemiological studies of athetosis. It is possible to speculate, however, that it is becoming a much rarer condition nowadays. The main reason for the decline of its frequency is the improvement of obstetric care with the reduction of the number of cases of cerebral palsy. Traditionally, pseudoathetosis is considered as a rare condition. It is uncertain, however, if this is true since many patients may remain without diagnosis because of the lack of functional impairment caused by this movement disorders.

Clinical Features and Diagnostic Criteria

Athetosis is characterized by sinuous, slow, irregular, and involuntary movements affecting distal limbs, especially the arms. The phenomenology is usually characterized by a combination of dystonia and chorea, but myoclonus and spasticity are also common. Similarly, pseudoathetosis is characterized by slow, distal, writhing movements of the fingers or toes, which tend to worsen with the suppression of visual input. Invariably, these patients have proprioceptive sensory loss and often a Romberg sign. There are no formal diagnostic criteria for these conditions. However, a history of perinatal injury in athetosis and peripheral neuropathy or central loss of propriopception in pseudoathetosis are highly useful to make the diagnosis.

Differential Diagnosis

Athetosis and pseudoathetosis should be distinguished from other hyperkinetic movement disorders affecting distal limbs. Chorea is unpredictable; myoclonus has a shock-like nature, with a brief duration, usually less than 200 ms; and tremor is characterized by its rhythmic and oscillatory nature. The most important treatable condition with progressive athetosis is Wilson's disease, due to abnormal copper metabolism.

Diagnostic Work-Up

The investigation of patients with athetosis should follow the guidelines to work up patients suspected to harbor a secondary dystonia. Of note, all patients should undergo tests for Wilson's disease (serum ceruloplasmin, serum copper, 24 h urine copper, liver function tests, and search for Kayser–Fleischer ring) and magnetic resonance imaging of the brain. Focused attention should be placed on the basal ganglia. In patients with pseudoathetosis, electromyography and, in case it is normal, magnetic resonance imaging of the spinal cord and even the brain are useful.

Management

No treatment is required for pseudoathetosis since it does not cause significant functional impairment. The situation is different, however, in athetosis where many patients are significantly disabled by the dyskinesia. Unfortunately, as a rule it is often resistant to all available therapeutic options. A few patients may improve with levodopa, clonazepan, baclofen, anticholinergics, or tetrabenazine. Most of them, however, are refractory to clinical treatment and even surgical treatment has not been successful. There are recent reports describing failure or poor results of baclofen pump or deep brain stimulation of the globus pallidus internal in alleviating dyskinesias in patients with cerebral palsy.

Prognosis

As a manifestation of static encephalopathy, athetosis usually remains stable along the time. However, as well described in the literature of cerebral palsy, some patients may develop worsening of the movement disorder at later age. The course of pseudoathetosis depends on the underlying cause: if there is improvement of the proprioception, the movement disorder may also decrease.

See also: Wilson's Disease.

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ATM Gene

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Glossary

Antisense morpholino oligonucleotides – A molecule used to modify gene expression using antisense technology to block access of other molecules to specific sequences within nucleic acids.

Apoptosis – A process of programmed cell death which eliminates cells in an organized manner without releasing harmful substances into the surrounding area.

Ataxia – Loss of balance or dysfunction of neural pathways that coordinate movements; a neurological sign for loss of coordination of muscle movements.

Autosomal recessive – A genetic condition that appears only in individuals who have received two mutated copies of an autosomal gene, one copy from each parent.

Double strand break (DSB) – Damage in both strands of DNA double helix.

Leucine zipper – Protein structural motif in which repeats of leucines are evenly spaced every seventh residue in the helical region and involved in DNA binding and protein–protein interaction.

Protein Kinase – An enzyme that modifies proteins by chemically adding a phosphate group.

Radiosensitivity – The relative susceptibility of cells, tissues, organs, and organisms to the effects of radiation.

Telangiectasia – Abnormal dilation of capillary blood vessels.

ATM Gene

The ATM gene is defective in patients diagnosed with ataxia-telangiectasia (A-T). A-T is a rare autosomal recessive disorder characterized by progressive cerebellar ataxia, ocular motor apraxia, dilation of blood vessels (telangiectasia), immunodeficiency, elevated levels of serum α-fetoprotein, and by an increase susceptibility to cancer, especially leukemia/lymphoma. A-T patients are usually diagnosed in their first few years of life and are usually wheelchair bound by age 10. The incidence is ~1 per 40 000–100 000 live births. At the cellular level, A-T is characterized by chromosomal instability, defects in cell-cycle checkpoint, premature senescence, accelerated telomere shortening, elevated oxidative damage, and extreme sensitivity to ionizing radiation and radiomimetic drugs.

In 1988, ATM was mapped to chromosome 11q22–23 by genetic linkage studies using large numbers of A-T families. However, it was not until 1995 that the gene was finally cloned by positional cloning, thereby offering a way to understand the disorder and develop possible therapeutic strategies (see **Figure 1**). Sequence analysis revealed that this gene includes about 150 kb of genomic DNA and encodes a major transcript of ~13 kb with a 9168 bp open reading frame (ORF) consisting of 66 exons. The main promoter of this gene is bidirectional and is shared by ATM and another gene, E14/NPAT/CAND3, whose function is not fully understood. The amino acid sequence of the ATM gene contains 3056 residues which results in an ~350 kDa protein that is localized mainly in the nucleus of all cells.

This ubiquitously expressed large protein belongs to the protein family of phosphatidylinositol 3-kinase (PI3K)-related protein kinases (PIKKs), which includes mammalian target of rapamycin (mTOR/FRAP), ATM-and-Rad3-related protein (ATR), TRAF and TNF receptor associated protein (TTRAP), DNA-dependent protein kinase catalytic subunit (DNA-PKcs) and the recently identified human homolog of *C. elegans* SMG1. All of these proteins are involved in cellular responses to DNA damage and some of them play regulatory roles in cell-cycle progression and/or damage induced cell-cycle checkpoints. The catalytic PI3 kinase domain of PIKK family members consists of about 300 amino acids located near the C-terminal end of the protein and is flanked by a domain called FAT (FRAP (mTOR), ATM, TTRAP) and a FATC (FAT at C-terminal) domain (**Figure 2**). The functions of the FAT and FATC domains are still largely unknown. Several regions distant from the PI3 kinase domain have been identified to have protein-binding activity. Recently Tip60 histone acetylase, which is essential for ATM activation, was shown to bind to the FATC domain of ATM.

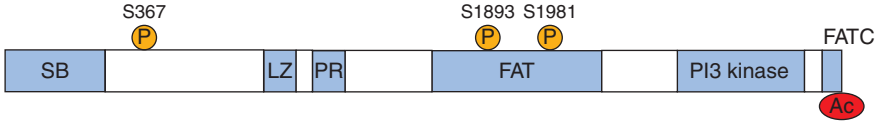

Figure 1 Schematic representation of ATM protein. Domains are shown in boxes. ATM autophosphorylation sites and acetylation site are also shown. SB, substrate binding region (1-246 a.a.); LZ, leucine zipper (1218-1238 a.a.); PR, proline rich (1373-1382 a.a.); FAT (1961-2566 a.a.); PI3 kinase (2712-2962 a.a.); FATC (3024-3056 a.a.).

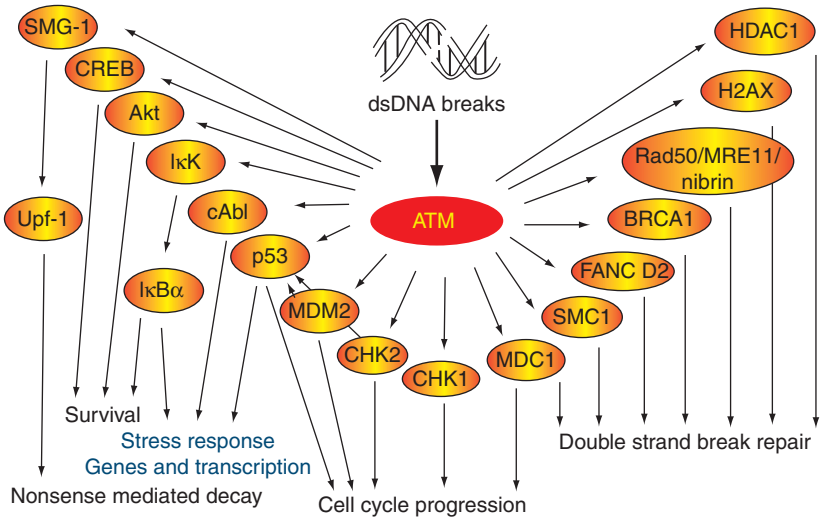

Figure 2 ATM targets.

At the N terminus, residues 1–246 act as binding sites for NBS, p53, and BRCA1 and are required for their activation in response to DNA damage (**Figure 2**). Regions within residues 811–1283 have been reported to bind β-adaptin, and a proline rich region (residues 1373–1382) has been shown to interact with c-Abl tyrosine kinase through its SH3 domain. While a putative leucine zipper motif at codons 1218 to 1238 has been identified in the ATM protein, this region has not yet been shown to be a site of protein–protein interaction and appears not to mediate the formation of ATM dimers.

ATM Activation and Functions

The complexity of the A-T disease symptoms is perhaps best reflected by the multitude of cellular roles played by the ATM protein. In vitro, ATM exists as an inactive dimer in undamaged cells. In this configuration, the FAT domain of one ATM monomer conceals the kinase domain of the other monomer, helping to keep ATM inactive. Following DNA damage, in particular in the form of double strand breaks (DSBs), ATM dimers are dissociated and the ATM monomers autophosphorylate each other on amino acid residues S1981, S367, and S1893 (**Figure 1**). In addition, acetylation is mediated by Tip60 acetylase; this is also required for the ATM protein to become fully active. Following the binding of activated MDC1 to DSB sites, the sensing proteins MRE-11/RAD50/NBS1 (MRN complex) are recruited and they bind DNA as a heterotetramer, to hold the two broken DNA ends together. This binding of the MRN complex is thought to recruit ATM to the site of the DSBs to form an expanding protein complex around the broken DNA ends. In the presence of DSB damage, activated ATM phosphorylates and transactivates a variety of protein targets involved in stopping the cell cycle, to allow DNA repair. These ATM targets include: p53, SMC1, FANCD2, H2AX, BRCA1, and Chk2 proteins (**Figure 2**). This activation process can be reset by the dephosphorylation of ATM by protein phosphatase 2A (PP2A), which also plays a pivotal role in modulating ATM's function(s) since inhibition of a PP2A-like protein phosphatase activity by the specific inhibitor okadaic acid (OA) induces the rapid accumulation of phosphorylation of ATM on Ser 1981. These results suggest that constitutive dephosphorylation of ATM by PP2A maintains ATM in an inactive state. This inactivation apparently serves to prevent unnecessary activation of cellular functions in the absence of genotoxic stress.

ATM Mutations and Heterozygous Carriers

Most A-T patients are compound heterozygotes, that is, they carry different paternal and maternal mutations in the ATM gene. Over 500 unique ATM mutations have been reported to date, and mutations are detected over the entire coding region of the gene, with no hot spots clearly identified. Approximately 85% of these mutations are predicted to produce premature termination codons (nonsense mutations), or secondary termination of translation caused by frameshifts mutations, insertions, deletions, or abnormal splicing defects. Thus, the majority of A-T patients produce either an unstable truncated ATM protein or none at all. Missense mutations account for <10% of all reported mutations in A-T patients and occasionally have small amounts of ATM protein and some of these have milder disease.

The frequency of A-T heterozygotes is estimated to be ∼1%, and heterozygotes display decreased levels of ATM (∼40–50%) and exhibit reduced ATM kinase activity. In addition, previous reports suggest that A-T carriers have a 4-fold increase risk for breast cancer and exhibit a slightly increased radiosensitivity over healthy controls. However, heterozygotes display no apparent A-T phenotype. Furthermore, the spectrum of ATM mutations observed in heterozygotes with breast cancer and no family history of A-T is very different from the mutations identified in individual with A-T.

Conclusion

ATM plays a critical role(s) in multiple biological pathways. Understanding the roles of ATM will lead us to explain how a single gene defect in A-T patients can cause so many deleterious symptoms in different organ systems. Within the 10 years after ATM gene was cloned, over 700 potential ATM protein targets for phosphorylation have been identified. However, in order to make more definitive functional predictions, we also need to understand the mechanistic and physiological relevance of phosphorylation of targets by ATM and other posttranslational modifications. At present there is no therapy available to cure or prevent the neurological deterioration of A-T. Aminoglycosides that help to read through premature stop codons have been reported to increase functional ATM protein levels in cells from A-T patients with nonsense mutations. Recently, it was reported that antisense morpholino oligonucleotides targeted to specific splicing mutations can restore normal splicing and produce functional ATM protein. It is also possible to alleviate some of the symptoms associated with immunodeficiency with intravenous γ-globulin treatment. Antioxidants reduce DNA damage from oxidative stress. Insight into ATM interacting proteins and ATM substrates, functional dissection of the ATM molecule and screening mutations may assist in the development of new and effective therapies for A-T.

See also: Ataxia; Ataxia-Telangiectasia.

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Atrophin-1

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Glossary

Aggregates – Stable accumulation of a protein in a specific area of the cell, usually due to the self interaction property of the protein.
Chromatin – Three-dimensional complex between the DNA and a number of different proteins that modify the accessibility of the genetic sequence and thus gene transcription.
Dentatorubral-pallidoluysian atrophy (DRPLA) – A neurodegenerative disorder of the central nervous system, causing motor deficits and dementia.
Domain – Part of a protein having a well-defined three-dimensional structure often emerging from a conserved amino acidic sequence.
Drosophila melanogaster – Fruit fly, the most amenable organism for genetic research, which is widely used to model neurodegenerative conditions.
Polyglutamine diseases – A family of neurodegenerative diseases having a common molecular origin in the expansion of glutamine stretches in the proteins causing the pathologies.

Definition and History

The human *atrophin-1* (*ATN1*) gene was identified in 1994 in the search for a candidate gene responsible for dentatorubral-pallidoluysian atrophy (DRPLA), a neurodegenerative disorder with genetic anticipation, characteristic of an unstable expansion of trinucleotide repeats. Indeed, the expansion of a CAG repeat tract within the coding sequence of *ATN1* (chromosomal location: 12p13.31) was identified in a series of DRPLA patients. In such individuals, the (ATN1) protein is expected to carry an abnormally long polyglutamine (polyQ) domain, classifying DRPLA as a polyglutamine disease. This group of autosomal dominant disorders includes Huntington disease (HD) and a number of spinocerebellar ataxias (SCAs). They have common features such as progressive neurodegeneration, ubiquitous expression of their respective gene product, and intracellular accumulation of a polyQ-expanded fragment of the protein into neuronal aggregates (cytoplasmic or nuclear). The latter characteristic is the hallmark of polyglutamine diseases. Nevertheless, the brain regions that are found degenerated in post-mortem DRPLA, HD, and SCAs patients are distinguishable as are their clinical features.

A trinucleotide expansion of *ATN1*, identical to the one found in DRPLA patients, was identified in a large family of African American with Haw River Syndrome (HRS), a neurological disorder with clinical and neuropathological features similar to those in DRPLA patients. Thus, DRPLA and HRS correspond to the same disease.

Epidemiology

DRPLA has been reported to occur mostly in Japan with an estimated frequency of 0.2–0.7 in 100 000 individuals. Remarkably, individuals with 20–35 CAG repeats, a mutable normal allele, are more common in the Japanese population in comparison with the Caucasian people. DRPLA is not exclusive to Japan, because few cases have been described in Europe (Portugal) and North America. Studies of two intragenic SNPs (single nucleotide polymorphisms) in introns 1 and 3 of *ATN1* have led to the conclusion that a founder DRPLA haplotype of Asian origin was introduced in Portugal to account for the high incidence of this disease in that country. Most cases recorded in Asian, Caucasian, and Afro-Americans can be traced to three haplotypes, one for each ethnic group.

Diagnosis Work-up/Tests

The diagnosis of DRPLA relies on the description of appropriate clinical features, a positive family history, and on the identification of an abnormally long CAG repeat tract within the *ATN1* gene. Molecular genetic testing is clinically available and corresponds to either a polymerized chain reaction (PCR) analysis of the CAG expansion or a Southern-blot analysis, when PCR is problematic.

Molecular Genetics

The CAG repeat length for the *ATN1* gene ranges from 6 to 35 CAG in unaffected individuals and from 48 to 93 in DRPLA patients, with a significant negative correlation between the length of the CAG repeat and the age of onset. Moreover, the clinical features of DRPLA, like those of SCA3, are influenced by the dosage of the expanded *ATN1* allele. This contrasts with HD, in which, patients homozygous for the pathogenic allele are clinically indistinguishable from heterozygous ones. Studies of CAG repeat size from single sperm DRPLA patients have revealed the amazing instability of the *ATN1* trinucleotide repeat, which displays a high variation in size compared with other polyglutamine diseases such as SCA3, HD, and spinal and bulbar muscular atrophy. In agreement with this observation, the genetic anticipation on the paternal transmission of DRPLA is the most prominent among CAG repeat diseases.

Molecular Aspects

The ATN1 protein is a 1185-amino acid polypeptide with an apparent molecular mass of approximately 200 kDa. It is

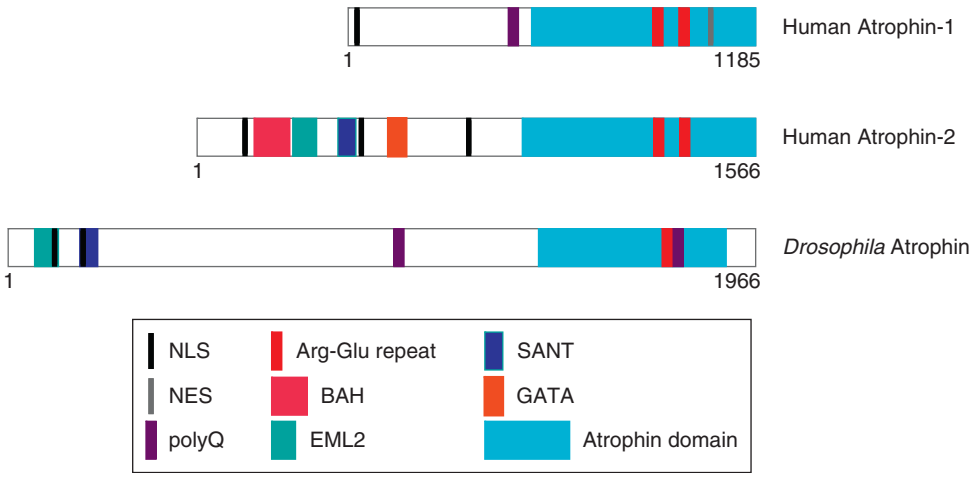

Figure 1 Protein architecture of Atrophins. Human Atrophin-1 and *Drosophila* Atrophin contain respectively one and two polyglutamine region (polyQ, purple box). The N-terminus of human Atrophin-2 is homologous to MTA-2, containing BAH, ELM2, SANT, and GATA domains (pink, grey blue, dark blue and orange box, respectively). The N-terminus of *Drosophila* Atrophin contains both an EML2 and a SANT domain. The C-terminus region common to both human and *Drosophila* Atrophins (light blue box) is the Atrophin domain. Human Atrophin-1 contains both a NLS (dark box) and a NES (grey box), while human Atrophin-2 and *Drosophila* Atrophin have respectively three and two NLS but no NES. NLS: Nuclear Localization Signal; NES: Nuclear Export Signal; BAH: Bromo Adjacent Homology; ELM2: Egl-27 and MTA-1 homology 2; SANT: SWI3, ADA2, N-CoR and TFIIIB Bd″ domain; GATA: DNA-binding domain that recognizes a six base-pair sequence with a GATA core.

ubiquitously expressed and detected both in the nuclear and cytoplasmic compartments of all cells analyzed so far. ATN1 is expected to shuttle between these two compartments, since it contains both a nuclear localization signal (NLS) and a nuclear export signal (NES). Interestingly, the cleavage of ATN1 occurs naturally and truncated fragments containing the expanded polyQ tract, but missing the NES, accumulate into the neuronal nuclei of animal models and in the human DRPLA brain tissue. This suggests that ATN1 toxicity is confined to the nucleus.

Human and mouse genomes have two *atrophin* genes: *ATN1* and *Atrophin 2* (*ATN2*), also called Arg–Glu repeat-encoding (*Rere*). Atrophin 2 (ATN2) was first described as an ATN1-related protein that physically interacts with ATN1, through a RERE repeat domain. The *ATN2* locus encodes two distinct polypeptides: a short (ATN2S) and a long (ATN2L) version of ATN2, the latter possessing additional conserved domains in the N-terminal region such as the BAH, ELM2, SANT, and GATA. These domains are disposed in a similar configuration to those found in MTA-2, a protein that contributes to the formation of the NURD (nucleosome remodelling and histone deacetylation) complex, a chromatin remodeling entity that represses transcription. ATN1 lacks these domains and resembles ATN2S more, the two proteins sharing 67% of homology in their C-terminal region (see **Figure 1**).

The *Drosophila* genome has a single *Atrophin* (*Atro*) gene that encodes a protein resembling full-length human ATN2 plus two polyQ motifs. Genetic studies in *Drosophila* have revealed that *Atro* acts as a co-repressor in several developmental processes such as the segmentation of the embryo, planar cell polarity, and imaginal disc patterning via the negative regulation of the EGFR (epidermal growth factor receptor) signaling pathway.

Although, in *C. elegans*, the product of *egl-27* gene has been described as an Atrophin orthologue, it resembles rather the MTA genes, lacking the most typical C-terminal domain of Atrophins.

Several lines of evidence indicate that the misregulation of transcription is the molecular mechanism underlying the pathogenesis of DRPLA. First, studies of the *Drosophila* Atro orthologue indicate that it participates in the developmental process acting as a co-repressor of transcription, via a direct interaction with well-known transcriptional repressors. Second, human ATN1 has been shown to physically interact with the nuclear receptor of the TLX family and with the transcriptional repressors ETO/MTG8 to ensure proper repression of their specific target genes. Third, a series of co-repressor factors such as Sin3a, Mi2, and HDAC colocalize with polyQ-expanded ATN1 nuclear aggregates. Furthermore, human ATN1 was recently described to operate as a potent transcriptional activator, demonstrating that the contribution of ATN1 to transcriptional regulation is rather complex and requires further investigations.

Little is known, however, about the consequences of polyQ expansion on ATN1 function. In one report, polyQ-expanded ATN1 was described to interact with the cAMP response element-binding protein (CREB)-binding protein (CBP), resulting in the suppression of CREB-dependent transcriptional activation and reduced neuronal survival and plasticity.

Animal Models of DRPLA

Mice expressing human ATN1 with an expanded polyQ domain exhibit ataxia, tremors, seizures, and premature death, a phenotype similar to the juvenile form of human DRPLA. Such animals have revealed the existence of nuclear fragments (120 kDa) of mutant ATN1, whose abundance increased with age and phenotype severity. This is in agreement with other reports that established that these fragments are particularly toxic and may underlie the pathogenesis of the disease. In addition, DRPLA mice exhibited age-dependent intergenerational and somatic instabilities of expanded CAG repeats similar to those observed in DRPLA patients.

A DRPLA Drosophila model, which relies on the expression of human or *Drosophila* polyQ-expanded Atrophins in fly neurons, can reproduce several characteristics of DRPLA disease: nuclear aggregates of polyQ containing Atrophin proteins, progressive degeneration of neurons, locomotor defects, and reduced viability. Recent data indicate that the misregulation of autophagy, a cellular mechanism that controls cell homeostasis, could account for the degeneration observed in the DRPLA fly model.

See also: Apraxia: Upper Limb; Ataxia with Isolated Vitamin E Deficiency; Ataxin; Bradyphrenia; Brainstem Reticular Myoclonus; Chorea–acanthocytosis; Choreiform Disorders; Cortical Myoclonus; Dentatorubropallidoluysian Atrophy; Huntington, George; Huntington's Disease: Genetics; Myoclonus; Myoclonus, Animal Models; Myoclonus, Epileptic; Palatal Myoclonus; Pseudoathetosis; SCA2; SCA3, Machado–Joseph Disease; SCA4; SCA5; SCA6; SCA8; SCA10; SCA12; SCA13, 14, 15, and 16; SCA17; Senataxin; Tocopherol Transfer Protein and Ataxia with Vitamin E Deficiency; Trinucleotide Repeat Disorders; Western Blot.

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Autonomic Dysfunction

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Glossary

Autonomic failure – Failure of the autonomic nervous system results in orthostatic and postprandial hypotension, bladder and bowel motility disturbances, impaired thermoregulation, anhidrosis and sexual dysfunction.
Autonomic synucleinopathies – Autonomic failure is a prominent feature of the LB disorders and MSA. These diseases are caused by accumulations of the protein α-synuclein in intracellular inclusions in neurons, glial cells. Thus the moniker autonomic synucleinopathies.
Lewy body (LB) disorders – LB are characteristic cytoplasmic eosinophilic neuronal inclusions first described by Frederic Heinrich Lewy in 1912. The LB disorders include three distinct but overlapping phenotypes: PD, DLB, and PAF. Autonomic dysfunction is a major feature of all three phenotypes.
Multiple system atrophy (MSA) – MSA is a term introduced by Graham and Oppenheimer in 1969. MSA includes disorders previously known as sporadic olivopontocerebellar atrophy (OPCA), with predominant cerebellar symptoms, striatonigral degeneration (SND), with predominant parkinsonian features, and the Shy–Drager syndrome (SDS), with predominant autonomic involvement.
Pure autonomic failure (PAF) – PAF was first described by Bradbury and Eggleston in 1925 as idiopathic postural hypotension. It is a sporadic, adult onset, slowly progressing, neurodegenerative disorder that is mostly confined to peripheral autonomic neurons. Although PAF is not a movement disorder, neuropathological data showing the presence of LB suggest a close connection with PD.

Introduction

The autonomic nervous system innervates almost all organs of the body. Impaired autonomic innervation results in characteristic clinical signs and symptoms

according to the affected viscera. These include orthostatic and postprandial hypotension, bladder and bowel motility disturbances, impaired thermoregulation, anhidrosis, and sexual dysfunction.

Disabling autonomic failure is the hallmark of two of the most prevalent neurodegenerative diseases: the *Lewy body disorders*, which includes Parkinson's disease (PD), dementia with Lewy bodies (DLB), and pure autonomic failure (PAF), and *multiple system atrophy* (MSA), which includes a parkinsonian and cerebellar phenotype. Both the LB disorders and MSA are caused by abnormal intracellular deposits of the protein α-synuclein; hence, the moniker *autonomic synucleinopathies* has been proposed to describe them.

Synucleinopathies can present clinically either with a movement disorder, cognitive impairment, or autonomic failure. As the disease progresses, these features are usually combined. There is, however, one synucleinopathy, PAF, in which involvement of the autonomic nervous system is the sole clinical feature (**Table 1**).

The LB Disorders

The LB disorders get their name from the characteristic cytoplasmic eosinophilic neuronal inclusions first described by Frederic Heinrich Lewy in 1912 found in the brain and peripheral autonomic neurons of affected patients. It is postulated that PD, DLB, and PAF are three different but overlapping phenotypes of a single neurodegenerative disorder, in which α-synuclein accumulates in LB. In patients with PD, the neurodegenerative process occurs mostly in the substantia nigra and other brain stem nuclei and to a lesser extent in peripheral autonomic neurons. Clinical findings are dominated by motor impairment with varying degrees of autonomic involvement. In DLB, there is extensive cortical degeneration as well as involvement of brain stem nuclei and autonomic ganglia, the clinical picture is dominated by severe cognitive impairment, although patients also have parkinsonian features and autonomic impairment. In PAF, the neurodegenerative process is mostly restricted to peripheral autonomic neurons, and autonomic failure is the sole clinical finding. These three distinct but overlapping phenotypes are likely the result of the specific anatomical distribution of the neurodegenerative process and sequential accumulation of LB. Clinically, all three LB disorders entail loss of postganglionic autonomic neurons and characteristic autonomic failure.

Parkinson's Disease

Around 90% of patients with PD have one or more symptoms of autonomic failure. These include constipation, urinary urgency or incontinence, orthostatic or postprandial lightheadedness and syncope, heat intolerance, and erectile dysfunction in men.

In most patients with PD, clinically significant autonomic failure occurs late, but there is a subset of PD patients in whom autonomic failure occurs early on in the disease process.

In addition to the prominent neuronal loss in the substania nigra, which accounts for the movement disorder, other brainstem nuclei including the dorsal motor nucleus of the vagus and locus coeruleus are affected in PD. These abnormalities together with degeneration of postganglionic autonomic nerves and enteric neurons explain the autonomic dysfunction in PD.

Cardiovascular abnormalities

Orthostatic hypotension (OH) is defined as a fall of at least 20 mmHg systolic and 10 mmHg diastolic BP accompanied by symptoms of cerebral hypoperfusion within 3 min of standing. In the autonomic synucleinopathies, OH is typically caused by impaired sympathetically mediated vasoconstriction in the systemic circulation, a reflex response that normally compensates for the gravitational fluid shifts to the lower body when in the upright position

Table 1 Neuropathological and phenotypic characteristics of the autonomic synucleinopathies

	MSA	*PD*	*DLB*	*PAF*
Neuropathology				
Glial cytoplasmic inclusions	+++	–	–	–
LB in substania nigra	–	+++	+	–/+
LB in cortex	–	+	+++	–/?
LB in autonomic ganglia	–	+	+	+++
Clinical phenotype				
Autonomic failure	+++	+/–	+	+++
Movement disorder	+++	+++	++	–
Cognitive impairment	–/?	+/++	+++	–

MSA, multiple system atrophy; PD, Parkinson's disease; DLB, dementia with Lewy bodies; PAF, pure autonomic failure; LB, Lewy bodies. + denotes presence and – denotes absence. Number of + denotes severity: +++, severe; ++, moderate; +, mild.

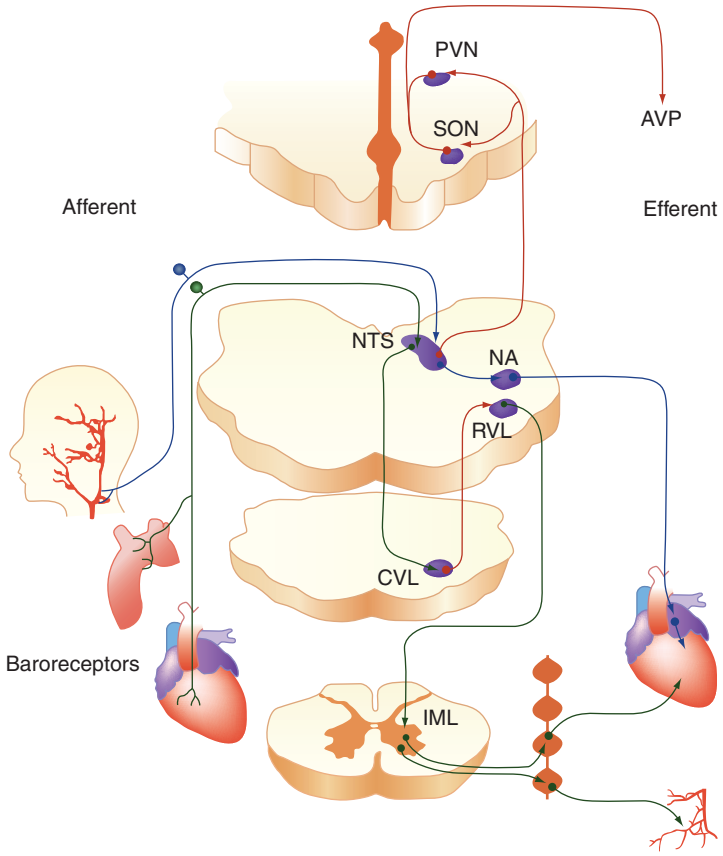

Figure 1 A schematic diagram of the baroreceptor reflex. The baroreflex is a negative feedback loop that regulates arterial BP. Arterial baroreceptors are located in the walls of the carotid sinus, aortic arch, and coronary vasculature and relay sensory information to the CNS through the glossopharyngeal (IXth) and vagus (Xth) nerves. These afferent neurons have their cell bodies in the petrosal (IXth) and nodose ganglia (X). The first synapse of the baroreflex is in the medulla, at the nucleus tractus solitarii (NTS), where baroreceptive information is integrated with inputs from other cardiovascular brain centers including the area postrema. Excitatory inputs project from the NTS to neurons in the caudal ventrolateral medulla (CVL). In turn the CVL provides an inhibitory influence to the rostroventrolateral medulla (RVL), which contains pacemaker neurons that generate sympathetic tone. RVL neurons project caudally through the spinal cord to synapse with preganglionic sympathetic neurons in the IML column. Axons from preganglionic sympathetic neurons leave the spinal cord to synapse in peripheral ganglia with postganglionic sympathetic neurons, which release norepinephrine at target organs. This results in arteriolar vasoconstriction, venoconstriction, tachycardia, and an increase in cardiac contractility. Parasympathetic tone is also modulated by the baroreflex. Projections from the NTS to the nucleus ambiguus (NA) excite preganglionic cardiac parasympathetic nerves. In addition, neurons in the NTS project rostrally to the supraoptic (SON) and paraventricular nuclei (PVN) of the hypothalamus and control vasopressin (AVP) release. An increase in systemic BP stretches arterial baroreceptors and increases the firing rate of afferent fibers. This activates NTS and CVL neurons, which in turn inhibits RVL neurons and 'withdraws' sympathetic outflow. Activation of the NTS also results is activation of the NA and an increase in parasympathetic outflow together with inhibition of vasopressin secretion. The end result is systemic vasodilatation, bradycardia and a decrease in cardiac contractility, which restores BP back to 'baseline' levels. In general, sympathetic withdrawal is accompanied by parasympathetic activation and vice versa. Sympathetic activation to different organs is not homogenously distributed and depends on the stimuli and afferent pathways involved. For example, mental stress induces sympathetic activation and increases BP, but causes vasodilatation in the forearm vasculature.

(**Figure 1**). Around 40% of patients with PD have OH. In patients with PD who have OH, beat-to-beat recordings of BP and heart rate during prolonged upright tilt reveal a progressive decline in BP with a smaller than normal increase in heart rate (**Figure 2**). If cerebral perfusion is significantly reduced syncope occurs. BP recordings during the Valsalva maneuver are also characteristically abnormal. The normal overshoot in BP after release of the strain (i.e., phase IV) is absent (**Figure 3**). This characteristic profile distinguishes OH due to autonomic failure from OH due to other causes, such as dehydration.

OH in PD is related to the duration and severity of the disease and is often worsened by treatment with levodopa and dopaminergic agonists. However, neither of these drugs is the primary cause of OH in PD.

Gastrointestinal abnormalities

Impaired gastrointestinal motility is the most frequent autonomic problem in PD. LB have been found in neurons in the Auerbach and Meissner plexuses throughout the gastrointestinal tract, from the esophagus to the colon. *Excessive drooling*, common in patients with PD, is caused

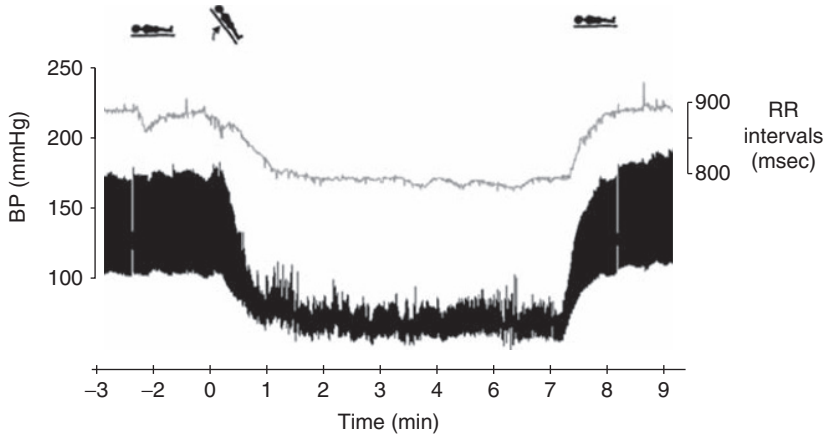

Figure 2 Beat-to-beat BP and electrocardiographic RR intervals during passive head-up tilt in a patient with autonomic failure. Note hypertension when supine and a precipitous fall in BP upon head up tilt. There is little shortening of RR intervals despite the pronounced fall in BP. Figurines denote posture.

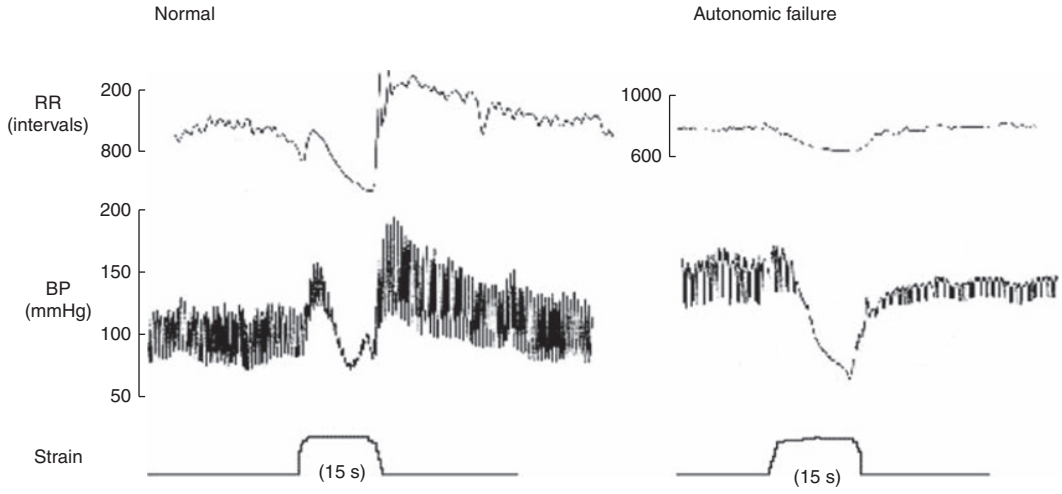

Figure 3 Beat-to-beat BP and electrocardiographic RR intervals during a Valsalva maneuver in a patient with autonomic failure and a healthy control. Note the absence of BP 'overshoot' after release of the strain in the patient with autonomic failure.

by a decrease in swallowing frequency rather than increased production of saliva. Treatment with anticholinergics is ineffective. Botulinum toxin injections in the salivary glands reduce drooling, but it increases the risk of dysphagia as the toxin diffuses into nearby muscles.

Dysphagia occurs in up to 50% of PD patients and is related to the severity of the disease. All three phases of swallowing: buccal, pharyngeal, and esophageal can be affected. Dysphagia is often more severe during an 'off' period and improves when the dose of levodopa becomes effective again. This suggests that impaired supranuclear control of oropharyngeal muscles may account for the abnormal swallowing in PD. Swallowing studies can be helpful in defining the phase of swallowing that is most affected and if there are silent aspirations. Soft diets and eating only during 'on' times help most types of dysphagia and reduce the risk of aspiration. Gastrostomy tubes and jejunostomies are a last resort but can be beneficial to allow adequate food, fluid, and medication intake.

Nausea and vomiting are common side effects of treatment with levodopa and direct dopaminergic agonists caused by stimulation of dopamine receptors in the area postrema of the brainstem located outside the blood–brain barrier. Carbidopa, a reversible inhibitor of Dihydroxyphenylalanine (DOPA) decarboxylase that prevents dopamine formation outside the brain effectively prevents nausea and vomiting associated with levodopa treatment. Domperidone, a dopamine antagonist with particular affinity for the D_2 subtype receptors in the peripheral nervous system is used successfully to reduce these symptoms.

Delayed gastric emptying is frequent in PD, resulting in early satiety, nausea, and abdominal distension. Delayed gastric emptying can also affect the clinical response to

levodopa. Delayed gastric emptying slows the delivery of levodopa into the absorptive sites of the duodenum and reduces its bioavailability, which leads to levodopa response fluctuations. Patients who experience motor fluctuations have been shown to have greater gastric retention 1 h after eating a meal than patients without fluctuations. Direct delivery of levodopa into the duodenum can markedly improve motor fluctuations. Frequent, small meals are recommended as a first line therapy.

Muscarinic receptor agonists such as bethanechol and carbachol produce a prokinetic effect by stimulating M3 receptors in intestinal smooth muscle. Unfortunately, their symptomatic benefit is limited at best and side effects such as nausea, vomiting, increased salivation, abdominal cramping, diaphoresis and flushing are common. D_2 receptor blockers also increase gastric motility. Metroclopramide, the most effective, cannot be used as it readily crosses the blood–brain barrier and worsens parkinsonism. Domperidone, which acts mostly on peripheral dopamine receptors, is an effective prokinetic agent but is not available in the US. Serotonin-4 receptor agonists such as cisapride and tegaserod stimulate the release of acetylcholine from enteric neurons and can improve gastric motility. Both agents were removed from the market in the United States as they prolong electrocardiographic QT interval.

Constipation is the most frequent autonomic problem in patients with PD. Loss of enteric and extrinsic parasympathetic neurons disrupt the normal peristaltic contractions of smooth intestinal muscle. Thus, colonic motility is reduced and stool transit time is prolonged, reducing the frequency of defecation. Pelvic floor dyssynergia and failure to relax or paradoxical contraction of the puborectalis muscle may also contribute to abnormal defecation. Megacolon and intestinal pseudoobstruction have been reported in PD. Patients should be encouraged to drink at least eight glasses of water a day, avoid low fiber foods such as baked goods and bananas, include high fiber raw vegetables in two meals per day to stimulate the gastrocolic reflex and increase physical activity. If necessary, stool softeners (e.g., docusate) at mealtimes may be used. Ten to 20 g of lactulose per day may also be beneficial in some cases. Discontinuing anticholinergics may increase bowel motility. Laxatives and weekly enemas may be required as part of an overall bowel regime. Treatment with mosapride, a serotonin-4 agonist and partial serotonin-3 antagonist, can improve constipation in PD. It also acts as an antiemetic by blocking serotonin receptors in the chemoreceptor trigger zone. Mosapride, in contrast to cisapride, does not block K channels or D_2 dopaminergic receptors, but is not yet available in the United States.

Urinary dysfunction

'Irritative' symptoms of urinary dysfunction such as urgency, frequency, and incontinence are frequent in patients with PD and are caused by uninhibited detrusor contractions. In contrast, urinary abnormalities in patients with MSA are usually retention and voiding difficulties, frequently requiring self-catherization.

Sexual dysfunction

Sixty percent of men with PD have erectile dysfunction together with impaired sexual arousal, lack of sex drive, and failure to orgasm. The cause of erectile dysfunction in PD is unknown, but may involve dopamine deficiency, as dopamine plays a role in libido and penile erection with arousal. Several drugs can cause sexual dysfunction. A thorough medication history is useful. Intracavernous injections or transurethral suppositories of alprostadil, a synthetic prostaglandin E1, induce penile erection, but their use is cumbersome. Sildenafil, an orally active inhibitor of the type V cyclic guanine monophosphate phosphodiesterase (the predominant isoenzyme in the human corpus cavernosum) has improved erectile dysfunction in small clinical trials of patients with PD. Patients with MSA, however, developed severe hypotension with this drug. Men using subcutaneous injections of apomorphine to treat motor fluctuations in PD noted that the treatment benefited their sexual function and induced penile erection. Drug trials to assess the effect of sublingual apomorphine to treat erectile dysfunction had promising results, although nausea occurs in a proportion of the patients. Some patients on high doses of antiparkinsonian therapy become hypersexual, despite inability to perform.

Sweating and thermoregulatory disturbances

Patients with PD can have increased, decreased or normal sweating. Based on studies using the quantitative sudomotor axon reflex test (QSART), postganglionic sympathetic cholinergic nerves innervating sweat glands appear to be intact in PD. In contrast, studies using skin humidity, electrical conductance, and body temperature as indices of sweat production have shown conflicting results.

Pure Autonomic Failure

Although PAF is not a movement disorder, neuropathological data showing the presence of LB suggest a close connection with PD. PAF was first described by Bradbury and Eggleston in 1925. It is a sporadic, adult onset, slowly progressing, neurodegenerative disorder that is mostly confined to peripheral autonomic neurons. PAF is characterized clinically by severe OH with varying degrees of autonomic impairment in other organs, but no other neurological abnormalities, specifically no parkinsonism or cerebellar ataxia. Men typically present with erectile dysfunction. Anhidrosis, dry mouth, constipation and problems with urination may occur. The typical age at onset is 60 years.

There are few neuropathology reports of patients with PAF. All reports have shown LB in autonomic nerves and, in some cases, in the brain stem as well. This suggests that PAF, despite the absence of parkinsonian features or dementia, is a neurodegenerative disorder related to PD and DLB.

Dementia with LB

DLB is the most frequent cause of degenerative dementia after Alzheimer's disease. The mean age at onset of DLB is 75 years, and has a slight male predominance. The majority of patients have cognitive or psychiatric manifestations as their initial presentation, but they may also present with parkinsonian or autonomic features alone. Whether DLB and PD with dementia are the same or two distinct disorders is controversial.

Neuropathology shows LB throughout the cortex, substania nigra and other brainstem nuclei, scattered within the spinal cord and in abundance in autonomic ganglia and in sympathetic neurons.

Autonomic abnormalities are a supportive feature in the diagnosis of DLB. Typically, dysautonomia occurs after the development of cognitive impairment; however, this is not always the case. Urinary incontinence and constipation occur frequently and OH with repeated falls and syncope is common and can precede other deficits by several years. Erectile dysfunction in men is common and often goes unnoticed or is wrongly dismissed as 'normal aging.'

Autonomic testing shows severe OH, lack of BP overshoot in phase IV of the Valsalva maneuver and decreased heart rate variability. Imaging of cardiac sympathetic terminals shows decrease amine uptake in cardiac postganglionic sympathetic neurons in DLB but not in Alzheimer's disease.

Multiple System Atrophy

The second type of neurodegeneration with prominent autonomic failure is MSA. MSA is a sporadic progressive neurodegenerative disorder that causes parkinsonism, cerebellar, pyramidal, and autonomic dysfunction. MSA affects neurons in the cerebellum, basal ganglia, brain stem, and spinal cord, but in marked contrast to LB disorders spares postganglionic autonomic neurons. MSA has two phenotypes: parkinsonian (designated MSAp) and cerebellar (designated MSAc) according to the predominant movement disorder. Autonomic failure occurs similarly in both phenotypes. There are no known genetic mutations responsible for MSA.

Age of onset is usually in the early 1950s, with men more commonly affected than women. MSA can present with either a movement disorder or autonomic deficits. Erectile dysfunction is common in men and half of female patients report decreased genital sensitivity. Rapid eye movement (REM) behavior disorder, characterized by violent movements during dreams, often precedes motor symptoms. Dementia is very unusual but emotional lability is frequent. Common features include marked postural instability, dysarthria, laryngeal stridor and antecollis, focal reflex myoclonus, Raynaud's phenomenon, dysphagia, snoring, and inspiratory sighs. Life expectancy is much shorter in MSA than in PD. The disease is usually rapidly progressive and survival is typically 6–9 years after diagnosis.

Neuropathology

The discovery of α-synuclein-containing inclusions in the cytoplasm of glial cells from patients with MSA provided the pathological hallmark for this disease. These glial cytoplasmic inclusions (GCI) are the equivalent of LB in PD. Degeneration of neurons at several levels of the central nervous system (CNS) impairs sympathetic and parasympathetic reflexes, while postganglionic neurons remain intact. Brainstem and cerebellar degeneration results in dysarthria, uncoordinated swallowing, and abnormal breathing particularly during sleep and recurrent aspirations. Postmortem examination shows depletion of tyrosine hydroxylase immunoreactivity in the rostral and caudal ventrolateral medulla (CVL), and intermediolateral columns (IML) of the spinal cord. There is also loss of dopamine-β-hydroxylase and tyrosine hydroxylase in the locus ceruleus, the main source of norepinephrine in the brain.

Cerebellar and Parkinsonian Phenotypes

Eighty percent of patients with MSA present with parkinsonian features (MSAp) while the remaining 20% first develop cerebellar deficits (MSAc). Patients with MSAp frequently have postural tremor, generalized akinesia, and rigidity, but the typical 'pill-rolling' resting tremor of patients with PD is rarely seen. Involvement is usually bilateral, but asymmetric symptoms are not infrequent. In MSAc cerebellar deficits predominate with gait and limb ataxia, pronounced scanning dysathria and oculomotor abnormalities. As the disease progresses, cerebellar and parkinsonian features are usually combined. Cerebellar abnormalities may be difficult to recognize when parkinsonism is pronounced.

Cardiovascular Abnormalities

In the majority of patients with MSA, postganglionic sympathetic neurons are intact. Lesions within central baroreflex pathways prevent the appropriate reflex activation (or inhibition) of postganglionic sympathetic neurons.

Failure to appropriately increase sympathetic activity with standing and after meals results in disabling orthostatic and postprandial hypotension. Likewise, a failure to suppress sympathetic outflow when supine results in, often severe, supine hypertension. Patients with MSA often have enhanced postganglionic sympathetic outflow to the vasculature, as revealed by the large fall in BP following ganglionic blockade with trimethaphan.

Autonomic testing reveals blunted baroreflexes characterized by progressive severe hypotension with upright tilt and a failure of the BP overshoot after release of the strain of the Valsalva maneuver.

Patients with MSA also have abnormal circadian rhythms of BP and heart rate. During the night, BP and heart fail to decrease, as it normally occurs in healthy subjects. Although hypertension only occurs when patients with MSA are supine, it does result in end-organ damage, including left ventricular cardiac hypertrophy. Elevation of the head of the bed on blocks is an effective treatment for nocturnal hypertension, as it reduces nocturia and helps expand intravascular volume.

Bladder Dysfunction

Dysuria, with or without chronic retention, is an early symptom in patients with MSA. It is frequently associated with a hypoactive detrusor and low urethral pressure. In contrast, patients with PD have urgency to void, with or without difficulty voiding, but without chronic retention, associated with detrusor hyperreflexia and normal urethral sphincter function. The striated muscle of the external anal and urethral sphincter is innervated by fibers that originate in the Onuf nucleus in segments S2–S4 of the spinal cord. This nucleus is particularly vulnerable in patients with MSA, but not in those with PD. Neuronal loss in the Onuf nucleus is reflected by signs of denervation and chronic reinnervation on EMG of anal and urethral sphincter muscle. Eventually most patients require daily selfcatheterization.

Sleep Disturbances

Sleep disturbances in MSA include sleep fragmentation, periodic limb movements, REM behavior disorder, sleep apnea, and excessive daytime sleepiness. Some of these disturbances can occur early in the course of the disease or may precede the development of the movement disorder, particularly REM sleep behavior disorder.

Vocal Cord Palsy

Vocal cord palsy is frequent in MSA and may lead to aspiration. Early recognition and treatment for laryngeal stridor may reduce mortality. In 104 patients with MSA, stridor was observed in 36. In 70% of the cases stridor occurred within the first 4 years; in 10 cases it developed in the first year of the disease. Laryngeal stridor was frequently accompanied by dysphagia and hoarseness.

Treatment

Treatment of Orthostatic Hypotension

OH can be effectively treated with a combination of nonpharmacological and pharmacological interventions. Patients should first sit when going from a supine to standing position. Straining during bowel movements or performing Valsalva-like maneuvers during isometric exercise reduces venous return to the heart, worsens OH and may trigger syncope, thus constipation should be treated aggressively. The use of physical countermaneuvers when upright such as leg crossing, standing on tip toes and muscle tensing increases venous return to the heart and enhances orthostatic tolerance. Eating frequent small meals is often effective in lessening postprandial BP falls. Custom-made full-length elastic stockings can be useful in preventing pooling in the lower extremities. Unfortunately, patients with movement disorders find them difficult to tolerate. Patients should liberalize their dietary salt intake and drink at least 2 l of water a day. Elevating the head of the bed 30° during the night reduces overnight sodium and water excretion by the kidney and lessens OH in the morning.

Treatment with fludrocortisone, a synthetic mineralocorticoid, when combined with a high salt intake raises BP. Potassium supplementation may be needed, because fludrocortisone increases renal potassium excretion. Octreotide and acarbose, reduce postprandial hypotension. Vasoconstrictor agents such as the selective α1-adrenoreceptor agonist midodrine increase BP and improve symptoms of OH. Side effects of midodrine include pilomotor reactions, pruritus, supine hypertension, and urinary retention.

Drugs that release norepinephrine from sympathetic nerve terminals may be effective in patients with MSA, since these patients have intact sympathetic terminals. Dihydroxyphenylserine (DOPS, droxidopa) is converted into norepinephrine after oral administration and has been used successfully in small trial of patients with autonomic synucleinopathies. All vasoconstrictor agents may lead to significant hypertension when the patient is supine. Treatment with recombinant erythropoietin and iron supplementation to correct the anemia, common in autonomic failure, increases upright BP and improves symptoms of OH. Acetylcholinesterase inhibitors (pyrostigmine) have been used, but their pressor effects are very modest.

Treatment of Supine Hypertension

Hypertension when supine is common in patients with autonomic failure. Patients should be instructed to avoid

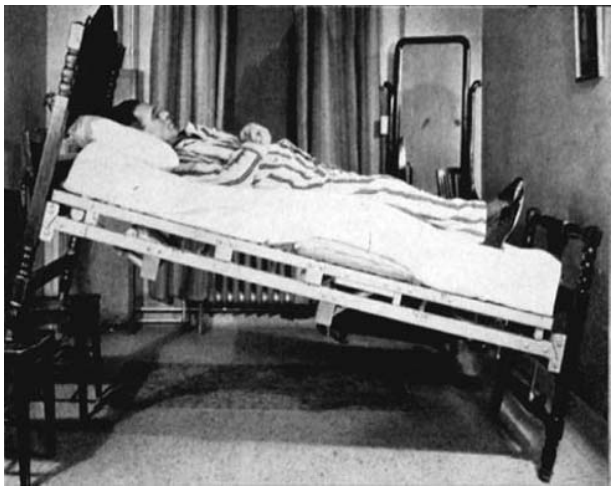

Figure 4 The 'head-up' bed as originally published by Maclean and Allen in 1940. Reproduced from Maclean AR and Allen EV (1940) OH and orthostatic tachycardia, treatment with the 'head up' bed. *Journal of American Medical Association* 115: 2162–2167.

being supine at all times and avoid taking antihypotensive agents before bed. Sleeping with the head of the bed elevated lessens nocturnal hypertension (**Figure 4**). The use of short acting antihypertensive agents such as transdermal nitroglycerin ($0.1–0.2\,mg\,h^{-1}$), oral nifedipine (30 mg) or hydralazine (50–100 mg) at night has been suggested. Unfortunately, these agents do not prevent nocturia and can, in the case of nifedipine, worsen nighttime sodium loss.

Differential Diagnosis among the Synucleinopathies

The two main diagnostic problems among the synucleinopathies are (1) the distinction between PAF and early 'premotor' MSA, PD, or DLB, and (2) the distinction between PD with autonomic failure and MSAp.

PAF versus Early 'Premotor' MSA, PD or DLB

When a patient presents with symptomatic OH and no other apparent neurological deficits and is thus presumed to have PAF it should first be ascertained whether the OH is neurogenic, that is, the result of dysfunction of the baroreflex. This can be accomplished with noninvasive autonomic testing showing lack of BP overshoot during Valsalva maneuver and lack of appropriate increase in heart rate when the BP falls. Simple bedside measurements can be helpful. For example, a marked increase in heart rate accompanying OH suggests volume depletion and 'rules out' autonomic failure. A careful drug history is important, as antihypertensive or antidepressants agent may be the culprit for OH. A detailed clinical history may reveal constipation, decreased sweating, bladder, and erectile dysfunction suggesting widespread autonomic denervation.

A careful neurological examination may uncover subtle parkinsonian or cerebellar signs indicating that, rather than having PAF, the patient is in the early 'premotor' stages of MSA. If no central neurological deficits are uncovered and peripheral neuropathies or autoimmune causes are ruled out, the most likely diagnosis is PAF. Early in the disease course, the diagnosis of PAF is always made tentatively because after a few years a patient who appeared to have PAF may develop extrapyramidal or cerebellar deficits and turns out to have MSA, or less frequently PD or DLB.

PD with Autonomic Failure versus MSAp

A patient that presents with parkinsonism and autonomic failure may have PD or MSAp. The distinction between these two disorders is challenging. A history of severe autonomic symptoms preceding motor deficits is much more frequent in MSA than in PD. Subtle cerebellar findings indicate that the patients has MSAp as they do not occur in PD, pyramidal tract features are more frequent in MSAp than PD and typical 'pill-rolling' asymmetric hand tremor strongly suggests PD. Contrary to PD, patients with MSAp have poor or no therapeutic response to levodopa. However, around half of MSA patients have at least some initial improvement, albeit transient. Patients with MSAp can develop axial levodopa induced dyskinesias, even in the absence of beneficial motor effects. Early urinary dysfunction, vocal cord palsy, early dysarthria, dysphagia, dystonia (including antecollis), focal reflex myoclonus, vasomotor changes in the hands ('purple hands'), laryngeal stridor, snoring, inspiratory sighs, pseudobulbar crying or laughing, early severe postural instability with wheelchair dependence all suggest MSAp, as their presence is rare in PD. Dementia is most severe and relentless in DLB; it occurs in the latter stages of PD, but not in MSA. Emotional incontinence, however, is frequent in MSA.

Sympathetic Neuroimaging in the Differential Diagnosis

Sympathetic cardiac neuroimaging has the potential to simplify the differential diagnosis among the synucleinopathies. Sympathetic neuroimaging using metaiodobenzylguanidine (MIBG) single photon emission computed tomography (SPECT) or fluorodopamine positron emission tomography (PET) consistently show that patients with LB disorders, including PAF, PD, and DLB have decreased amine uptake in postganglionic sympathetic neurons innervating the heart. In contrast patients with MSA have preserved amine uptake in these neurons.

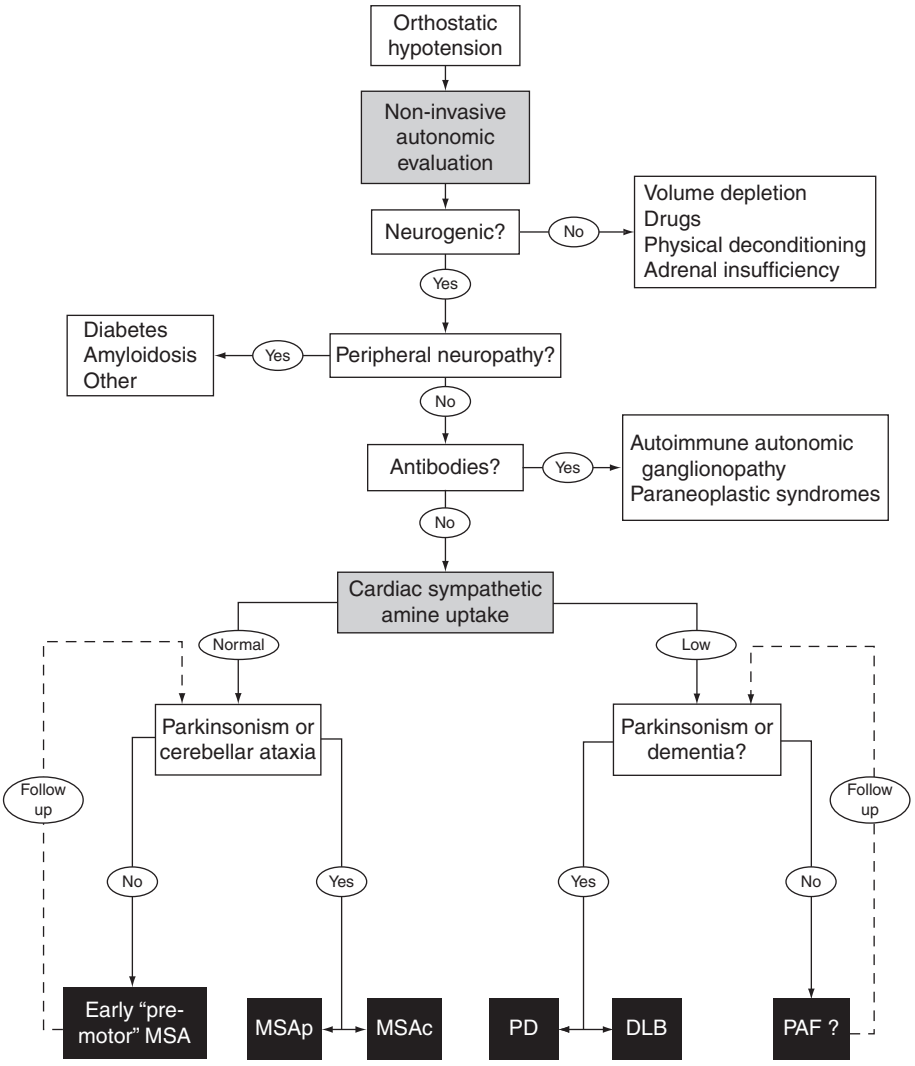

Figure 5 A proposed algorithm for the differential diagnosis of the autonomic synucleinopathies. See text for details. MSA, multiple system atrophy; MSAc, multiple system atrophy with predominant cerebellar ataxia; MSAp, multiple system atrophy with predominant parkinsonism; PD, Parkinson's disease; DLB, dementia with Lewy bodies; PAF, pure autonomic failure.

These findings reflect degeneration of postganglionic sympathetic neurons in LB disorders and sparing of these neurons in MSA.

Figure 5 shows a proposed algorithm for the differential diagnosis of the synucleinopathies. In a patient with neurogenic OH in whom a peripheral neuropathy or an autoimmune cause has been excluded, if myocardial amine uptake is low and the patient does not have parkinsonism or cognitive impairment, the most likely diagnosis is PAF. As previously mentioned, the diagnosis of PAF is tentative as this may be the initial presentation of PD or MSA, which will become apparent after a few years.

If a patient with neurogenic OH has normal myocardial amine uptake and parkinsonism or cerebellar ataxia, the diagnosis is MSA. If neither parkinsonism nor cerebellar ataxia are present, it is likely that he is in the early 'premotor' phase of MSA.

See also: Dementia with Lewy Bodies; Multiple System Atrophy; Parkinson's Disease: Definition, Diagnosis, and Management; Synucleinopathies.

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Relevant Websites

www.movementdisorders.org – Movement Disorder Society.

B

Basal Ganglia

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Glossary

Dopamine – Major neurotransmitter used by many neurons in the central nervous system. It mediates its effects through activation of two major families of receptors called D1 and D2 receptor families. It plays an important role in reward and addiction. Dopaminergic neurons in the substantia nigra pars compacta degenerate in Parkinson's disease.

Parkinson's disease – Second most common neurodegenerative disease after Alzheimer's disease characterized by the severe loss of dopaminergic neurons in the substantia nigra was first described by James Parkinson in 1817. The main symptoms are slowness of movements, muscular rigidity, rest tremor, and postural instability. Some patients also suffer from nonmotor symptoms such as depression and cognitive deficits.

Striatum – Large mass of subcortical gray matter located in the telencephalon considered as the main input station of extrinsic information to the basal ganglia circuitry. It is made up of the caudate nucleus, putamen, and nucleus accumbens.

Substantia nigra – Subcortical brain structure located in the mesencephalon made up of two parts called the pars compacta (dopamine neurons) and pars reticulata (GABAergic neurons). This structure plays a role in addiction, reward, and motor control.

Subthalamic nucleus – Small almond-shaped subcortical brain structure located ventral to the thalamus in the caudal part of the diencephalon. It is a key structure of the basal ganglia that plays a major role in Parkinson's disease pathophysiology. It is one of the main targets for surgical therapy in Parkinson's disease.

Definition and History

The basal ganglia are a group of subcortical brain nuclei, first described by the seventeenth century neuroanatomist Thomas Willis. They were originally named based on their location in the basal regions of the cerebral hemispheres. Although the modern view of the basal ganglia includes functionally connected structures in the basal forebrain, namely the striatum and the globus pallidus (GP), they also comprises other structures, such as the subthalamic nucleus (STN) and substantia nigra located more caudally at the basis of the diencephalon and ventral midbrain, respectively. As a crucial part of the extrapyramidal motor system, these nuclei are involved in the control of voluntary movements, but also participate in high order cognitive and limbic functions. As such, basal ganglia diseases such as Parkinson's and Huntington's diseases traditionally known as motor disorders are, in fact, much more complex disturbances that reveal motor, cognitive, emotional, and neuropsychiatric symptoms. Tourette's syndrome, obsessive compulsive disorders (OCD), and attention deficits, which likely result from neurochemical changes in the basal ganglia, are also characterized by complex motor and nonmotor deficits.

The basal ganglia are phylogenetically conserved in all vertebrates, having evolved more conspicuously in amniote species (reptiles, birds, and mammals). In birds and reptiles, these nuclei exert their influence on motor functions mostly via outputs to the midbrain, while the mammalian basal ganglia mediate their motor and nonmotor effects mainly through regulation of thalamocortical neurons linked to motor and prefrontal cortices.

Components of the Basal Ganglia

In primates, the components of the basal ganglia are the dorsal striatum (caudate nucleus and putamen), the ventral striatum (nucleus accumbens), the external and internal

segments of the globus pallidus (GPe and GPi, respectively), the STN, the substantia nigra that comprises the pars reticulata and pars compacta (SNr and SNc, respectively), and the ventral tegmental area (VTA). In rodents, the caudate nucleus and putamen form a single structure commonly called the caudate–putamen complex, while the GP and the entopeduncular nucleus (EPN) correspond functionally to the primate GPe and GPi, respectively. As for many other anatomical terms, the names of these structures are derived from Latin and usually indicate a remarkable structural feature of each brain region. For instance, striatum means 'to present a striated appearance.' The scarcity of cells in the GP gives this structure a faint aspect in comparison with surrounding structures, and thus the name 'pale globe.' The term 'substantia nigra' (black substance) is derived from the presence of the dark pigment neuromelanin in these neurons. Finally, the complex formed by the putamen and GP is called 'lenticular or lentiform nucleus' (lens-shaped body) because in coronal sections, it appears as a double lens.

Parallel and Segregated Cortical–Basal Ganglia Loops

The basal ganglia are part of neural circuits that involve the cerebral cortex and thalamus. According to the functions of the cortical regions from which they originate, three main functionally segregated loops can be identified: sensorimotor, limbic, and associative. In each of these circuits, functionally related cortical areas project topographically to specific areas of the striatum (see **Figure 1**). Thus, the sensorimotor loop involves the putamen posterior to the anterior commissure, which receives its main inputs from the somatosensory, primary motor, premotor, and supplementary motor areas of the cerebral cortex. The associative loop involves the head and tail of the caudate nucleus and parts of the putamen rostral to the anterior commissure. These areas receive inputs from the dorsolateral prefrontal, lateral orbitofrontal, posterior parietal, and temporal association cortices. Finally, the limbic loop, which involves the ventral striatum, including the nucleus accumbens and the rostroventral caudate nucleus and putamen, transmits inputs from the anterior cingulate and medial orbital frontal cortices, as well as the amygdala and the hippocampus. This segregation of cortical information is maintained at all levels of other basal ganglia nuclei and in the basal ganglia-receiving regions of the thalamus. Functional interactions between these loops likely occur through corticocortical connections.

Because of its role in the pathophysiology of movement disorders, the sensorimotor circuit has been most extensively studied. Channels of information flow from motor and somatosensory cortices related to specific body

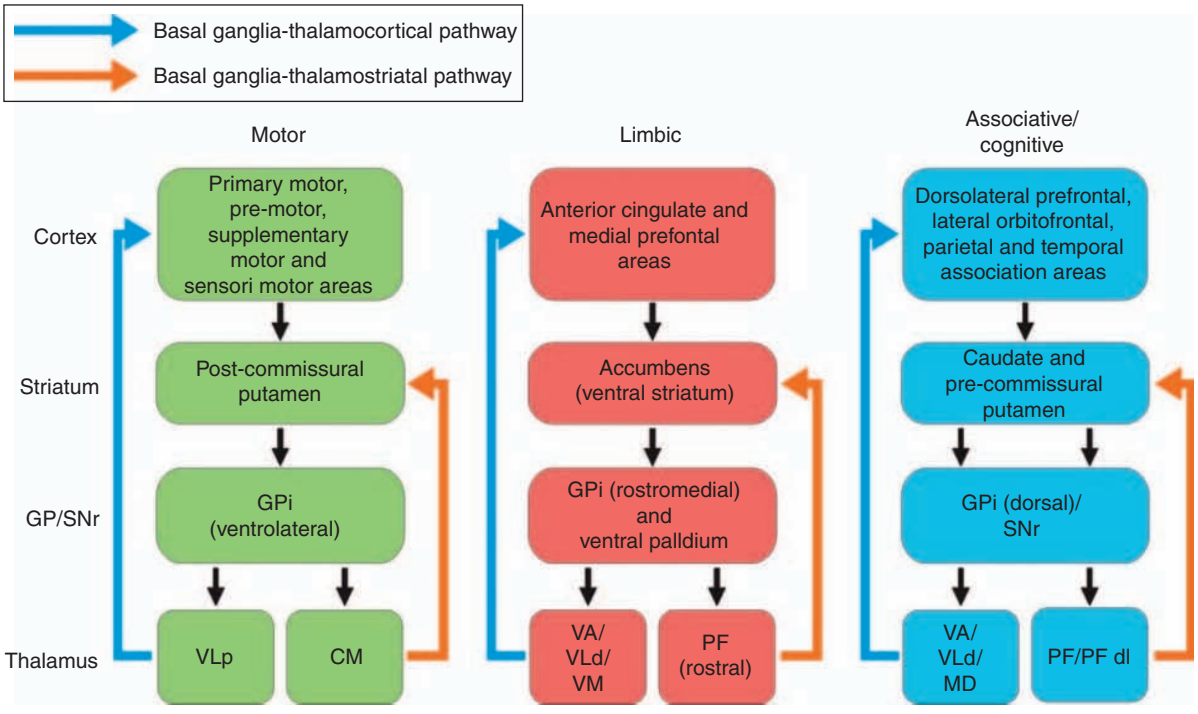

Figure 1 Segregated basal ganglia–corticothalamic and basal ganglia–thalamostriatal loops. For simplicity, some pathways have been omitted. CM, centromedian nucleus of thalamus; GPi, globus pallidus internal segment; PF, parafascicular nucleus of thalamus; PF dl, dorsolateral part of PF; SNr, substantia nigra reticulata; VA, ventral anterior nucleus of thalamus; VLp, posterior part of the ventrolateral nucleus of thalamus; VLd, dorsal part of ventrolateral nucleus of thalamus; VM, ventromedial nucleus of thalamus.

parts converge onto common regions of the postcommissural putamen, which then transmits the information to specific areas of the ventrolateral GPi. In turn, the motor basal ganglia outflow is conveyed to segregated areas of the ventral motor thalamic nuclei and the brainstem pedunculopontine nuclei (PPN) to influence motor behaviors through ascending thalamocortical projections or descending projections from the PPN to the reticular formation and spinal cord.

Cellular and Hodological Organization of the Basal Ganglia

Cell Types in the Basal Ganglia

The main input nucleus of the basal ganglia, the striatum, is composed of spiny and aspiny neurons, characterized by the presence or scarcity of spines on their distal dendrites, respectively. The medium-sized spiny neurons (MSNs), which account for as much as 90–95% of the total striatal neuronal population, are the projection neurons of the striatum, and they use γ-aminobutyric acid (GABA) as neurotransmitter.

The aspiny cells are interneurons that use GABA or acetylcholine as neurotransmitters. The cholinergic interneurons are the largest neurons in the neostriatum, and they likely correspond to the so-called tonically active neurons (TANs) characterized by their tonic firing rate. The cholinergic interneurons are important intrinsic regulators of MSNs and play a key role in learning.

Three major subtypes of GABAergic interneurons have been identified based on their chemical content and physiological activity: (1) the parvalbumin cells, also referred to as 'fast spiking interneurons' based on their high frequency of firing; (2) the nitric oxide synthase/neuropeptide Y/somatostatin interneurons, also known as 'persistent and low-threshold spike neurons,' due to their characteristic low-threshold calcium spikes and prolonged calcium dependent plateau potential; and (3) the calretinin interneurons, which seems to be functionally similar to the 'persistent and low-threshold spike neurons.' These GABAergic interneurons, especially the parvalbumin cells, exert powerful monosynaptic inhibition onto MSNs, thereby playing an important role in regulating striatal outflow.

In contrast to the striatum, the other basal ganglia nuclei have a more homogeneous cellular organization, being largely made up of projection neurons and only a few (if any) interneurons. The GPe, GPi, and SNr comprise GABAergic projection neurons with significant intrinsic axon collaterals arborization, whereas the STN projection cells are glutamatergic with limited intranuclear connectivity. The SNc is made up almost exclusively of dopaminergic neurons, but receives local GABAergic influences from axon collaterals of SNr projection neurons.

Extrinsic Connectivity of the Basal Ganglia

The striatum receives glutamatergic afferents from the cerebral cortex and thalamus. Inputs from the cortex originate from most cortical areas. In rodents, pyramidal corticostriatal neurons can be divided into two major subtypes; the intratelencephalic (IT) neurons of which axonal projections remain within the confines of the telencephalon, and the pyramidal tract (PT) neurons that send their main axon into the PT and have collateral projections to striatum. However, the functional role of PT corticostriatal neurons in rodents and the existence of such neurons in primates remain controversial.

The thalamostriatal projections use glutamate as their transmitter and originate mainly from the caudal intralaminar thalamic nuclei, specifically the centromedian and parafascicular nuclei (CM/PF). Nonetheless, these projections have significant contributions from the rostral intralaminar, midline, associative, and motor-related nuclei. Until recently, the thalamostriatal system was largely neglected or considered to play a minor role in the basal ganglia circuitry. However, it has now been demonstrated that this projection is massive, highly specific, and physiologically relevant. The CM/PF complex is also considered as a new therapeutic target for deep brain stimulation in movement disorders.

The intrastriatal arborization and synaptic connectivity of afferents from the CM/PF complex are characteristically different from corticostriatal inputs and other thalamic afferents. Thus, while cortical innervation to the striatum is widely distributed, and provides only few axonal varicosities to individual striatal cells, single axons from CM/PF neurons form dense clusters of terminals concentrated in small portions of the striatum. At the synaptic level, most cortical and a significant subset of thalamic inputs terminate almost exclusively on dendritic spines of MSNs. In contrast, most CM/PF afferents target preferentially dendritic shafts. Besides these anatomical features, recent evidence indicates differences in glutamate release probability and long-term plasticity between thalamostriatal and corticostriatal synapses.

Along with the striatum, the STN is considered an input nucleus of the basal ganglia. In primates, the corticosubthalamic projection arises mostly from motor cortices, including primary, supplementary, presupplementary, premotor, and cingulate motor areas in the frontal lobe. Inputs from the primary motor cortex are somatotopically organized and confined to the dorsolateral part of the STN, whereas other motor inputs overlap in the dorsomedial sector of the nucleus. Primary motor cortex and supplementary motor cortex inputs display a reverse somatotopic arrangement in the monkey STN. Through the corticosubthalamic route, the cerebral cortex provides strong excitation to the GPi and SNr, with faster conduction velocity than information flowing through striatofugal

pathways. Because of its fast conduction and direct access to basal ganglia output nuclei, this connection is known as the 'hyperdirect pathway.' It has been suggested that the hyperdirect pathway plays an important role in a center-surround model of action selectivity in the GPi, by inhibiting irrelevant motor programs. However, the anatomical and physiological basis for such model remains to be further studied. Besides the cortex, the STN receives glutamatergic inputs from the thalamus and the PPN.

Other extrinsic inputs to the basal ganglia originate from the amygdala and hippocampus, which target mainly limbic striatal regions, and brainstem afferents from serotonergic, cholinergic, and noradrenergic cell groups in the raphe, PPN, and locus coeruleus, respectively.

Intrinsic Connectivity of Basal Ganglia

The main targets of extrinsic inputs to the striatum are GABAergic MSNs, which are divided into two groups based on their dopamine receptor expression, peptide content and main basal ganglia projection targets. The so-called 'direct pathway' neurons project directly to the basal ganglia output nuclei, GPi and SNr, and express preferentially D1 dopamine receptors, whereas the 'indirect pathway' neurons project mainly to the GPe and express D2 dopamine receptor. As discussed in detail elsewhere, the degree of segregation of these two pathways has been challenged over time and remains controversial.

The striatum receives a prominent dopaminergic input from SNc and VTA, which plays a critical regulatory role over cortical glutamatergic influences through pre- and postsynaptic mechanisms at the level of spines on MSNs. Dopamine neurons are the sources of complex information related to movement, reward-related stimuli and aversive events to the striatum. Although the exact sources of such information to midbrain dopamine neurons remain unknown, specific subcortical nuclei including the lateral habenula (LHb), the superior colliculus (SC), and the PPN likely contribute significantly to the regulation of nigral dopaminergic outflow (see **Figure 2**).

Even though the striatum is the main basal ganglia target of midbrain dopaminergic neurons, the GP and the STN also receive modest nigral dopaminergic input. Furthermore, the local dendritic release of dopamine from SNc neurons may play an important role in regulating the activity of SNr GABAergic neurons. Therefore, the characteristic loss of SNc dopaminergic neurons that occurs in Parkinson's disease can have widespread influences throughout the basal ganglia circuitry, not only in the striatum, but also in extrastriatal targets.

Basal Ganglia Outflow

The GPi and the SNr are the output nuclei of the basal ganglia. Both nuclei receive functionally segregated inputs from the striatum (through direct and indirect routes), and in turn send GABAergic projections to their thalamic and brainstem target structures. Furthermore, some of the pallidal and nigral targets project back to the basal ganglia, creating feedback circuits (**Figure 1**).

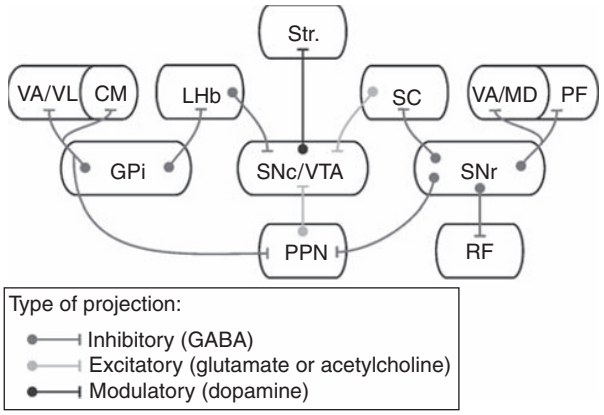

Figure 2 Output pathways of the GPi and SNr, and subcortical inputs to the SNc. In the GPi, a population of neurons project to the thalamus and the PPN, while a different cell group projects to the LHb. In contrast, the degree of collateralization in the SNr is more heterogenous. For simplicity, only major projections are represented. CM, centromedian nucleus of thalamus; GPi, globus pallidus internal segment; LHb, lateral habenula; PF, parafascicular nucleus of thalamus; PPN, pedunculo pontine nucleus; RF, reticular formation; SNc, substantia nigra compacta; SNr, substantia nigra reticulata; Str, striatum; VA/VL, ventral anterior and ventrolateral nuclei of thalamus; VA/MD, ventral anterior and mediodorsal nuclei of thalamus; VTA, ventral tegmental area.

Efferent projections of GPi

The GPi sends a topographic projection to the ventrolateral (VL) and ventral anterior (VA) nuclei of the thalamus. Efferent projections from the sensorimotor GPi (ventrolateral two thirds) are segregated from associative (dorsal third) and limbic (rostromedial pole) GPi inputs in the thalamus. Sensorimotor pallidothalamic projections are somatotopically organized and further segregated into different channels based on their main sources of motor-related cortical influences. The VA/VL nuclear complex is the main thalamic recipient of GPi outflow, but these projections are highly collateralized and also provide significant inputs to the caudal intralaminar nucleus CM and to the PPN in the brainstem (**Figure 2**). Through these projections, cortical information can be sent back to frontal cortical regions via segregated basal ganglia–thalamocortical loops or specific striatal regions via basal ganglia–thalamostriatal projections (**Figure 1**). Alternatively, basal ganglia outflow can gain direct access to descending motor systems via the PPN that sends back glutamatergic and cholinergic projections to most basal ganglia nuclei, but also gives rise to significant

descending influences on motor-related neurons in the lower pons, medulla, and spinal cord.

Another segregated population of neurons located along the borders of GPi sends projections to the LHb (**Figure 2**), a small circumscribed component of the so-called epithalamus located in the dorsal part of the caudal diencephalon. Similar to other pallidofugal pathways, the pallidohabenular projection is topographically organized and made up of different functional channels of information that terminate in specific sectors of the LHb. In turn, the LHb sends inhibitory projections to ventral midbrain dopaminergic neurons in the SNc and VTA. Through this system, the pallidohabenular projection may initiate reward-related signals in midbrain dopaminergic neurons (see above). Based on recent findings showing that the LHb has the potential to control both reward-seeking and punishment-avoidance behaviors through its projections to the ventral midbrain, the extrinsic regulation of LHb neurons by GPi can have widespread influences over motor, cognitive, and limbic-related behaviors.

Efferent projections of SNr

The thalamic targets of the SNr include the medial magnocellular divisions of the VA (VAmc) and the mediodorsal nucleus (MDmc). These thalamic regions, different from those that receive GPi inputs, project to anterior regions of the frontal lobe including the principal sulcus, orbital cortex, frontal eye fields, and areas of premotor cortex. A subset of SNr neurons also gain access to thalamocortical neurons that project to the area TE in the inferotemporal cortex, suggesting a possible role of SNr in high order processing of visual perceptions. Many nigrothalamic neurons send axon collaterals to thalamostriatal neurons in PF.

The SNr also sends a massive and topographically arranged projection to the intermediate layers of the SC. These nigral fibers terminate mainly on tectospinal neurons, and are critically important in the control of saccadic eye movements. In turn, a recently described tectonigral projection is considered as a potential source of unpredicted, biological salient, sensory events to midbrain dopaminergic neurons in the SNc, thereby providing a substrate for midbrain dopaminergic responses to sensory prediction errors. Other targets of the SNr are the orofacial motor nuclei in the medullary reticular formation and the noncholinergic neurons in the PPN (**Figure 2**).

Models of Basal Ganglia Function and Dysfunction

The most influential model of the sensorimotor basal ganglia circuit was proposed in the late 1980s to explain how basal ganglia dysfunction could result in hypokinetic movement disorders such as Parkinson's disease, and hyperkinetic movement disorders such as Huntington's disease. This functional 'direct and indirect pathway' model of the basal ganglia circuitry has been instrumental in our understanding of the pathophysiology of basal ganglia disorders and the development of surgical therapy for Parkinson's disease. The readers are referred to other chapters in the Encyclopedia for a more detailed account of the functional anatomy and physiological organization of this model.

Motor and Nonmotor Functions of the Basal Ganglia

Although the basal ganglia have long been recognized as critical components of the extrapyramidal motor system, there is strong anatomical and functional evidence that they also play major role in cognitive and limbic-related behaviors. First, as outlined in this chapter and illustrated in **Figure 1**, each basal ganglia structure and its thalamic targets comprise segregated functional territories that process sensorimotor, associative, and limbic information. Since the original introduction of the concept of segregated basal ganglia–thalamocortical loops by Alexander, DeLong, and colleagues in the mid-1980s, this model of organization has generated significant interest and has been further supported using more sophisticated anatomical tracing methods and physiological approaches. However, two major issues remain unclear about this model of basal ganglia information processing. The exact substrate of cross-communication between the various channels of information must be further characterized. Although suggestions have been made that such cross talk most likely occurs through the complex corticocortical circuitry, others have argued that subsets of basal ganglia neurons may also contribute to these functional interactions. Another important issue to unravel is the mechanism by which segregated basal ganglia output neurons lose their functional specificity in Parkinson's disease. Whether this reflects a lack of dopamine modulatory influences at the cortical or subcortical levels must be determined.

Additional strong evidence for the role of basal ganglia in nonmotor functions comes from clinical and postmortem human studies, showing that patients who suffer of traditionally known 'motor' basal ganglia disorders such as Parkinson's and Huntington's diseases, also present clear cognitive and emotional disturbances in attention, working memory, set shifting, set formation, and actions planning, even at early stages of the disease process. Furthermore, pathologies characterized by emotional, cognitive, and psychiatric deficits, including OCD, Tourette's syndrome, attention deficit disorders, and depression, involve neurochemical disruption of basal ganglia networks and/or pathology of specific basal ganglia nuclei. Some of the psychiatric and nonmotor side-effects that result from

ablative surgery or deep brain stimulation of the GPi or STN also indicate that the basal ganglia function extends far beyond mere motor control. In fact, our limited understanding of the exact role of basal ganglia in motor control is another evidence of the complex mechanisms by which these brain nuclei integrate and process sensorimotor information. Functional data obtained so far suggest that the basal ganglia are involved in both the preparation and execution of movements as well as learning of motor sequences and habits.

Acknowledgments

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See also: Basal Ganglia, Functional Organization; Direct Pathway; Dopamine; Dopamine Receptors; Indirect Pathway; Substantia Nigra; Subthalamic Nucleus.

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Basal Ganglia, Functional Organization

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Glossary

Basal ganglia – A group of subcortical brain nuclei that are connected to thalamus and the cortex. The basal ganglia consist of the striatum, the globus pallidus with its external and internal segment, the substantia nigra with its pars compacta and pars reticulata, and the subthalamic nucleus.

Dendritic spines – Extensions of dendrites that can be detected at the light- and electron microscopic level. In terms of basal ganglia anatomy, dendritic spines are a distinct feature of medium spiny neurons in the striatum. Dendritic spines are an important termination point of cortical and thalamic inputs to the striatum. It is thought that the information transfer via dendritic spines is strongly regulated through the presence or absence of the neurotransmitter dopamine.

Direct and indirect pathways – A common anatomical scheme used to classify the intrinsic connections between the basal ganglia nuclei that receive extrinsic inputs (the striatum), and the basal ganglia that provide output to other structures (the internal pallidal segment and the substantia nigra pars reticulata). The direct pathway is monosynaptic, while the indirect pathway is polysynaptic.

(Hemi-)Ballism – A rare movement disorder characterized by the development of involuntary movements of the limbs on one side of the body, which are often proximal large-amplitude movements. The disorder is typically caused by strokes or other lesions of the subthalamic nucleus on one side of the brain, and is therefore usually unilateral (hemiballism).

Huntington's disease – Huntington's disease is an autosomal dominant trinucleotide repeat disorder. This genetic condition leads to progressive degeneration of neurons in the cortex, striatum, and other brain regions. Clinically, the disease manifests itself with a combination of neuropsychiatric symptoms (such as mood disturbances, behavioral

abnormalities, and cognitive impairments) and the appearance of involuntary movements (chorea).
Movement disorders – A group of diseases dominated by disturbances of movement in the absence of weakness. Movement disorders are usually associated with an impairment of the ability to carry out coordinated movements. These disorders are generally grouped into disorders in which the overall amount of movement is reduced (hypokinetic disorders such as Parkinson's disease), and disorders with an excess of movements, which are typically involuntary (hyperkinetic disorders, such as ballism or Huntington's disease).
Parkinson's disease – A complex neurodegenerative disease, characterized clinically by the appearance of poor movement (akinesia), slowness of movement (bradykinesia), tremor at rest, and muscular rigidity These symptoms are caused by dopamine loss in the basal ganglia and can be treated with dopaminergic replacement therapy. Other parkinsonian features include gait instability, autonomic symptoms such as constipation or blood pressure fluctuations, and cognitive impairment. These symptoms probably arise from pathology outside of the basal ganglia and are not effectively treated with dopamine.

Functional Anatomy of the Basal Ganglia

Basal Ganglia Structures

The basal ganglia are a group of anatomically interconnected subcortical nuclei, including the striatum, which is divided into a ventral and dorsal portion (consisting of the caudate nucleus (CN) and the putamen), the external and internal segments of the globus pallidus (GPe, GPi, respectively), the pars compacta and the pars reticulata of the substantia nigra (SNc, SNr, respectively), and the subthalamic nucleus (STN).

Striatum

The striatum is the major input structure of the basal ganglia. It receives projections from large portions of the cerebral cortex, brain stem, and from several thalamic nuclei. The most common striatal cell type is the GABAergic 'medium spiny' neuron (MSN), named so because of the abundance of dendritic spines. In rodents, these neurons constitute more than 90% of all striatal neurons; in primates, this percentage is likely to be smaller (70–75%). MSNs are the primary striatal recipients of extrinsic inputs and is the only striatal neuron type with extrinsic projections. Output from these cells is directed to GPe and GPi, as well as the ventral pallidum and the SNc. These GABAergic projections can be distinguished by the cotransmitters they express and by other biochemical specifics. GPe-projecting MSNs express enkephalin and D2-type dopamine receptors, while GPi/SNr-projecting MSNs express substance P and D1-family dopamine receptors.

Several classes of local interneurons regulate MSN activity. The most abundant interneuron type is the large aspiny cholinergic interneuron. These neurons receive glutamatergic inputs from the thalamic centromedian and parafascicular nuclei (CM/PF), and GABAergic inputs from neighboring interneurons and local MSN axon collaterals. Together with dopaminergic inputs from the midbrain (see below), these cells may play a role in procedural learning by providing MSNs with information regarding the behavioral saliency of external stimuli. All of the other identified interneurons are GABAergic. These interneurons can be further subclassified, based on their electrical activities, and on anatomic features, such as the fact that they express specific proteins (including parvalbumin, calretinine, and nitric oxide synthetase). The functions of most of these interneuron types are not known. However, parvalbumin-containing interneurons have been shown to receive cortical inputs, and may alter the activities of neighboring MSNs as part of a feed-forward inhibitory process.

Other basal ganglia structures

GPe, GPi, and SNr consist of GABAergic projection neurons. While there is substantial collateral interaction among GPe cells, there is less local interaction among GPi and SNr cells. GPe cells are part of the intrinsic basal ganglia circuitry, while GPi and SNr are the major output nuclei of the basal ganglia, with projections to specific thalamic nuclei (ventral anterior and ventrolateral nuclei VA/VL, and CM/PF). Additional projections reach nuclei in the brainstem, such as the pedunculopontine nucleus (PPN), and the lateral habenula.

The STN is a dense cellular structure, situated between the thalamus and SNr. It receives inhibitory projections from GPe, and excitatory connections from the cerebral cortex, thalamus, and brain stem. STN neurons are glutamatergic (excitatory), and their axons reach GPe, GPi, and SNr, as well as midbrain and brainstem nuclei (such as PPN and SNc). This nucleus is seen as a major driving force of pallidal and nigral activity. It has gained prominence in recent models of basal ganglia function, specifically because abnormalities in this nucleus have been described to occur in movement disorders such as Parkinson's disease (PD). The fact that portions of all basal ganglia–thalamocortical circuits (see below) pass through this small nucleus has made it a primary target for surgical interventions in patients

with movement disorders and other disorders of basal ganglia origin.

The SNc, along with portions of the ventral tegmental area (VTA), is comprised of dopaminergic cells that project heavily to the striatum and, to a lesser degree, to the other nuclei of the basal ganglia. Dopaminergic fibers terminate preferentially on dendritic spines of striatal MSN, and may modulate cortical and thalamic inputs that also end on the spines. The dopaminergic control over corticostriatal transmission is seen as central to striatal functioning, specifically to the role of the basal ganglia in procedural learning.

Other neuromodulators, such as serotonin (released from projections of the raphe nuclei in the brainstem) and norepinephrine (released from terminals of projections of the nucleus coeruleus) may also play a significant role in the striatal and extrastriatal basal ganglia functions. However, the functions of these systems are not well understood till date.

Basal Ganglia Circuits

Topography, segregation of activity

Like most other brain regions, the basal ganglia do not function in isolation but are strongly related to other brain regions. They are components of cortico-subcortical reentrant pathways, which include thalamus and the cerebral cortex. Interestingly, these circuits appear to remain largely segregated throughout their subcortical course, although interactions between them may take place at the cortical levels.

Several major circuits have been identified and are named after the functions of the cortical areas from which they originate (**Figure 1**). The 'motor' circuit is centered on the precentral cortical motor fields, the 'oculomotor' circuit, originates from the frontal and supplementary eye fields, prefrontal circuits involve the dorsolateral prefrontal and lateral orbitofrontal cortex (LOFC), and a 'limbic' circuit is centered on the anterior cingulate and medial orbitofrontal cortex (MOFC) (**Figure 2**). Each of these circuits is comprised of several subcircuits. The anatomic building blocks of these circuits are similar, and it seems fair to assume that the different basal ganglia–thalamocortical circuits function as modules that perform the same type of processing on different functional types of input (determined by the respective functional roles of the cortical areas that provide input). The specific operations performed by the basal ganglia have not been determined.

A similar modular arrangement may also exist for circuits formed by the cerebellum, thalamus, and cortex which function largely in parallel to the basal ganglia-traversing circuitry. In terms of behavioral control, cerebellar circuits may be more involved in the online adjustment of movement, while the basal ganglia circuitry may influence functions such as adaptation, reward processing, or procedural learning.

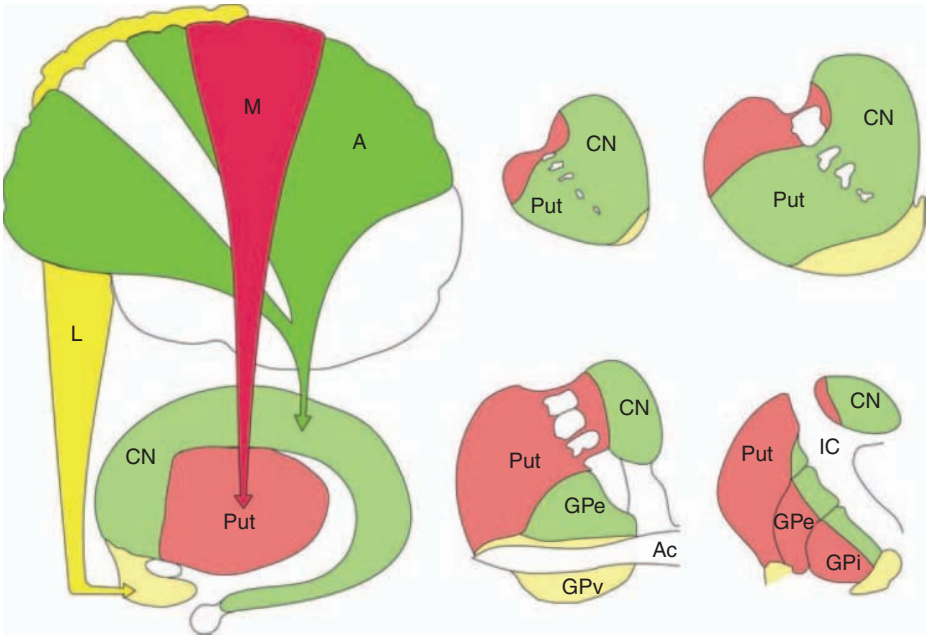

Figure 1 Organization of cortico-basal ganglia interactions. The basal ganglia topographically receive inputs from the cerebral cortex which serve to divide the basal ganglia into distinct functional territories. This simplified diagram shows cortical and corresponding basal ganglia areas that belong to the motor circuit (red, labeled 'M'), the limbic circuit (yellow, labeled 'L'), and the associative circuit (green, labeled 'A'). CN, caudate nucleus; GPe, external pallidal segment; GPi, internal pallidal segment; GPv, ventral pallidum; Put, putamen. Modified from Parent A and Hazrati LN (1995) Functional anatomy of the basal ganglia. I. The cortico-basal ganglia-thalamo-cortical loop. *Brain Research Reviews* 20: 91–127, with permission from Elsevier.

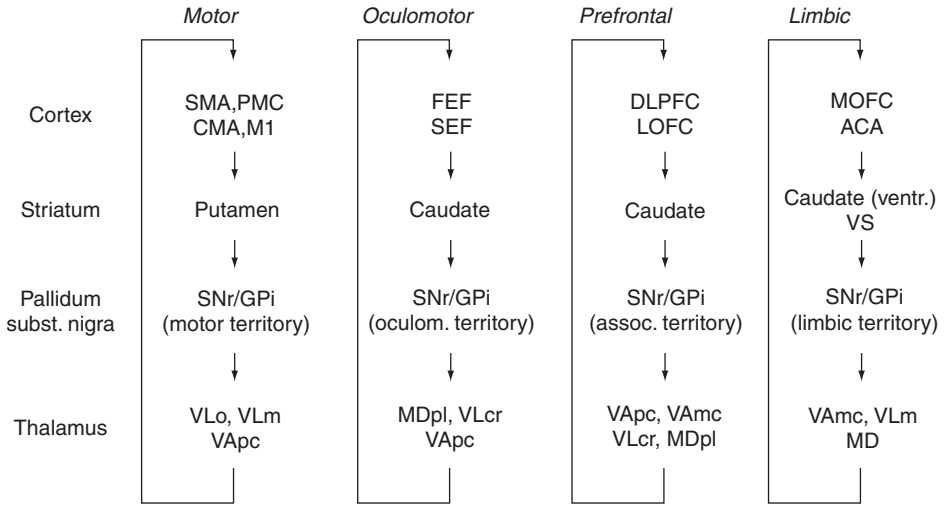

Figure 2 Circuit anatomy of cortex–basal ganglia–thalamocortical circuits. ACA, anterior cingulate area; CMA, cingulate motor area; DLPFC, dorsolateral prefrontal cortex; FEF, frontal eye fields; GPi, internal pallidal segment; HD, Huntington's disease; LOFC, lateral orbitofrontal cortex; M1, primary motor cortex; MDpl, mediodorsal nucleus of thalamus, pars lateralis; MOFC, medial orbitofrontal cortex; OCD, obsessive-compulsive syndrome; PD, Parkinson's disease; PMC, premotor cortex; SMA, supplementary motor area; SEF, supplementary eye field; SNr, substantia nigra pars reticulata; TS, Tourette's syndrome; VApc, ventral anterior nucleus of thalamus, pars parvocellularis; VAmc, VA nucleus of thalamus, pars magnocellularis; VLm, ventrolateral nucleus of thalamus, pars medialis; VLo, VL nucleus of thalamus, pars oralis; VLcr, VL nucleus of thalamus, pars caudalis, rostral division; VS, ventral striatum. Reproduced from Wichmann T and Delong MR (2006) Deep brain stimulation for neurologic and neuropsychiatric disorders. *Neuron* 52: 197–204, with permission from cell press.

As is shown in **Figure 1**, each of the basal ganglia-thalamocortical circuits utilizes portions of striatum, GPe, GPi, SNr, STN, and parts of the VL, VA, and mediodorsal thalamus (MD), respectively. Of the different circuits passing through the basal ganglia, the motor circuit has been the most intensely investigated, because abnormalities in this circuit play a major role in the development of the motor abnormalities in PD and other movement disorders. This circuit arises from the precentral motor fields, and engages the putamen, 'motor' portions of GPe, STN, and GPi/SNr, as well as parts of the VL thalamus. The circuit contains groups of neurons which discharge in conjunction with either the preparation for, or the execution of, limb movements.

The basal ganglia projections to the VL thalamus appear to modulate the activity of cortico-thalamocortical circuits. The basal ganglia also send projections to the intralaminar nuclei of the thalamus (CM/PF). The interaction of these nuclei with the cerebral cortex is limited. Instead, CM/PF send topographically organized projections to the striatum. These thalamostriatal projections close a feedback loop by which basal ganglia output influences activity at the major input stage of the basal ganglia.

Through descending projections to the PPN and other brainstem nuclei, the basal ganglia may directly influence brainstem and spinal motor mechanisms. The PPN is also a part of several feedback circuits through its projections to the basal ganglia and the thalamus.

Direct, indirect, and hyperdirect pathways

GPi and SNr receive most of their inputs via pathways that originate in the striatum. The connections that link the striatum and GPi/SNr can be split into several pathways with possibly opposing functions (**Figure 3**). These input and output structures of the basal ganglia are connected via a *direct*, monosynaptic connection, and via an *indirect* pathway that passes first to GPe and from there to GPi/SNr, either monosynaptically or via the intercalated STN. In addition, the output nuclei receive inputs from the STN that reflect cortico-subthalamic inputs, the so-called *hyperdirect* pathway. As mentioned earlier, these pathways can be distinguished histochemically. The degree of separation between direct and indirect pathway, and the interactions between these pathways and the hyperdirect pathway are not fully defined, but are obviously of great importance in terms of the function of the basal ganglia circuitry as a whole.

The striatal neurons that give rise to the direct and indirect pathways appear to receive inputs from different populations of cortical neurons. Thus far, this has been demonstrated only in rodents. There is also limited evidence that direct pathway neurons may receive stronger inputs from CM/PF than the indirect pathway neurons, although there is a rich network of interneurons and axon collaterals in the striatum which would be capable of transferring information between the two pathways. CM/PF inputs to the striatum appear to be more concentrated and focal than the cortical inputs. These two

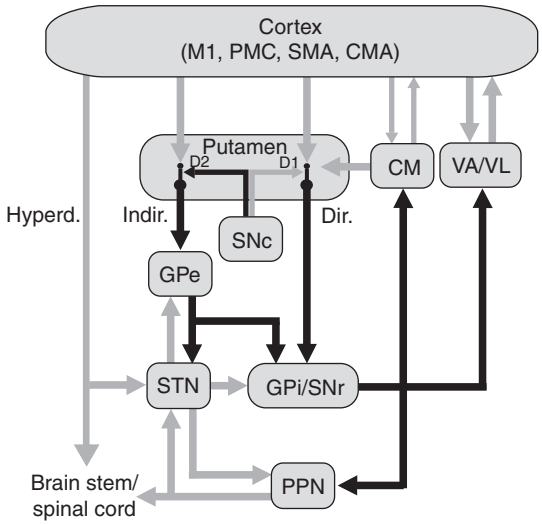

Figure 3 Basal ganglia–thalamocortical motor circuit. Black arrows indicate inhibitory connections; gray arrows indicate excitatory connections. CM, centromedian nucleus; Dir., direct pathway; D1, D2, dopamine receptor subtypes; Hyperd., hyperdirect pathway; Indir., indirect pathway; PPN, pedunculopontine nucleus; SNc, substantia nigra pars compacta; STN, subthalamic nucleus. For other abbreviations, see legend of **Figure 1**. Reproduced from Galvan A and Wichmann T (2008) Pathophysiology of parkinsonism. *Clinical Neurophysiology* 119: 1459–1474, with permission from Elsevier.

types of glutamatergic inputs can be distinguished anatomically by their expression of different types of the vesicular glutamate transporter (vGluT); the corticostriatal inputs express vGluT1, while the thalamic inputs express vGluT2. The use of these markers has demonstrated different termination patterns of the two glutamatergic inputs. While cortical inputs tend to end on striatal spines, a large proportion of the thalamic inputs from CM/PF are found along shafts of MSN dendrites.

Basal Ganglia Function

Ever since the demonstration that movement disorders such as PD, Huntington's disease (HD), or dystonia are associated with basal ganglia pathology, these nuclei have been seen primarily as playing a role in the control of movement. However, the realization that nearly all disorders of the basal ganglia are associated not only with movement abnormalities but also with disturbances in cognition and mood has led to the current view that the basal ganglia have broad functions in the control of behavior, and that the anatomical organization of these structures may provide the framework for understanding these findings.

The diverse functions of the basal ganglia are reflected in the segregated circuit anatomy that is outlined above. The motor circuit is thought to play roles in several behavioral functions, ranging from the control of individual movement parameters, such as the amplitude or velocity of movement, to the initiation or execution of internally triggered movements, sequencing of movements, switching between movements or motor programs, or a role in procedural learning. The oculomotor circuit is concerned with the control of saccadic eye movements, and with head and neck movements during orienting behaviors. The associative prefrontal circuits are implicated in executive functions. Finally, the limbic circuit participates in mood regulation, motivation, and responses to reward.

Hypotheses regarding the role of the direct and indirect pathway topography have been specifically developed with regard to the motor circuit. Similar functional interactions may also be true for the other circuits. One function of the motor circuit may be to regulate the overall amount of movement or to facilitate cortically initiated movements. Activation of the direct pathway by cortical inputs (for instance, in relation to planned or ongoing movements) would inhibit the activity of the output nuclei (GPi/SNr), and thereby disinhibiting thalamocortical projection neurons. This would result in greater activity of thalamocortical and cortical neurons, and presumably facilitation of movement. In contrast, activation of striatal neurons that give rise to the indirect pathway would have a net excitatory effect on GPi/SNr activity and would act to inhibit thalamocortical neurons, and to inhibit or stabilize the activity in the thalamus and brainstem, thereby suppressing potential competing movements or terminate ongoing movements or postures.

Dopamine is thought to exert opposing effects on the direct and indirect pathways. Increased release of dopamine may activate the direct pathway (via D1-receptors) and inactivate the indirect pathway (via D2 receptors). Together these changes would act to reduce basal ganglia output to the thalamus. Conversely, a reduction of the release of dopamine would result in disinhibition of the indirect pathway, and reduced facilitation of the direct pathway, leading to increased basal ganglia output. Dopamine is also released at extrastriatal sites within the basal ganglia. For instance, dopamine released from local dendrites of SNc neurons may activate D1-receptors on terminals of the striatonigral projection. This may then result in increased local GABA release in the SNr, and subsequent inhibition of the activity of SNr neurons. Basal ganglia output may also be shaped by nonlinear effects that go beyond straight excitation or inhibition. These effects may be similarly influenced by dopamine and other neuromodulators. While phenomena such as rebound bursting

or changes in oscillatory basal ganglia activity are well-documented to occur during normal basal ganglia function, their behavioral significance is not known.

Among the most actively discussed functions of the basal ganglia is their role in the regulation of habit formation and procedural learning. Procedural learning is a form of memory formation in which implicit rules of behavior are learned, often without the subject's knowledge. The basal ganglia may help to generate responses to recurrent behavioral situations, and to provide preformed procedures (or 'chunks of behavior') to the cerebral cortex that can then be executed at reduced computational cost when specific behavioral conditions are met. Central to the formation and storage of such procedures appears to be the modulation of the strength of specific corticostriatal synapses through adaptive processes such as long-term potentiation or long-term depression. Procedural learning and habit formation is not dependent on a single basal ganglia circuit but may involve transfer of information between circuits over time: in the process of learning motor procedures, limbic and associative areas of the basal ganglia may be involved first, followed by a gradual shift of activity patterns away from the initial areas and toward the motor circuit.

Role of Abnormal Basal Ganglia Function in Human Disease

Circuit Disorders

The fact that basal ganglia function is best understood in terms of their interaction with cortex, thalamus, and brainstem has given rise to the view that 'basal ganglia' disorders are in reality 'circuit' disorders, which affect not just basal ganglia function, but also has profound effects on related brain areas. A wide spectrum of motor and nonmotor disorders has been described as the consequence of dysfunction of these circuits. Pathophysiological details have been elaborated specifically for PD, while much less is known about other movement disorders and neuropsychiatric conditions.

Parkinsonism

The cardinal motor features of PD, that is, akinesia/bradykinesia, tremor at rest, and muscular rigidity, result from decreased dopaminergic transmission in the motor portions of the basal ganglia, in particular in the putamen, due to progressive loss of dopaminergic neurons in the SNc which project to this portion of the striatum. Dopamine loss in the putamen has recently been shown to also affect the morphology of nondopaminergic neural elements in the striatum. The most salient change secondary to dopamine loss is the reduction in the number of dendritic spines on MSNs. The reason(s) for this change are not clear, but it is likely that the spine loss may strongly affect cortico- and thalamostriatal transmission onto striatal neurons.

Other features of the disease such as depression, autonomic dysfunction, sleep disorders, cognitive impairment, and gait/balance problems may result in part from decreased dopamine levels within the nonmotor portions of the basal ganglia, but there is strong evidence that widespread pathological changes outside of the dopaminergic system (such as in brainstem, thalamus, and cerebral cortex) play a major role in the development of these symptoms. Due to the lack of suitable animal models, these extra-dopaminergic aspects of the diseases are poorly understood. We will focus on the aspects of the disease that result from dopamine deficiency and that can be studied in animal models of the disease and, to some extent, in patients.

Numerous studies of single cell activity in the basal ganglia of Parkinsonian primates have found increased levels of neuronal discharge in the STN and GPi with decreased discharge in GPe, indicating an increased level of inhibition of the thalamus and other targets of pallidal outflow and, thus, reduced and slowed movements. Such studies have suggested that parkinsonism is associated with substantial changes of corticostriatal transmission at corticostriatal synapses which then acts to strongly influence the activity of striatal efferents. At a very simplistic level, it is proposed that the activity along the striato-GPe pathway is increased because of dopamine loss at the inhibitory postsynaptic D2-type dopamine receptors in the striatum, resulting in over-inhibition of the GPe, disinhibition of STN cells, and excessive stimulation of GPi/SNr. In addition, a reduction of activity over the direct (striato-GPi/SNr) pathway is proposed, as a result of the reduced activation of the (stimulatory) D1-type dopamine receptors in the striatum. Dopamine loss at other sites within the basal ganglia (in STN, GPi, and SNr) may also play a role in these changes.

Parkinsonism is associated with changes in firing patterns in the basal ganglia which are likely the result of striatal dopamine loss. Single neuron and local field potential recording studies have demonstrated that pathologic oscillations in the 10–25 Hz range of frequencies throughout the basal ganglia and cortex are associated with parkinsonism. These oscillations are speculated to disturb normal patterns of oscillatory (and presumably other) activities at the cortical level. In addition, the proportion of cells in STN, GPi, and SNr which discharge in bursts is greatly increased in parkinsonism, and cells are known to show an abnormally high level of synchrony in their firing.

Functional imaging of the cerebral cortex in parkinsonian patients has demonstrated that the altered subcortical activity has indeed strong effects on cortical activity patterns. It is not known how such abnormalities are then translated into the movement abnormalities in parkinsonian subjects. Although far less explored, altered basal ganglia output to brainstem areas such as the PPN, or to the intralaminar thalamic nuclei may also contribute to parkinsonism.

Hyperkinetic Disorders

Hyperkinetic disorders are a heterogeneous group of diseases characterized by the presence of excessive involuntary movements. Prominent examples for diseases in which these occur include Huntington's chorea and hemiballism. Hemiballism is the most clear cut example of a hyperkinetic disorder resulting from discrete basal ganglia damage: discrete lesions of the motor region of the STN are responsible for the development of involuntary movements of the contralateral limbs. Reduction of the excitatory (glutamatergic) STN output has been shown to lead to a reduction of GPi/SNr activity which would then act to disinhibit thalamocortical projection cells, leading to involuntary movements. The hyperkinetic aspects of the movement disorder in HD are thought to be due to the degeneration of striatal neurons (potentially through excitotoxic processes triggered by abnormal glutamatergic transmission in the striatum) that belong to the indirect pathway. This may secondarily lead to release of GPe neurons from GABAergic inhibition, resulting, in turn, in excessive inhibition of STN neurons.

While the reduction in overall GPi activity appears to be critical for the production of excessive movement, the specific type of movement seen in hyperkinetic diseases (such as chorea, ballismus, or dystonia) may be determined by differences in the neuronal discharge of single neurons or networks of neurons in GPi/SNr. The specific features of these different disorders have not been determined.

Disturbances of Cognitive Functions or Mood

Obsessive compulsive disorder (OCD) may, at least in part, be due to dysfunction of the basal ganglia–thalamocortical circuits originating from the orbitofrontal and cingulate cortices. These abnormalities are far less defined than they are in movement disorders. However, functional imaging studies in human patients have shown prominent activity changes in OCD in the ventral striatum (VS) and in the midbrain. Tourette's syndrome (TS), that is, the combination of OCD-like symptoms with vocal or motor tics, is also associated with abnormalities in the limbic circuit, in addition to the changes in the areas of the motor circuit.

Functional Neurosurgery

The knowledge that the aforementioned 'circuit disorders' are associated with dysfunction in circumscribed regions of the basal ganglia has resulted in renewed interest among neurosurgeons and neurologists in the treatment of advanced forms of these conditions with highly targeted surgical interventions, such as lesioning or deep brain stimulation. In PD patients, lesions or high frequency stimulation of GPi or STN were found to be highly effective in reducing off-time and producing longer on-times without medication side effects. Similarly, impressive results were also obtained in patients with tremor and dystonia. The utility of neurosurgical interventions is also now being explored in neuropsychiatric conditions such as OCD or TS. While the specific brain target site of the intervention is crucial for the therapeutic success of these procedures in these diseases, the exact mode of intervention (ablation or stimulation) may be less critical. This suggests that the primary effect of the interventions may be nonspecific, perhaps acting simply to remove (with ablation) or to override (with stimulation), abnormal basal ganglia output, and freeing up thalamic and cortical mechanisms.

Concluding Remarks

The basal ganglia together with the cerebral cortex and thalamus are components of parallel cortico-subcortical circuits that play a role in both motor and nonmotor behaviors. The traditional view that the basal ganglia are primarily involved with movement and play a role in the control of specific aspects of movement is largely based on the fact that basal ganglia pathology often results in prominently disordered movement and/or in involuntary movements. It is now becoming clear that these structures may have important functions in the control of higher-order aspects of behavior, linking emotion, cognition, behavior, and movement, and that they may have specific relevance for adaptive shaping of behaviors.

The circuit models of basal ganglia function and dysfunction continue to evolve. The traditional view that the basal ganglia simply relays cortical activity back to cortex is being replaced by more general organizational schemes in which large-scale oscillatory and nonoscillatory activities of local or spatially distributed ensembles of neurons play a major role and in which surgical intervention not only activates or inactivates basal ganglia activity, but also modulates firing patterns and other features of basal ganglia activity.

The current circuit models of basal ganglia function and dysfunction have had a major impact on the treatment of diseases such as PD, tremor, and dystonia, and in the renaissance of neurosurgical approaches to the treatment of neuropsychiatric disorders such as TS or OCD.

See also: Basal Ganglia; Direct Pathway; Dopamine; Dystonia; Huntington's Disease; Indirect Pathway; Parkinson's Disease: Definition, Diagnosis, and Management; Substantia Nigra; Subthalamic Nucleus.

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Beam Walking Test

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Glossary

Methylphenyltetrahydropyridine (MPTP) – Substance used to induce specific destruction of dopamine producing cells of the subtantia nigra.

The evaluation of motor deficits in small animals is faced with problems of specificity, that is, tests should be measuring true motor capabilities uncontaminated by tests which rely on reflexive or memory aspects of behavior; or depend on subjective criteria; or on complex motor functions such as stride length; or on fine motor function, as does the pole test, which tests bradykinesia. The beam walking test described here is an inexpensive and simple test of motor function which has the additional advantage of not being subject to practice effects and is specifically designed to detect motor deficits in aged rats and in animals with pharmacologically altered dopaminergic striatal functions.

The apparatus consists of 2-m wooden strips supported by two pedestals at each end. The pedestals are of different heights (42.5 and 100 cm) in order to allow for an inclination of 15°. This inclination is enough to stop animals from crawling over the beam. The width of the strips varies and 3, 6, 12, 18, and 24 mm strips are available. Variably strip widths are achieved by merely clamping strips together in order to obtain desired widths. At the end of the inclined strip, a cage is placed, so that the animals could step into the home cage. **Figure 1** illustrates the apparatus and gives a picture of rats traversing the beam.

It is important to make sure that the entire apparatus be placed at a height of at least 1 m above the ground, so as to make sure that the animal fears the height and really attempts to reach the goal box.

All rats must be trained to walk over a beam for 5 days before testing. The test procedure is identical for all rats tested and performed in the same environment preferably in the morning. The rat is placed on the lower end of the beam and the time needed to reach the home cage is recorded. A ceiling of 120 s is employed at the end of which the rat is removed and placed in the cage by hand and receives, if it is the case, a score of 120 s. The beam width sequence used in each testing session is determined with a table of random numbers. Pilot studies show that this manipulation almost completely eliminates practice effects. The measure utilized for each rat is 'total time' to reach the cage. However, during testing, rats frequently have episodes of immobility. Accordingly, a second measure is taken designated as 'no movement time'. This measure reflects the amount of time that animals merely stood immobile with what appeared as olfactory and visual exploration of surroundings.

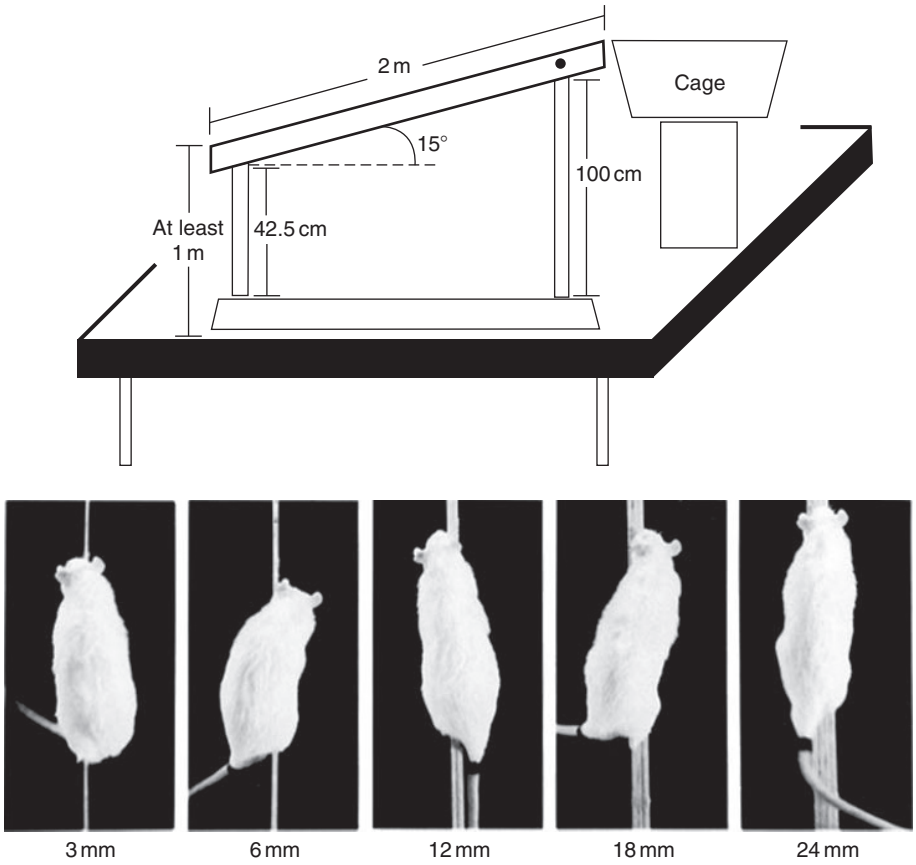

Figure 1 The upper part of the Figure is a diagram of the set up, the lower part is a top view photograph showing the relation between beam widths and size of rats.

It is important to use young rats as controls, but since young rats are usually about half the weight of older rats, a lead belt weighing 100 g is placed around the chest of young rats, in order to determine whether weight is an important factor in the capacity to traverse the beam. The 100 g weight represents an increase of about 40% of the total body weight of the young rats.

This test has been shown to be very effective in detecting pure motor capabilities in rats which have a tendency to show deterioration because of aging processes, but also in those whose striatal dopaminergic function is pharmacologically altered. Anyone who uses this equipment can measure with a great degree of precision, the displacement capacity of the animals. In fact, in this test, very old rats show a similar hesitant motor displacement when placed in very narrow strips, which reminds us of the hesitant march of either advanced Parkinson patients or very aged persons.

Recently a beam walking apparatus was designed and reported to detect behavioral impairments in methylphenyltetrahydropyridine (MPTP) treated mice. Deprenyl was reported to improve the mice's capabilities for traversing the beam. This beam walking test and the one described here seem to be the two best tests detecting pure motor functions. Anyone of the two are highly recommended for detecting pharmacological compounds capable of improving motor capabilities or testing striatal motor function or dysfunction.

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Belly Dancer's Dyskinesia

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Glossary

Dyskinesias – Generic term used to describe involuntary movements.
Dystonia – Twisting, repetitive involuntary movements superimposed on abnormal postures produced by sustained muscle contraction.
Electromyography – Study of the electrical characteristics of muscle activity. In the context of movement disorders, this may include recording the patterns of muscle recruitment and investigation of reflex activity and stimulus sensitivity.
Myoclonus – Sudden, brief, shock like involuntary movements.
Tardive movement disorders – Involuntary movements (dyskinesias) developing after long-term exposure to dopamine antagonists (e.g., neuroleptics).

Definition and History

The term 'belly dancer's dyskinesia' was introduced by Iliceto et al. to describe the unusual slow rhythmic writhing contortions of the abdominal wall and multidirectional displacements of the umbilicus produced by involuntary contractions of the abdominal wall and respiratory muscles. A range of movement disorders has been recognized as producing belly dancer's dyskinesia.

The original report of the 'belly dancer's dyskinesia' included five patients who developed a complex motion of the umbilicus and writhing abdominal movements produced by variable contraction of the rectus abdominus, oblique muscles, and the diaphragm. Spread of muscle activity to paraspinal and perineal muscles was observed in some patients. The movements were discomforting and often associated with pain. In three patients, the movements developed after abdominal surgery. In further two cases, the movements followed childbirth by apparently uncomplicated vaginal delivery. The clinical pattern of sustained muscle contraction and long duration bursts (400–1000 ms) of electromyographic (EMG) activity with superimposed jerky component were considered to reflect a dystonic origin of the involuntary movement. Similar belly dancer's dyskinesia with associated pain developing after abdominal surgery (colonic resection) was later described as segmental myoclonus. In this case, the abdominal muscle activity consisted of long duration bursts of EMG activity lasting for 200–600 ms, and unlike other reports, spread of muscle activity to quadriceps muscles was noted. These examples of belly dancer's dyskinesias, in common with other focal dyskinesias, illustrate the recognized association of pain and involuntary movements at the site of previous trauma.

A further case report described dystonic movements of the abdominal wall developing 5 months after pontine and extrapontine myelinolysis complicated correction of severe hyponatremia. The movements were slow and had a superimposed jerky element, consistent with a delayed onset dystonia reported previously in osmotic dysequilibrium syndromes.

An undulating motion of the abdominal wall was described in a young girl who was later discovered to have an intramedullary thoracic cord tumor. The movements persisted during sleep and were unaffected by voluntary movement or breathing, suggesting an autonomous generator located in segments of the spinal cord isolated from normal descending motor pathways.

Spontaneous arrhythmic abdominal movements similar to a belly dancer's dyskinesia have been recorded as a manifestation of paroxetine (selective serotonin reuptake inhibitor) induced spinal myoclonus, spreading from the abdominal wall to thoracic and lumbar paraspinal muscles. This patient also had evidence of a compressive thoracic radiculopathy, which the authors postulated may have contributed to the movement disorder. The EMG bursts accompanying the abdominal movements in this case were characterized by brief duration (100–500 ms), 3 Hz motor unit discharges with occasional high frequency discharges, suggesting a peripheral contribution to the movement disorder. Spinal myoclonus was also considered the cause of asymmetric, predominantly right sided, abdominal movements in a 63-year-old man. Detailed electrophysiology demonstrated stimulus sensitivity and spread of muscle activity to thoracic and lumbar paraspinal muscles, suggesting that a spinal reflex was driving the abdominal movements.

Abdominal movements as a manifestation of tardive dyskinesia have been described as 'rocking belly movement.' Similar tardive movements comprising continuous sinuous abdominal movements superimposed on episodic tightening of the axial musculature, breathing difficulties, and anxiety were reported following the exposure to clebopride (a substituted benzamide related to metoclopramide).

Slow undulating protrusion and retraction motion of the abdominal wall representing a peak dose levodopa induced dyskinesia were observed in a patient with presumed multiple system atrophy.

Diaphragmatic flutter can also lead to abdominal wall movement and belly dancer's dyskinesia. It is characterized by contraction of one or both domes of the diaphragm at frequencies of 1–8 Hz superimposed on normal tidal breathing. The diaphragmatic movements depress the abdominal contents during each descent, leading to repetitive protrusion and retraction of the anterior abdominal wall, creating a jerky or pulsatile motion. Additional muscles including the intercostals, scalenes, epiglottis, paraspinal, and abdominal muscles may be recruited and may contribute to the observed abdominal movements. The fluttering diaphragm movements are best observed on video fluoroscopy. The movements are intermittent and fluctuate during the breathing cycle. Deep inspiration and breath holding may suppress the movements.

Abdominal movements are the most frequent manifestation of diaphragmatic flutter. The intensity of the movements may be forceful enough to produce an audible sniffs, succession splash, and gurgling noises. Respiratory (tachypnoea, hyperventilation) and gastrointestinal (belching, hiccups, retching) presentations are also described.

Belly dancer's dyskinesias are of cosmetic concern and most are difficult to treat, despite numerous trials of pharmacological agents.

See also: Dystonia, Traumatic; Palatal Myoclonus; Spinal Segmental Myoclonus; Tardive Syndromes.

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Benign Paroxysmal Torticollis of Infancy

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Glossary

Ataxia – Lack of coordination.
Benign – Not malignant or life threatening.
Cervical dystonia – Involuntary contraction of muscles of the neck causing awkward posture and abnormal movements of the head and neck.
Hypotonia – Decreased muscle tone.
Paroxysmal – Intermittent, recurring.
Torticollis – From Latin, meaning 'twisted neck.'

Definition and History

Benign paroxysmal torticollis (BPT) of infancy was first described by Snyder in 1969. The condition is characterized by recurrent episodes of torticollis that begin in infancy and resolve by 2–5 years of age. The torticollis may alternate from side to side, may last for minutes to days, and may cycle by several weeks to months until it resolves. Associated features include hypotonia, pallor, vomiting, ataxia, irritability, and drowsiness. Infants with this condition may develop benign paroxysmal vertigo (BPV) in childhood and migraine later in life.

The etiology continues to unfold. When first described, BPT was felt to be due to a peripheral vestibular disturbance. Since then, others have pointed to the cerebellum and vestibulocerebellar connections as sources of the condition. More recently, it is felt that BPT is a precursor of migraine in children.

Pathogenesis and Physiology

When first described by Snyder in 1969, the etiology of BPT was felt to be a disturbance of the peripheral vestibular system, such as a labyrinthitis. This was based on the

fact that a number of the first cases reported lacked vestibular responses to caloric testing and some had decreased hearing. Later, cases of BPT were reported in which testing of the vestibular response and hearing were normal. Possible etiologies proposed were vascular abnormalities affecting the cerebellum or vestibulocerebellar connections, or a migraine equivalent. More recently, several cases of BPT were described in which there were family members with familial hemiplegic migraine and mutations in the calcium channel gene CACNA1A. The authors propose that BPT may be a childhood migraine equivalent and possibly associated with a calcium channelopathy. They postulate that the channelopathy may have different manifestations at different stages of development. The torticollis seen during an episode of BPT has been studied by surface EMG recordings placed on the sternocleidomastoid muscle. Continuous electrical discharge has been recorded and felt to be consistent with a dystonia of the muscle. Some have proposed that the dystonia may in fact be an atypical motor aura which is mediated by calcium channel abnormalities affecting the cerebellum. The International Headache Society-International Classification of Headache Disorders 2nd edition (IHS-ICHD II) classifies BPT under migraine and subcategory of childhood periodic syndromes that are commonly precursors of migraine. Further studies need to be carried out to enhance our understanding of this condition.

Epidemiology/Risk Factors

BPT is an under-recognized entity. There does not appear to be a gender or ethnic predominance. To date, a single gene defect has not been linked to the disorder. However, there have been cases in which there is a positive family history of torticollis in infancy as well as in family members with migraine or familial hemiplegic migraine. Recently, there were two cases described from families with known mutations in the CACNA1A gene and familial hemiplegic migraine.

Clinical Features

Frequently, the torticollis will appear in the morning upon awakening. An infant will awake with head tilted to one side or the other, and eyes facing the opposite direction. There is usually not a precipitating illness or event. The head can usually be brought to the neutral position. Episodes can last from several minutes to days and resolve completely. There may be associated features which accompany the torticollis and include decreased tone, pallor, vomiting, lethargy, and irritability. Often the child will be unsteady or ataxic. The neurologic exam is generally normal except for the torticollis and ataxia during an episode and normal in between attacks. As the infant grows older, the frequency of the attacks decreases and ultimately they resolve. These episodes may then be replaced with episodes of vertigo, or BPV of childhood. Individuals may then go on to develop migraine in adulthood.

Differential Diagnosis

Torticollis can be seen in a number of entities in childhood. The presentation of early onset, recurring torticollis, with previously described associated features and no other focal neurological deficits, should lead to a diagnosis of BPT. However, when evaluating a child for new onset torticollis, several processes should be included in the differential after a thorough history and physical examination have been completed. Drug-induced dystonia should be excluded by a thorough drug history and specifically asking for the use of medications such as phenothiazines and metoclopramide. Posterior fossa tumors and atlantooccipital subluxation leading to spinal instability should be ruled out. Other cervical lesions would include Chiari malformation, cervical abscess, or trauma. Upper respiratory tract infections, superior oblique palsy, retropharyngeal abscess, seizures, and Sandifer syndrome are also included in the differential. Sandifer syndrome is a condition which includes spasmodic torsion dystonia with arching of the back and opisthotonic posturing of the neck, back, and upper extremities, and is associated with gastroesophageal reflux or hiatal hernia.

Diagnostic Work Up/Tests

A proper history and physical examination are essential in making the diagnosis of BPT. Neuroimaging, included MRI of the brain and cervical spine should be carried out to rule out structural lesions. Electroencephalograms (EEGs) are often ordered to rule out the possibility of a seizure given the associated features which can accompany the torticollis. In the case of BPT, however, both neuroimaging studies and EEG are normal. Referral to a Gastroenterologist may be worthwhile if other associated features of gastroesophageal reflux are noted.

Management

Once the diagnosis is made, no specific therapy is indicated as the episodes are self-limiting. Children should be monitored for the development of BPV or migraine later in life.

Prognosis

Episodes of recurring torticollis usually resolve by 2–5 years of age. As stated, infants can go on to develop vertigo

in childhood or migraines as adults and should be monitored and treated accordingly. Prognosis overall is good.

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Benzodiazepines and Movement Disorders

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Glossary

CBD – Cortical basal degeneration.
Dystonia – A movement disorder causing abnormal postures.
GABA – γ-Aminobutyric acid, an inhibitory neurotransmitter in the brain and spinal cord.
MSA – Multiple system atrophy.
Myoclonus – A movement disorder causing muscle jerks.
PSP – Progressive supranuclear palsy.

Introduction and Pharmacology

Benzodiazepines are members of a class of medications that have anxiolytic, hypnotic, amnestic, anticonvulsant, and skeletal muscle relaxant effects. Although there are over 30 drugs in this class and many have overlapping effects, they can roughly be divided by their clinical use into hypnotic sedatives and anxiolytics.

Members of the latter group include alprazolam, diazepam, lorazepam, and clonazepam which are the ones that are chiefly used in the treatment of movement disorders and will be discussed in this chapter.

Pharmacokinetics

Benzodiazepines are well absorbed by following oral administration. Lorazepam is well absorbed after sublingual administration as well. Absorption of lorazepam is also rapid and complete following intramuscular administration, whereas the absorption of diazepam after intramuscular injection is slow and erratic.

The distribution, clearance, and metabolism of benzodiazepines are somewhat complex. They are highly bound to plasma proteins but are also lipophilic and rapidly penetrate the CNS. This initial redistribution phase is followed by a slower phase in which the drugs and their active metabolites accumulate into less vascular tissues such as fat, and then more slowly diffuse back into plasma and prolong the clearance and some of the clinical effects. This is especially prominent with diazepam.

Benzodiazepines are metabolized into both active and inactive metabolites depending on the drug. Diazepam is converted to nordiazepam, an active metabolite with a far longer duration of action, as well as to oxazepam, before being converted to inactive compounds. Alprazolam is also converted to active metabolites, whose duration of action is roughly similar to the parent drug. Clonazepam and lorazepam, in contrast, have no active metabolites. The metabolism of benzodiazepines occurs in the liver

and the duration of action may be quite prolonged in patients with hepatic insufficiency.

CNS Pharmacology

Benzodiazepines largely act by binding to a portion of the γ-aminobutyric acid ($GABA_A$) receptor, referred to as benzodiazepine receptors (BzR). Occupancy of the BzR receptor by a benzodiazepine produces a conformational change in the GABA receptor which increases the binding of GABA. This in turn, increases the permeability of an associated chloride channel and hyperpolarizes the associated neuron. There are effects on other ion channels; the hypnotic effects of benzodiazepines may be mediated by alterations in calcium permeability, and anticonvulsant effects may partially depend on effects on sodium channels.

The actions of benzodiazepines vary throughout the CNS. BzRs are found in high density in the cerebral cortex, cerebellum, substantia nigra, and inferior colliculus, with somewhat lower densities found in the striatum and spinal cord. In addition, there are multiple subtypes of $GABA_A$ receptors. These receptors are a pentameric structure, including α, β, and γ subunits. Sedation and anticonvulsant properties appear to be mediated through binding onto the $GABA_A$ receptors which are made up of α_1 subunits, whereas anxiolysis and muscle relation are mediated by $GABA_A$ receptors that have the α_2 subunit.

Tolerance: A common property of all benzodiazepines is that tolerance develops with chronic administration, reflecting downregulation of the BzR density in target tissues. The degree of tolerance varies between patients and to different clinical effects. Tolerance may develop more rapidly and completely to sedation, for example, than to motor effects. However, a declining effect to benzodiapezepines occurs in most patients and limits the effectiveness of therapy. Strategies to avoid tolerance should include using the medications for intermittent, rather than constant use if possible, choosing short acting drugs if appropriate, and limiting the dose and duration of treatment.

Dependence: both psychological and physical dependence occur with long term administration of benzodiazepines. Sudden withdrawal or a rapid reduction in the dose may produce a state of heightened anxiety, tremulousness, tachycardia, and can produce seizures.

Hypokinetic Movement Disorders

Parkinson's Disease

A number of different symptoms commonly experienced in patients with Parkinson's disease may be improved by adjunctive use of a benzodiazepine. In addition to control of anxiety and insomnia, which are very common in Parkinson's disease, several motor symptoms and sleep associated disorders may be improved with the use of a benzodiazepine.

Motor symptoms

Although levodopa, dopamine agonists, anticholinergics, amantadine, and MAO B inhibitors are effective for most motor symptoms in Parkinson's disease, not all motor symptoms can be adequately treated.

Tremors that occur despite the standard antiparkinsonian drug treatments may improve with a benzodiazepine, particularly if the tremors worsen with fatigue, excitement, or social anxiety (such as dining in a restaurant or public speaking). If these exacerbations are predictable, intermittent use of alprazolam or lorazepam, taken an hour beforehand, may reduce the severity of tremor and improve functioning. As tolerance tends to develop over time, frequent or scheduled use of these agents may be less effective. One exception, though, is in patients with a generalized anxiety disorder. In these patients, treatment with a longer acting anxiolytic such as diazepam or clonazepam may improve both the anxiety and tremor.

Dystonia is another motor symptom which generally improves following the administration of a benzodiazepine. Dystonia can occur in a number of different settings. A number of different benzodiazepines can be used to treat dystonia. A longer acting drug, such as clonazepam or diazepam taken before sleep, can be helpful in reducing early morning dystonia. Some patients experience unpredictable 'off' episodes during the day, and painful dystonic spasms can be especially prominent. In these episodes, an agent with a quick onset of action, such as alprazolam, may be helpful in reducing both the pain and the severity of dystonia.

In addressing both tremor and dystonia in the context of Parkinson's disease, adjustment of antiparkinsonian medications is first line approach, making benzodiazepines secondary medications, unless there are concomitant issues with anxiety or insomnia that would make them appealing choices.

Sensory and psychological symptoms

Anxiety is quite common in Parkinson's disease, affecting over half of the patients. In addition to antidepressants that have anxiolytic effects, benzodiazepines have an important role in treatment. In the chronically anxious patient, clonazepam, lorazepam, or diazepam may be helpful. However, these medications can also worsen depression if taken long term, and other medications should be tried first.

Anxiety and dysphoria are extremely common symptoms during 'off' episodes as well. Some patients have mood fluctuations that are more bothersome than motor fluctuations; moods may swing widely between euphoria

and depression, anxiety, dysphoria, or panic like attacks. In these patients, alprazolam or lorazepam, taken on an as needed basis, can be helpful. If severe and frequent, longer acting benzodiazepines may be needed.

Sensory symptoms, including coldness, tingling, aching, and stiffness also can occur, either as a constant or intermittent symptom; similar to anxiety, these symptoms may be worse or only occur during 'off' periods and may also respond to benzodiazepines.

Parasomnias

REM behavior disorder (RBD) is characterized by the acting out of dreams that are vivid, intense, and violent. These movements occur due to a loss of normal atonia that occurs during REM sleep that is produced by actions of pontine nuclei on descending motor pathways in the lower brainstem and spinal cord. In patients with RBD, a loss of inhibition of these pontine nuclei seem to be the anatomical basis for the disorder, due to loss of dopaminergic, noradrenergic, and cholinergic inputs into these structures. Clonazepam is the drug of choice for this condition, both in patients with Parkinson's disease as well as in other patients. It is effective in up to 90% of patients, relieving symptoms at doses of 0.5–1 mg at night. In contrast to other conditions, tolerance generally does not develop. With long term treatment, some associated behaviors such as sleep talking or limb movements may reemerge, but the more violent, potentially injurious behaviors usually remain controlled.

Restless leg syndrome (RLS) and periodic limb movement disorder (PLMD) are also very common symptoms in patients with Parkinson's disease. As with RBD, these conditions are not specific to Parkinson's disease but affect most patients when studied by polysomnography. These conditions cause an urge to move the limbs when awake (RLS) and periodic, semiregular limb movements during sleep (PLMD). These conditions are generally controlled with dopaminergic medications, but benzodiazepines are useful adjuncts in some patients with these conditions. As with dystonia, a longer acting benzodiazepine such as diazepam or clonazepam may be a good choice if used nightly.

Secondary parkinsonism (PSP, MSA, CBGD)

In addition to rigidity and bradykinesia, dystonias commonly occur in patients with these illnesses. Unlike Parkinson's disease in which dystonias more commonly waxes and wanes with other motor symptoms, the dystonias that occur with these conditions are relatively constant. Limb dystonia that occurs in CBGD can become extremely marked and may evolve into fixed contractures. As discussed in the preceding section, both intermediate and long acting benzodiazepines may be useful adjuncts in the control of dystonia.

Myoclonus is also a common accompaniment to CBGD and, as discussed below, typically responds well to lorazepam or clonazepam.

Hyperkinetic Movement Disorders

Dystonias

In addition to botulinum toxin injections, oral medications, including anticholinergics and benzodiazepines, are useful adjunctive drugs in many patients with focal or generalized dystonia. This may include patients with primary dystonia, such as cervical dystonia or Meige syndrome, as well as in secondary dystonias such as tardive dystonia, stroke, or in patients with a degenerative disorder in which dystonia is present. Benzodiazepines are a mainstay in the treatment of cerebral palsy in which dystonia or athetosis is a major feature. They can be effective in reducing all aspects of dystonia, such as pain, dystonic tremor, and posturing, although the effects may be somewhat modest.

Acute dystonic reactions are episodes of severe dystonia that typically follow administration of an antiemetic or a dopamine antagonist. It is generally reversed with parenteral doses of antihistamines or anticholinergics, but is also effectively treated with parental doses of lorazepam or diazepam.

In most patients with constant symptoms, clonazepam is the best tolerated, but in other patients with intermittent symptoms, alprazolam or lorazepam may be the better choices. A common setting in which benzodiazepines may be especially useful is in patients receiving botulinum toxin injections; as the effects of the injections wear off, treatment with clonazepam or lorazepam, with or without other oral medications, may be helpful.

One challenge in some patients is that moderate or high doses of a benzodiazepine may be needed to improve dystonia and sedation, ataxia, depression, and confusion, generally limit treatment in most patients over time. Sudden withdrawal of any benzodiazepine may cause sudden worsening of dystonia and should be avoided.

Tolerance to this class of drugs may also limit treatment in some patients, and intermittent or short term treatment may be indicated in some patients.

Tic Disorders

In some patients with Tourette's syndrome or other tic disorders, benzodiazepines may be effective, particularly when treating tics with a fast, clonic appearance or tics driven by anxiety, although no study has ever shown a direct effect of benzodiazepines on tic counts. Clonazepam is the preferred drug as it is less sedating, but if intended for intermittent use (such as treating tics that occur in social situations), a shorter acting benzodiazepine such as

alprazolam or lorazepam may be more appropriate. Although less effective than dopamine antagonists, the use of a benzodiazepine does not carry the risks of tardive dyskinesia or cardiac arrhythmias and may be more appropriate in patients with a mild tic disorder. The anxiolytic effects of a benzodiazepine may also be beneficial and may be a necessary part of a treatment regimen in patients with both severe tics and psychiatric disease.

Although helpful, there are significant limitations in the treatment of tic disorders with benzodiazepines. Patients with severe motor tics or with disruptive phonic tics generally do not respond adequately to benzodiazepines. This class of drugs is largely ineffective in the treatment of obsessive compulsive disorder. In adolescents and young adults especially, benzodiazepines carry a real risk of drug misuse and dependency, of impairing school performance and driving, and can be dangerous when combined with alcohol. Tolerance also develops with long term use of benzodiazepines in the treatment of tic disorders.

Myoclonus and Hemifacial Spasm

Myoclonus can occur as a primary disorder as well as a secondary symptom in a large number of other neurological and systemic medical disorders and can originate from many regions in the central and even peripheral nervous system.

One pattern of myoclonus, in which random jerks can occur in multiple body parts, is the common manifestation of metabolic encephalopathy, particularly hepatic and renal failure.

Unlike other movement disorders in which benzodiazepines have a more minor effect or adjunctive role, several myoclonic disorders generally respond well to clonazepam. Epileptic myoclonus, palatal myoclonus, and myoclonus of spinal origin seem to respond well to clonazepam. Myoclonic dystonia, a condition in which patients experience a mixture of dystonia and superimposed myoclonic jerking, also responds well. Other benzodiazepines may be beneficial but their effectiveness is somewhat less well established.

In contrast to other conditions, tolerance does not seem to develop as readily in the treatment of myoclonus with benzodiazepines.

Hemifacial spasm, a condition in which the periorbital and perioral muscles exhibit synchronous contraction, is usually due to vascular compression of the facial nerve and may cause fast, clonic contractions as well as slower movements of the affected region.

Essential Tremor

In addition to beta blockers and primidone, benzodiazepines may also reduce the severity of essential tremor in some patients. Both shorter acting drugs such as alprazolam and lorazepam, and longer acting drugs, such as diazepam and clonazepam, may be used.

Some variants of tremor may respond particularly well to benzodiazepines. Clonazepam is effective in some patients with orthostatic tremor, a rapid, tremor like movement that affects the legs and trunk when standing. Cerebellar action tremor may also improve partially with large doses of clonazepam.

Because of the tendency to develop tolerance with continued use, intermittent or short term use of shorter acting benzodiazepines may be more effective over time.

Stiff Person Syndrome

This condition (formerly termed stiff man syndrome) is an autoimmune disease, producing fluctuating stiffness of trunkal and proximal limb muscles.

In most patients, plasma and CSF antibodies directed against glutamic acid decarboxylase (GAD) are found. This enzyme synthesizes GABA, and anti GAD antibodies have been shown to block GABAergic neurotransmission.

Benzodiazepines have a central role in treatment. Along with other medications such as baclofen, tizanidine, and immunosuppression or IVIG, high doses of diazepam or other long acting benzodiazepines are needed.

Tetanus

Tetanus is a neuromuscular disease which results from an intoxication resulting from an infection by an anaerobic bacteria, *Clostridium tetani*, most commonly following puncture wounds and lacerations. This bacteria secretes a potent neurotoxin, tetanospasmin, which prevents release of neurotransmitters from neurons. Inhibitory GABAergic and glycinergic intereurons in the spinal cord and brainstem are particularly susceptible. This leads to failure of inhibition of motor reflex responses to sensory stimulation. Although there are several clinical forms, the most common form is generalized tetanus. After a 4–21 day incubation period after infection, symptoms generally begin in the cranial musculature and include trismus, facial grimacing, dysphagia, neck stiffness, and spasms, and then spread distally, affecting the extensor muscles of the trunk and extremities and can cause generalized severe spasms (opisthotonus). Dysautonomia and laryngeal spasm can occur and can be life threatening.

In addition to a number of other supportive treatments, diazepam is a mainstay of treatment. High doses, including an infusion of up to 40 mg h^{-1}, may be needed in severely affected individuals.

See also: Dystonia; Hemifacial Spasm; Myoclonus; Palatal Myoclonus; Palatal Tremor; Periodic Limb Movements; REM-behavior Disorder; Restless Legs

Syndrome; Stiff Person Syndrome and Variants; Tics; Tics, Complex; Tics, Simple; Tourette Syndrome; Tremor; Tremor, Essential (Syndromes); Tremor, Holmes.

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Beta-blockers and Movement Disorders

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Glossary

Beta blocker – A competitive antagonist of one or more of the three beta adrenergic receptor subtypes (1, 2, and 3).
Long-loop sensorimotor reflex – A long-latency stretch reflex loop that includes the cerebral cortex.
Mechanical-reflex tremor – A tremor that is produced by the inherent tendency of a body part to oscillate, caused by the mechanical properties of the limb. Segmental and long-loop sensorimotor reflexes become involved when the tremor is enhanced by fatigue, hyperthyroidism, drugs, anxiety, or other states of increased adrenergic stimulation (enhanced mechanical-reflex tremor).

Definition

Beta blockers are competitive antagonists of one or more of the three beta adrenergic receptor subtypes (1, 2, and 3). All three beta receptors are coupled to stimulation of adenyl cyclase. The systemic effects of beta receptor stimulation and inhibition are well known, but the effects on the peripheral and central nervous system are not clearly defined, particularly as they pertain to movement disorders. Selective β-3 antagonists are not available for clinical use, and their relevance to the field of movement disorders is unknown. Consequently, only β-1 and β-2 antagonists are considered in this review.

Pharmacology

Propranolol is the prototypic beta blocker. It is nonselective, meaning that it blocks β-1 and -2 receptor subtypes. It also has high lipid solubility, so it is believed to enter the central nervous system more readily than beta blockers with low lipid solubility. However, little is known about the penetration and binding of these drugs in the central nervous system.

Beta blockers have been used extensively in the treatment of tremor, and lipid solubility and receptor sensitivity have not been reliable predictors of clinical efficacy (**Table 1**). Lipid solubility and receptor sensitivity are of relative importance. Plasma concentration and receptor affinity are also important.

Pathophysiology

All voluntary and involuntary limb movements are mediated through peripheral sensorimotor loops and the associated musculoskeletal system. This mechanical-reflex system can be the source of involuntary movement (e.g., clonus, physiologic tremor) and can facilitate the transmission of involuntary movements that emerge from central motor pathways. Pathologic tremors (e.g., Parkinson, essential and cerebellar), in particular, are enhanced by increased reflex sensitivity and by faster muscle twitch times. The effect of mechanical-reflex dynamics on other dyskinesias has not been studied.

Stretch reflex sensitivity is increased by peripheral infusion of catecholamines. This effect is due possibly to peripheral enhancement of muscle spindle sensitivity. Peripheral infusion of epinephrine or isoproterenol also reduces the relaxation time of muscle contractions, resulting in less tetanic attenuation of high-frequency fluctuations in muscle force (**Figure 1**). Such peripheral mechanical-reflex modifications could affect the amplitude of involuntary movements, regardless of any additional role played by central nervous system pathways. Peripheral beta blockade will reduce involuntary movements to the extent that they are enhanced

Table 1 Pharmacologic properties of common beta blockers

Drug	*Receptor sensitivity*	*Lipid solubility*	*Plasma half-life (h)*	*Efficacy for ET*[a]
Propranolol	β-1 ≈ β-2	High	4	Level A
Sotalol	β-1 ≈ β-2	Low	12	Level B
Nadolol	β-1 ≈ β-2	Low	22	Level C
Atenolol	β-1 > β-2	Low	6	Level B
Metoprolol	β-1 > β-2	Moderate	5	Level U

[a]Based on the American Academy of Neurology Practice Parameter for essential tremor by Zesiewicz et al.

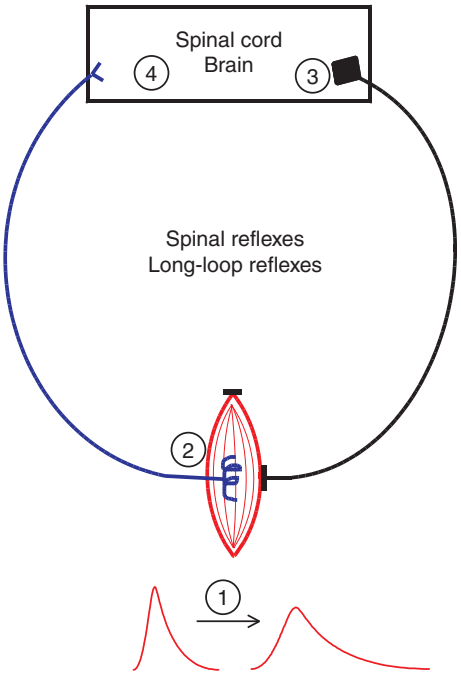

Figure 1 A schematic diagram of the putative sites of action of beta blockers in the suppression of tremor. (a) Slower muscle contraction and relaxation, resulting in greater attenuation of high-frequency fluctuations in motor drive, (b) reduced sensitivity of muscle spindles, (c) reduced sensitivity of alpha and gamma motoneurons, and (d) suppression of abnormal central neuronal network firing or unstable long-loop sensorimotor reflex pathways, which may produce oscillation, other dyskinesias, and systemic release of catecholamines.

by adrenergic stimulation of peripheral mechanical-reflex components (e.g., spindles and skeletal muscle).

Stretch reflex sensitivity is also influenced centrally by catecholamines. Beta adrenergic receptors are found in the spinal cord and brain, particularly the hippocampus, cerebellum, and cortico-basal ganglia-thalamocortical loop. Thus, central beta blockade might suppress tremor and other abnormal involuntary movements directly through lower motoneuron sensitivity and through a disruption of abnormal neuronal network behavior. Central beta blockade might also work indirectly through an attenuation of centrally-mediated conditions (e.g., stress, anxiety) that result in increased blood levels of catecholamines (**Figure 1**).

Management

Abnormal tremor produced by fatigue or increased endogenous release of catecholamines is called enhanced physiologic tremor. Marsden and colleagues demonstrated that catecholamine induced tremor is mediated at least in part by peripheral β-adrenergic receptors. Whether the effect is β-1, β-2, or both is unclear. Beta blockers are understandably effective for enhanced physiologic tremor caused by fatigue, anxiety, and other conditions in which there is heightened central or peripheral adrenergic stimulation of mechanical-reflex pathways.

Beta blockers have been shown to reduce essential tremor through peripheral β-blockade. The mechanisms are unclear, although reduced spindle (stretch reflex) sensitivity and reduced contractile speed of skeletal muscle are two possibilities. Central mechanisms are also at play in essential tremor because peripheral intraarterial infusion of propranolol has less effect on essential tremor than chronic oral therapy.

No beta blocker has been found to be superior to the nonselective β-blocker propranolol, which also has high lipid solubility and, therefore, presumably enters the CNS better than drugs with low lipid solubility. However, atenolol has been shown to have an effect on essential tremor, and it is predominantly a β-1 blocker with low lipid solubility. The failure of some essential tremor patients to respond to beta blocker suggests that other pharmacologic and innate personal susceptibility factors are at play.

Beta blockers have also been shown to reduce Parkinson tremor through peripheral β-blockade. A central mode of action is also likely. The benefit of beta blockade is often disappointingly small in patients with Parkinson disease, suggesting that β-adrenergic mechanisms may play less of a role in this disease, compared with essential tremor. The effect of beta blockers on other pathologic tremors (e.g., dystonic, cerebellar, orthostatic, and rubral) has not been studied extensively but is anecdotally small or nil in most patients.

Beta blockers have been found to reduce lithium-induced tremor, thyrotoxic tremor, and other tremors that are produced by stimulation of segmental and long-loop sensorimotor reflex pathways (enhanced mechanical-reflex tremor). Similar results have been reported for akathisia.

Precautions

Beta blockers are generally well tolerated, and serious side effects are rare. They should be avoided in patients with asthma, uncompensated heart failure, heart block, and sick sinus syndrome. Fatigue, lightheadedness, and bradycardia are the most common side effects. Erectile dysfunction and depression are often feared but are less frequent than commonly believed. Abrupt cessation of beta blockers can cause severe exacerbations of coronary artery disease and migraine.

Propranolol is rapidly and completely absorbed through the gastrointestinal tract, but most of the absorbed drug is metabolized during its first passage through the liver. This first-pass effect varies greatly among healthy people and is, of course, affected by liver disease and other drugs metabolized in the liver. Consequently, there is a 20-fold variation in plasma levels for a given dosage in healthy people. In general, the beta blockers with greater lipophilicity are metabolized mostly by the liver, while the more hydrophilic drugs are mainly excreted by the kidneys. It is best to begin with a low dosage of these drugs and titrate the dosage slowly, as tolerated and as needed.

See also: Tremor; Tremor, Essential (Syndromes); Tremor, Holmes; Tremor: Drug-induced.

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Binswanger's Subcortical Arteriosclerotic Encephalopathy

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Definition and History

In 1894, Otto Binswanger reported eight patients with slowly progressive mental deterioration and pronounced white matter changes on a macroscopic examination of the brain performed in one of them. In a communication to the German psychiatrists in Munich, Alzheimer subsequently reported the microscopic features, including severe gliosis of the white matter and hyalination, intimal fibrosis, and onion-skinning of the long medullary arteries, and firstly used the terms 'Binswanger form' or 'encephalitis subcorticalis chronica Binswanger's.'

Subsequently, several other synonyms, such as 'subcortical arteriosclerotic encephalopathy of Binswanger's type' or 'chronic microvascular leukoencephalopathy' were proposed. Today, Binswanger disease (BD) is considered as a form of vascular dementia characterized by diffused white matter lesions and a varying degree of lacunar infarction in the basal ganglia and white matter. However, more than one century after its initial

description, intense controversy still surrounds the clinical manifestations, pathophysiology, and prevalence of BD.

Pathogenesis/Pathophysiology

BD is characterized by ischemic brain damage in the distal watershed periventricular areas and of the deep central white matter. The pathological spectrum can show significant differences in severity and intensity of the lesions. Some brains may reveal milder forms of ischemic change with absence of lacunes but loss of myelin and nerve fibers sparing the arcuate U fibers, whereas others show multiple small deep infarcts and severe loss of myelin and axons.

These parenchymal brain lesions are associated with alterations in the walls of the small penetrating medullary arteries arising from the leptomeningeal border zone and supplying the periventricular white matter. They may be affected by tortuosity that exacerbates the pressure drop related to their long course, hyalinization, concentric thickening of the media, interruption or destruction of the inner elastic membrane with proliferation, and fibrosis of the intima transforming these arteries to rigid 'earthen pipes' and progressively resulting in luminal narrowing and vessel occlusion. These arterioscelerotic changes mainly result from high blood pressure and atherosclerosis but are sometimes related to rare disorders such as pseudoxanthoma elasticum, antiphospholipid antibodies syndrome, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), and amyloid angiopathy. Morphological changes deprive the blood vessels of their function of regulating the blood flow, increasing the susceptibility to injury from hypoperfusion, and ischemic damage. The causal pathway between vascular changes and leukoaraiosis is not well understood. Misery perfusion, hypotensive and hypertensive spells, blood–brain barrier disorders, edema, acidosis, endothelial dysfunction, and coagulation activation seem to be involved. The main clinical symptoms observed in BD (dementia, parkinsonism) could result from a disruption of frontal–subcortical circuits by lacunar infarcts or deep white matter changes.

Epidemiology and Risk Factors

BD was for years considered a relatively rare disorder diagnosed only at necropsy. The sensitivity of magnetic resonance imaging (MRI) to subcortical white matter pathology has rekindled interest in the disorder and raised the possibility of its antemortem diagnosis. The exact prevalence of the disease still remains a matter of debate and strongly depends on the clinical, radiological, and pathological criteria used to make the diagnosis. However, BD seems to be one of the most common forms of vascular dementia in the elderly.

Based on the pathological studies, it has been suggested that there may be two types of small vessel disease that can be differentiated on brain imaging. The first involves atheroma at the origins or proximal portions of the larger (200–800 μm diameter) perforating arteries and is associated with single or a few larger lacunar infarcts without leukoaraiosis. The second involves a diffuse arteriopathy of the smaller perforating arteries, 40–200 μm in diameter, resulting in multiple smaller lacunar infarcts with leukoaraiosis such as observed in BD. While the first group is mainly associated with hypercholesterolaemia, diabetes, and myocardial infarction, BD seems to be mostly related to age and hypertension.

Clinical Features and Diagnostic Criteria

The onset, between 54 and 66 years, sometimes even at 75 years, is often marked by an insidious appearance of the focal cerebral signs. However, a sudden stroke is the opening event in one-third of the cases. The main clinical symptom of BD is progressive mental deterioration. Subcortical lesions are often considered to be associated with abnormalities of information processing speed, executive function, and emotional lability. The neurobehavioral features of Binswanger's syndrome include apathy, lack of drive, mild depression, and alterations of mood. Binswanger's syndrome also includes neurological deficits with pyramidal and language disorders, pseudobulbar disturbances (e.g., dysarthria, dysphagia, forced laughing and crying, small stepped gait), cerebellar (limb ataxia) and extrapyramidal signs (e.g., deterioration of gait, slowness and decrease of associated movements, impairment of posture when standing, trunk and limb rigidity), and lateral homonymous hemianopias. Associated vascular abnormalities, in particular arterial hypertension, are found in the majority of patients. The subsequent course is a chronic one over a period of 5–10 years, punctuated by frequent falls, epileptic attacks, syncopes, urinary incontinence, and sometimes acute stroke. Thus, impairment may develop either gradually or stepwise. In a minority of the subjects, the clinical spectrum may be characterized by the absence of hypertension, neurological signs, and dementia or any clinical sign (asymptomatic cases diagnosed on pathological studies). This clinical picture, as well as the pathological one, somewhat weakens the usefulness of the standardized clinical criteria proposed for the diagnosis of BD in vivo.

Differential Diagnosis

The slowly progressive dementia may lead to an erroneous diagnosis of Alzheimer's disease. The presence of gait disturbance, urinary incontinence, and ventriculomegaly may be mistaken for normal pressure hydrocephalus.

A familial form of BD presenting in younger patients in the absence of vascular risk factors should raise the possibility of CADASIL and other rare hereditary small vessel diseases.

Diagnostic Work-up/Tests

The advent of neuroimaging shifted the focus of attention on BD from pathological to clinical findings. The major findings revealed by morphological neuroimaging are (see **Figure 1**) (1) irregular hypodensity on computed tomography (CT) or hyperintensity on T2-wieghted MRI of the periventricular white matter, extending into the adjacent white matter, (2) moderate or severe symmetrical confluent hypodense/hyperintense lesions in central white matter, not continuous with the periventricular ones, (3) multiple lacunes or infarctions in the central white matter, corona radiata, internal capsule, centrum semiovale, thalamus, basal ganglia, or pons with absence of either large or multiple cortical lesions, (4) enlargement of the third and the lateral ventricles, and (5) microbleeds. Cerebral blood flow (CBF) studies performed with MRI, positron emission tomography (PET), and single photon emission computed tomography (SPECT) have found hypoperfusion in the pathological and normal-appearing white matter sometimes associated to cortical hypoperfusion, mainly in frontal areas. Moreover, evaluation of acetazolamide reactivity has demonstrated alteration of the perfusion reserve in BD. The place of other functional imaging studies investigating neurochemical changes (PET and SPECT) or structural modification (MRI spectroscopy) in the investigation of BD remains to be evaluated in prospective studies.

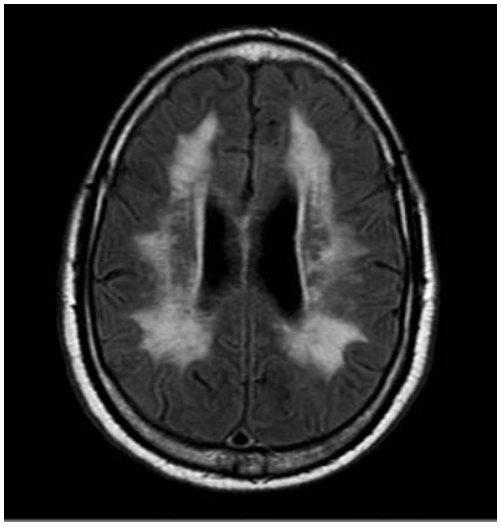

Figure 1 Brain MR: FLAIR sequence demonstrating diffuse hyperintensities of the periventricular white matter.

Prognosis and Management

Leukoaraiosis associated to BD has been associated with an increased risk of small deep infarcts, intracerebral bleeding after thrombolysis or under anticoagulation, dementia, poststroke disability, poorer prognosis following infratentorial stroke or after carotid endarteriectomy, and vascular mortality.

Appropriate control of arterial hypertension and elimination of other vascular risk factors should be the mainstay of therapy in patients with BD. Antiplatelet agents, such as aspirin, dipyridamole, or clopidogrel are indicated to lower the levels of platelet activation. Finally, medications such as pentoxifylline or propentofylline have been proposed to lower fibrinogen levels, but their benefit remains to be investigated in future trials.

See also: Akinetic-Rigid Syndrome; Bradykinesia; Parkinson's Disease: Definition, Diagnosis, and Management; Parkinsonism: Vascular.

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Blepharospasm

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Glossary

Basal ganglia – Deep region of the brain involved in initiating and maintaining movement.
Blepharospasm – A form of focal dystonia that affects muscles of eye closure.
Botulinum toxin – Toxin produced by clostridium botulinum that can cause muscle weakness and botulism.
Dystonia – A neurologic disorder that causes abnormal involuntary contraction of muscles.
Idiopathic – A condition for which no known cause can be determined.
Meige syndrome – Segmental cranial dystonia that includes a combination of blepharospasm and lower facial dystonia.

Definition and History

Blepharospasm is a form of focal dystonia characterized by involuntary eye closure. This chronic neurologic disorder may be progressive and is sometimes disabling. Involuntary muscle spasms of the orbicularis oculi muscles may be clonic or tonic causing excessive eye blinking, palpebral fissure narrowing, or complete eye closure. The majority of cases are idiopathic but blepharospasm may also be secondary. It may be focal or a component of segmental or generalized dystonia. Treatment options include oral medications, botulinum toxin injections, and surgical management.

Pathogenesis and Pathophysiology

Like other focal dystonias, blepharospasm is thought to arise from basal ganglia dysfunction. Postmortem studies of brains of patients with adult-onset dystonia usually do not show any specific pathology. Both positron emission tomography (PET) and magnetic resonance imaging spectroscopy have shown evidence of hypometabolism in the lentiform nuclei and other regions of the basal ganglia. Neurophysiologic studies in patients with blepharospasm have demonstrated an increase in the duration of the corneal reflex supporting the hypothesis of increased excitatory drive from the basal ganglia to brainstem nuclei. Reciprocal inhibition, which refers to the inhibition of activity in antagonistic muscles during contraction of the agonist, has also been shown to be reduced in dystonia. These findings support the concept of abnormal circuitry involving abnormal basal ganglia input on brainstem and spinal interneurons.

Genetic factors may also be important in the etiology of blepharospasm and other adult-onset focal dystonias. Although the genetics of adult-onset dystonia are poorly understood, dystonia may be transmitted by an autosomal dominant gene with reduced penetrance. However, no specific gene mutation has been identified in adult-onset dystonia. Childhood-onset dystonia due to the DYT1 mutation typically begins in a limb and is more likely to become generalized than adult-onset dystonia.

Epidemiology and Risk Factors

The incidence of blepharospasm has been estimated to range from 16 to 133 per million. An epidemiologic study in Olmstead Co., Minnesota, found a calculated incidence of 1.2 persons per a population of 100 000 per year. Onset typically occurs in the fifth and sixth decades and it is more common in women than men by a ratio of 3:1.

A history of previous head trauma, family history of dystonia, and the existence of other eye diseases may be risk factors for developing blepharospasm. Age and female gender are also risk factors for the development of blepharospasm and spread of muscle involvement. Ocular trauma may precede the onset of symptoms, but it remains uncertain what role trauma plays in the development of blepharospasm. Trauma may be a trigger for symptom onset in susceptible individuals.

Clinical Features and Diagnostic Criteria

Symptoms may begin in one eye but may inevitably become bilateral. Early symptoms may be mild and nonspecific such as eye irritation, burning, and photophobia. Symptoms of eye irritation and strain may be attributed to other ophthalmologic conditions such as 'dry eyes.' Excessive eye blinking may persist or progress to episodes of sustained eye closure. Patients often have a combination of these symptoms.

Involuntary muscle spasms occur in orbicularis oculi muscles, resulting in increased blinking, brief eye closure, and sustained forceful eye closure. Episodes of eye closure may persist for seconds or even minutes. Contraction of the pretarsal portion of the orbicularis oculi results in eye

closure with an inability to open the eyes or to maintain eye opening. This is often associated with contraction of the frontalis muscle in an attempt to open the eyelids and results in brow elevation. The dystonic spasms of blepharospasm may also spread to muscles of the lower face and jaw. Meige syndrome, or segmental cranial dystonia, involves both upper and lower facial muscles.

Symptoms may be triggered initially by bright lights, blowing wind, movement, and stress. As symptoms progress, daily routine activities such as reading, driving, and watching television may be impaired. Up to 15% of patients may become legally blind.

Various sensory 'tricks' have been used by patients to relieve symptoms. Simple activities such as touching the face, pulling on eyelids, and talking or singing have been found to temporarily improve symptoms in some patients. The presence of a sensory trick supports the diagnosis of idiopathic dystonia and implies that the peripheral nervous system may play a role in the pathophysiology of dystonia.

Adult-onset focal dystonia may remain localized or it may spread to contiguous regions but rarely becomes generalized. There appears to be a greater risk of spread of disease in patients with blepharospasm compared with other focal dystonias with up to one-third of patients with blepharospasm experiencing spread, primarily to the lower face and jaw. Blepharospasm has also been associated with a more rapid rate of spread than other focal dystonias, with most spread occurring within 1–2 years of onset.

Secondary blepharospasm may be a symptom of many neurologic disorders although the most common cause of secondary blepharospasm is tardive dystonia due to chronic exposure to neuroleptic agents. Blepharospasm can be seen in Parkinson's disease and other parkinsonian syndromes. It may be an early symptom in patients with progressive supranuclear palsy. Other neurologic disorders that may be associated with blepharospasm include Tourette's syndrome, Huntington's disease, and Wilson's disease. Patients with stroke, multiple sclerosis, and severe head trauma may also develop focal dystonia although blepharospasm is not usually associated with focal lesions. A psychogenic etiology can be difficult to confirm but should be considered in cases of sudden onset or in the presence of other nonorganic findings. Secondary blepharospasm may be clinically identical to idiopathic blepharospasm.

No specific diagnostic study is available to confirm the diagnosis or determine the underlying cause of idiopathic blepharospasm. In the workup of blepharospasm, laboratory studies are performed to rule out treatable secondary causes of blepharospasm or to better understand the prognosis in patients with a secondary cause. Imaging studies may be done to rule out structural lesions but are usually not necessary in a patient with a typical history and otherwise normal neurologic exam. Laboratory studies are usually performed to screen for metabolic, inflammatory, and other potentially treatable disorders.

The diagnosis of blepharospasm is made on clinical grounds. A detailed history as well as careful neurologic examination can usually distinguish idiopathic from secondary dystonia. Neurologic signs apart from dystonic movements are not present in idiopathic dystonia and other signs support the diagnosis of secondary dystonia.

The history of subtle eye abnormalities and gradual progression of symptoms of involuntary eye closure should strongly suggest the diagnosis. Since blepharospasm is often part of a more wide-spread segmental or generalized dystonia, a complete examination is necessary to document the extent of involvement for prognostic and treatment considerations. A history of exposure to dopamine blocking agents (i.e., neuroleptic agents, antiemetics) suggests the possibility of tardive dyskinesia or dystonia.

Differential Diagnosis

Conjunctival and corneal lesions associated with blepharitis, due to inflammatory or infectious processes, may cause eye irritation and excessive blinking. Ophthalmologic examination may be necessary and patients often present to an ophthalmologist initially because of eye related complaints. Ptosis due to any neuromuscular disorder may resemble blepharospasm, although this should be easily differentiated by clinical examination. Hemifacial spasm resembles blepharospasm but is usually unilateral. Upper and lower facial muscles are often involved and facial weakness may be present, especially in long-standing cases. Hemifacial spasm is most often caused by vascular compression of the facial nerve and is considered to be a peripherally induced form of myoclonus.

Management

The approach to the management of blepharospasm is similar to the treatment of all focal dystonias. Treatment options in the management of blepharospasm include oral medications, intramuscular injections of botulinum toxin, and surgical intervention. A combination of these approaches may be necessary for severe cases or in patients with more wide-spread involvement. The treatment of underlying disorders may improve symptoms in patients with secondary dystonia, although symptomatic treatment is the same regardless of the etiology.

Mild cases may be managed effectively with benzodiazepines, including clonazepam and lorazepam. Anticholinergic medications have been shown to be the most effective pharmacologic agents in the treatment of moderate to severe dystonia. Trihexyphenidyl is the most commonly used anticholinergic drug but dose-limiting side effects often preclude its effectiveness. Baclofen and

tetrabenazine may also be considered but pharmacologic treatments are only modestly effective in most patients.

Injection of botulinum toxin into dystonic muscles has become the treatment of choice for focal dystonias, including blepharospasm. The treatment of blepharospasm was among the first FDA indications for botulinum toxin type A when it was approved in 1989 and it continues to be the most effective treatment available. Botulinum toxin blocks the release of acetylcholine presynaptically and results in chemical denervation of treated muscles. Relaxation of overactive muscles provides significant clinical benefit in about 90% of blepharospasm patients. The average duration of response is 12–14 weeks and treatment can be given on a routine basis. Multiple clinical trials have demonstrated the safety and efficacy of botulinum toxin in the treatment of focal dystonia. The most common side effect associated with this treatment is ptosis caused by the diffusion of toxin into the levator palpebrae.

Patients who do not respond adequately to pharmacologic therapy or botulinum toxin injections may be candidates for surgical treatment. Partial myectomy, or resection of the orbicularis muscle, can reduce the severity of spasm in medically refractory patients. Patients who undergo myectomy may continue treatment with botulinum toxin, often with improved response and longer duration of benefit. Experience with deep brain stimulation for the treatment of blepharospasm is limited but may be considered in patients with segmental or generalized dystonia who do not respond to less invasive measures.

Prognosis

Idiopathic blepharospasm is a chronic neurologic disorder. Spontaneous remission rarely occurs and is more likely in younger patients and in patients with a short duration of symptoms. Progression of symptoms and spread of muscle involvement occur relatively early in blepharospasm and little change is expected after 5 years of disease. Disease spread is more likely in idiopathic blepharospasm relative to other adult-onset focal dystonias.

Symptomatic treatments are effective in the majority of patients. However, no treatment has been shown to alter the natural course of the disorder or cure the underlying disease. Treatment can have a significant impact on the quality of life in patients with idiopathic and secondary blepharospasm.

See also: Basal Ganglia; Basal Ganglia, Functional Organization; Botulinum Toxin; Dopamine; Dystonia; Meige's Syndrome; Spasm.

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Blood Oxygenation Level Dependent (BOLD)

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Glossary

Deoxyhemoglobin – Hemoglobin without oxygen attached, leaving it paramagnetic.

Diamagnetic – Having the property of a weak repulsion from a magnetic field.

Hemodynamic response – Change in the magnetic resonance signal on T2* images following local neuronal activity. A decrease in the amount of deoxygenated hemoglobin causes the hemodynamic response to increase.

Magnetic resonance – Absorption of energy from a magnetic field that oscillates at a particular frequency.
Oxyhemoglobin – Hemoglobin that has oxygen attached leaving it diamagnetic.
Paramagnetic – Having the property of being attracted to a magnetic field.

Blood oxygenation level dependent (BOLD) functional magnetic resonance imaging (fMRI) has emerged as one of the most widely used techniques to study brain function in vivo in humans. Like any such technique, BOLD fMRI has evolved due to developments in engineering, physics, applied mathematics, biology, and neuroscience. The changes in blood flow and blood oxygenation in the brain are closely linked to neural activity. When nerve cells are active, they consume oxygen carried by hemoglobin in red blood cells from local capillaries. The local response to this oxygen utilization is an increase in blood flow to regions of increased neural activity, occurring after a delay of approximately 1–5 s. This hemodynamic response rises to a peak over 4–5 s, before falling back to baseline. This leads to local changes in the relative concentration of oxyhemoglobin and deoxyhemoglobin and changes in local cerebral blood volume in addition to this change in local cerebral blood flow. BOLD fMRI is based on this neurovascular response.

The discovery of the BOLD response occurred due to several fundamental developments. In 1936, an American chemist and Nobel laureate Linus Pauling and his student Charles Coryell conducted systematic investigations into the hemoglobin molecule. They discovered that hemoglobin has magnetic properties. Oxygenated hemoglobin is diamagnetic (zero magnetic moment) and deoxygenated hemoglobin is paramagnetic (significant magnetic moment). Completely deoxygenated blood has a magnetic susceptibility 20% greater than fully oxygenated blood. Magnetic resonance (MR) pulse sequences configured to be sensitive to T2* show more signal when blood is highly oxygenated and less signal when blood is deoxygenated. This prediction was verified in a paper by Thulborn and colleagues. They found that the decay of transverse magnetization depended on the proportion of oxygenated hemoglobin within a test tube of blood. They also noted that the effect varied with the field strength of the magnet.

The theoretical development of nuclear magnetic resonance, MRI technology, and commercially available scanners has also allowed BOLD fMRI to develop at a rapid pace. In the late 1940s, two physicists named Felix Bloch and Edward Purcell published seminal papers which characterized the measurement of MR in bulk matter. These two individuals shared the Nobel Prize in 1952, for their work in physics. The basic setup used by Bloch's group provided the backdrop to most MR scanners today. They had a strong static magnetic field, a transmitter coil that sends electromagnetic energy to the sample, and a detector coil that measured energy emitted back from the sample. It is the relaxation back to the static field which most MR applications rely upon today. About two decades later, Damadian demonstrated that cancerous cells from a rat had a different relaxation time than noncancerous cells, and thereby provided one of the first biological applications of nuclear magnetic resonance. In 1973, a paper by Paul Lauterbur tested the idea that if the strength of the magnetic field varied over space, the resonant frequency of protons of different locations could also vary accordingly. He showed that measuring energy emitted to the detector coil at different frequencies could identify how much of that object was present at each location. This provided the first MR image. In 1976, Peter Mansfield improved upon the work of Lauterbur by developing the basis of echo-planar imaging, which provided the ability to acquire one image slice at a time, rather than the one-dimensional approach used in the past. In the 1980s and 1990s, MRI scanners became more and more prevalent for both research and clinical medicine. In 2003, Paul Lauterbur and Peter Mansfield shared the Nobel Prize in Medicine.

In the early 1990s, there were several important papers that led to the development of BOLD fMRI. Ogawa and colleagues hypothesized that manipulating the proportion of blood oxygen would affect the visibility of blood vessels on T2*-weighted images. They confirmed this hypothesis in anesthetized rodents using 7 Tesla MRI. The rats breathed in different proportions of oxygen. When the rats breathed 100% oxygen or 100% carbon monoxide, their brains showed very few blood vessels, yet the structural differences were evident. When the rats breathed normal air, which contains about 21% oxygen, the images contained thin dark lines throughout the cerebral cortex. When the oxygen content was reduced to 0%, the lines became more prominent. Ogawa and colleagues concluded that these thin lines represented magnetic susceptibility effects caused by the presence of paramagnetic deoxygenated hemoglobin in blood vessels. This effect observed by Ogawa and colleagues became known as BOLD contrast fMRI. In another study, this same group manipulated the gases inhaled by anesthetized rats and found similar effects for high field BOLD contrast and electroencephalography (EEG).

In 1992, the first fMRI studies using behavioral tasks to elicit the BOLD response were published by three different groups. Kwong and colleagues used gradient-echo-planar imaging at 1.5 Tesla to show BOLD contrast changes in the visual cortex following light stimulation. Ogawa and colleagues reported a similar finding in the

visual cortex. In the first demonstration related to the motor system, Bandettini and colleagues showed that when subjects repeatedly touch their fingers with their thumb reliable BOLD contrast changes could be observed in the motor cortex.

The neurovascular contributions to neuroimaging have received considerable focus over several decades. It is now widely recognized that several changes in neurovascular coupling affect the BOLD signal. The usual signal increases reported in BOLD fMRI studies are due to the fact that neural activation causes an increase in cerebral blood flow. It also increases glucose utilization that is larger than the oxygen consumption rate. The result from an increase in neural excitation is a reduction in deoxyhemoglobin, which in turn increases signal strength. It has also been shown that the BOLD response depends on cerebral blood volume.

Despite the cascade of biological changes that occur between a measurable neural recording and the BOLD fMRI signal, there are strong correlations between neural recordings and the BOLD response. Logothetis and colleagues have inserted microelectrodes into the extracellular space during BOLD fMRI studies in animals. They recorded broad band frequency content of these signals detecting single unit activity, multiple unit spiking activity, and local field potentials. The findings obtained thus far indicate that the low-frequency content of the local field potential provides the best correlation with the fMRI BOLD response. The studies of Logothetis and colleagues suggest that regions where BOLD fMRI responses are found may not have single unit activity in the specific region. The BOLD fMRI response, instead, reflects large population activity from many neurons that had an influence on the low-frequency content measured at the microelectrode.

Analysis of BOLD fMRI studies has evolved since the initial three studies in 1992. It is estimated that since the seminal papers in 1992, over 1000 fMRI papers are published each year and eight were published each day in the year 2007. The analyses used in the BOLD fMRI studies rely upon the general linear model which is implemented in software packages such as statistical parametric mapping (SPM) and analysis of functional neuroimages (AFNI). Another widely used analysis approach is a region of interest analysis that is focused on a specific set of regions which are defined anatomically. A region of interest analysis is particularly useful in parametric fMRI studies and pharmacological fMRI studies. In addition, recent studies have developed analyses which characterize the connectivity between anatomical regions using different approaches.

See also: Basal Ganglia; Basal Ganglia, Functional Organization; Diffusion Tensor Imaging in Parkinson's Disease; Electroencephalography (EEG); Event-Related Potentials: Slow Potentials; Magnetoencephalography (MEG); Neuroimaging, Parkinson's Disease; Paired Pulse TMS; rTMS; SPECT Imaging in Movement Disorders; Substantia Nigra; Subthalamic Nucleus.

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Botulinum Toxin

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Glossary

Blepharospasm – Involuntary eye closure due to contractions of orbicularis oculi, procerus, and corrugator muscles.
Botox – Botulinum toxin type A generic name assigned by the FDA: onabotulinumtoxin A.
Botulinum toxin (BoNT) – Botulinum otulinum neurotoxin.
Cervical dystonia (also known as torticollis) – This focal dystonia involving the neck muscles causes abnormal turning, flexion, extension and other movements and postures of the neck and head.
Dysport – Botulinum toxin type A generic name assigned by the FDA: abobotulinumtoxin A.
Dystonia – Neurological disorder manifested by sustained, repetitive, patterned contractions of muscles causing abnormal movements and postures.
Hemifacial spasm – Abnormal twitching involving one side of the face.
Immunoresistance – Loss or responsiveness to BoNT treatment due to the development of blocking antibodies.
Myobloc/Neurobloc – Botulinum toxin type B.
Sialorrhea – Drooling due to overproduction or impaired clearance of saliva.
Spasmodic dysphonia – Laryngeal dystonia resulting in involuntary approximation (adductor dysphonia) or separation (abduction dysphonia) of the vocal cords.
Writer's cramp – Focal hand dystonia interfering with writing and other specific tasks.
Xeomin – Botulinum toxin type A.

Definition and History

The history of botulinum toxin (BoNT) dates to 1817, when Christian Andreas Justinus Kerner first recognized that food-borne botulism was due to a toxin that paralyzed skeletal muscles and parasympathetic function. He proposed the term botulinum toxin and suggested that it could be used to treat involuntary spasms and movements. In 1895, Emile Van Ermengem first isolated the bacterium clostridium botulinum after an outbreak following a funeral ceremony in the Belgian village Ellezelles. Edward Schantz first cultured Clostridium botulinum and isolated the toxin in 1944, and in 1949, Burgen and his colleagues found that BoNT blocked neuromuscular transmission by blocking the release of acetylcholine. It had not been until 1973 that the therapeutic value of BoNT was recognized by Alan Scott, who demonstrated that strabismus in monkeys could be corrected by BoNT injections into the extraocular muscles. The first report of clinical application of BoNT was published in 1984, when it was demonstrated to be safe and effective in the treatment of blepharospasm. Subsequent double-blind, placebo-controlled, and open-label studies provided evidence that BoNT was a powerful therapeutic tool in a variety of neurologic and other disorders. Although its widest application is still in the treatment of disorders manifested by abnormal, excessive, or inappropriate muscle contractions, its use is rapidly expanding to include the treatment of a variety of ophthalmologic, gastrointestinal, urologic, orthopedic, dermatologic, secretory, painful, and cosmetic disorders (**Table 1**).

Pharmacology and Physiology of Botulinum Toxin

The therapeutic value of BoNT is due to its ability to cause chemodenervation and to produce local paralysis when injected into a muscle. There are seven immunologically distinct toxins (A–G); type A has been studied most intensely and used most widely. Synthesized as single-chain polypetides (molecular weight of 150 kD), these toxin molecules have relatively little potency until they are cleaved by trypsin or bacterial enzymes into a heavy chain (100 kD) and light chain (50 kD). The three-dimensional structure of the BoNT complex is known. When linked by a disulfide bond, these dichains exert their paralytic action by preventing the release of acetylcholine (Ach). While the

Table 1 Botulinum neurotoxins

Neurotoxin	*Substrate*	*Localization*
BoNT – A, E	SNAP-25	Presynaptic plasma membrane
BoNT – B, D, F	VAMP/synaptobrevin	Synaptic vesicle membrane
BoNT – C	SNAP-25, Syntaxin	Presynaptic plasma membrane

heavy chain of the toxin binds to the presynaptic cholinergic terminal, the light chain acts as a zinc-dependent protease that selectively cleaves proteins that are critical to fusion of the presynaptic vesicle with the presynaptic membrane. This is accomplished via a three-step process that involves binding to the acceptors on presynaptic membrane (heavy chain), internalization (endocytosis), and an enzymatic action (light chain). BoNT/A enters neurons by binding to the synaptic vesicle protein SV2, which acts as the BoNT receptor. The light chains of BoNTs act by cleaving the SNARE (soluble *N*-ethlymaleimide sensitive factor attachment protein receptor or soluble *N* ethylmaleimide sensitive factor attachment protein receptor (SNAP) receptor or neuronal synaptosome-associated proteins) proteins that are involved in the docking of presynaptic Ach vesicle before releasing Ach into the neuromuscular junction. The light chains of both BoNT/A and BoNT/E cleave SNAP-25, but at different sites. The light chains of BoNT B, D, and F prevent the quantal release of Ach by proteolytically cleaving synaptobrevin-2, also known as VAMP (vesicle-associated membrane protein), an integral protein of the synaptic vesicle membrane. BoNT/C cleaves both SNAP-25 and syntaxin, another plasma membrane-associated protein. Although BoNT may enter the central nervous system, it is unlikely that this results in any clinically meaningful effects.

The original commercial preparation of BoNT was the type A BoNT, marketed as BOTOX® (Allergan, Inc., Irvine, CA, USA). This purified neurotoxin complex is supplied as 100-mouse unit vials of freeze-dried BoNT/A. Another clinically available form of BoNT/A is Dysport® (Beaufour-IPSEN, France-UK). Other BoNT/A preparations used clinically include Xeomin® (Merz Pharmaceuticals GmbH, Frankfurt, Germany), a purified, freeze-dried BoNT/A, which is free from complexing proteins. Besides BOTOX®, Dysport®, and Xeomin®, the other type of BoNT/A currently in clinical trials is PureTox® (Johnson & Johnson, USA). In addition, there is a Chinese form of BoNT/A (Prosigne or CBTX-A, Lanzhou Biological Products Institute, China). Currently, only one preparation of BoNT/B is marketed worldwide and is known by the brand name Myobloc® (US) or Neurobloc® (Europe) (Solstice Neurosciences Inc, Malvern, PA, USA).

It is important to note that the biologic activity, measured in units, is different for the different products. When administered intravenously or intramuscularly to monkeys, the LD50 for the BOTOX was estimated to be 40 U kg^{-1}, and about 3000 U when extrapolated to a 75 kg man. In addition to the biologically active toxin, many products include various amounts of nontoxin proteins include hemagglutinins and other proteins that presumably stabilize the three-dimensional structure of the toxin. The toxins dissociate in basic conditions (pH $>$ 7), but remain relatively stable under neutral (pH = 7; BOTOX®, Dysport®) or acidic (pH = 5.6, Myobloc®/Neurobloc®) conditions. Xeomin® and PureTox® are free of complexing proteins. Although each preparation should be considered unique in its potency and properties, various studies have suggested that the potency ratio between Dysport® and BOTOX® is about 3 to 1 and between Myobloc/Neurobloc® and BOTOX® as 50 or 60 U to 1, whereas Xeomin® and BOTOX® seem to be equivalent in their potency. In this review, we use BOTOX® units unless specified otherwise.

While side effects occasionally result form local diffusion of BoNT, remote or systemic adverse effects are quite rare. Patients with postpolio syndrome and Eaton–Lambert syndrome, however, have been reported to have generalized weakness after local BoNT. Other contraindications to the use of BoNT include myasthenia gravis, motor neuron disease, concurrent use of aminoglycoside antibiotics, and pregnancy, although women, inadvertently injected during pregnancy, reported no untoward side effects to the fetus.

The optimal treatment benefits depend on a large number of factors, including the selection of the appropriate target, dosage, and dilution, as well as the technique used and experience of the clinician. One of the major controversies related to injection techniques is the use of electromyography (EMG) in selecting the abnormally active muscles and in guiding the injection needle to the appropriate target muscle. While some clinicians favor this approach, there is little evidence to indicate that EMG significantly improves the outcome.

Immunogenicity of Botulinum Toxins

Although the various neurotoxins are antigenically different, they contain a common subunit structure and cross-reactive epitopes may cause cross-neutralization of antibodies. This has been demonstrated particularly between BoNT/A and BoNT/B. The original preparation of Botox contained 25 ng of neurotoxin complex protein per 100 U, but in 1997, the Food and Drug Administration (FDA) approved a new preparation that contains only 5 ng per 100 U, which has been associated with lower antigenicity. Methods used to detect blocking antibodies include the mouse protection assay, the mouse phrenic nerve hemidiaphragm test, and many other research and commercial tests. A unilateral brow injection (UBI) is a useful clinical test as inability to frown on the injected side confirms the absence of clinically meaningful immunoresistance. Depending on the technique used to detect blocking antibodies, the risk of antibodies to Botox has markedly decreased and is now estimated to be about 1–2% of patients receiving the product repeatedly for up to 4 years. While low antigenicity has been predicted with formulations of BoNT without complexing proteins (e.g., Xeomin® and PureTox®), no long-term data are available to support this notion. The presence of blocking

antibodies, directed to the heavy chain of the BoNT molecule, usually indicates that the patient has developed immunoresistance and will not respond to the next injection. Delaying the subsequent injection by at least 18 months, considered as the minimum time for the antibodies to vanish from the patient's immune system, may be associated with a positive response. Most patients who develop blocking antibodies, however, have an increased risk of developing antibodies again and these patients seem to also have an increased risk of developing blocking antibodies to a different type of BoNT. Thus patients who have developed blocking antibodies to BoNT/A may initially respond to BoNT/B but are likely to soon develop immunoresistance to the alternate type of BoNT.

Clinical Applications of Botulinum Toxins

Blepharospasm

In 1987, we reported the results of a double-blind, placebo-controlled trial of BoNT in 28 patients with cranial-cervical dystonia, including blepharospasm, oromandibular dystonia, and cervical dystonia (CD), the results of which were in part used by the FDA to approve BoNT in 1989 as a therapeutic agent in patients with strabismus, blepharospasm, and other facial nerve disorders, including hemifacial spasm. Subsequently there have been many open-label studies confirming the safety and efficacy of BoNT in the treatment of blepharospasm, but because of paucity of double-blind, placebo-controlled trials, the Therapeutics and Technology Assessment Committee of the American Academy of Neurology (TTAC-AAC) concluded that there is only level B (probably effective) evidence for the efficacy of BoNT/A for the treatment of blepharospasm. Most studies have concluded that the average latency from the time of the injection to the onset of improvement was about 3–5 days and the average duration of benefit was about 12–14 weeks. While about a third of all treatment sessions are followed by some side effects (ptosis, blurring of vision or diplopia, tearing, and local hematoma), only 1–2% affect patient's functioning, and complications usually improve spontaneously in <3 weeks. The relationship between blepharospasm, BoNT, and occurrence of dry eyes in some patients is not well understood. The efficacy of BoNT in the treatment of blepharospasm is largely dependent on the skills and experience of the physician. Several studies have suggested that in addition to injecting the medial eyebrows (corrugator and procerus muscles) an injection into the pretarsal rather than preseptal portion of the orbicularis oculi is associated with a significantly lower frequency of ptosis. Furthermore, ptosis and other complications, such as tearing, can be prevented by injecting initially only 5 U in the lateral portion of the upper lid and 5 U medially and by injecting 5 U only into the lateral portion of the lower lid.

In a double-blind, parallel-group, multicenter study, 304 patients with blepharospasm received either Xeomin or Botox, both the treatments produced statistically significant improvements from baseline in the Jankovic Rating Scale (JRS) at week 3 (primary efficacy variable; Xeomin: −2.90; Botox: −2.67; $p < 0.0001$ from baseline for both), with no difference between treatments, indicating that Xeomin were clinically noninferior to Botox. The most common adverse event was ptosis (6.1% Xeomin and 4.5% Botox). The efficacy and safety of Xeomin in the treatment of blepharospasm was also confirmed by a prospective, double-blind, placebo-controlled, randomized, multicenter study involving 109 patients (mean total dose of Xeomin per treatment visit was 64.8 U), the JRS severity subscore was significantly reduced compared with placebo ($p < 0.001$). The most commonly reported adverse effects related to Xeomin versus placebo were eyelid ptosis (18.9 vs. 8.8%), dry eye (16.2 vs.11.8%), and dry mouth (16.2 vs. 2.9%).

Oromandibular Dystonia

Oromandibular dystonia is among the most challenging forms of focal dystonia to treat; it rarely improves with medications; there are no surgical treatments; and BoNT therapy can be complicated by swallowing problems. Clenching, trismus, and bruxism are frequent manifestations of primary (idiopathic) as well as secondary oromandibular dystonia. Patients with dystonic jaw closure, treated with injections into the masseter and temporalis muscles, generally respond better than those with jaw-opening dystonia. Although most patients with jaw opening dystonia benefit from injections into the submental muscle complex, some may also require injections into the lateral pterygoid muscles. As with blepharospasm, the improvement is usually noted within the first 5 days and persists for about 3–4 months. Early treatment of oromandibular dystonia with BoNT may prevent dental and other complications, including the temporomandibular joint syndrome.

Laryngeal Dystonia (Spasmodic Dysphonia)

Until the introduction of BoNT, the therapy of spasmodic dysphonia has been disappointing. Several studies have established the efficacy and safety of BoNT in the treatment of laryngeal dystonia and this approach is now considered by most to be the treatment of choice for spasmodic dysphonia. This approach usually requires a multidisciplinary team, consisting of an otolaryngologist experienced in laryngeal injections and a neurologist knowledgeable about motor disorders of speech and voice. There are three approaches currently used in the BoNT treatment of spasmodic dysphonia: (1) unilateral

EMG-guided injection of 5–30 U; (2) bilateral approach, injecting with EMG-guidance 1.25–4 U in each vocal fold; and (3) an injection via indirect laryngoscopy without EMG. Irrespective of the technique, most investigators report about 75–95% improvement in voice symptoms. Patients with the adductor form of spasmodic dysphonia produced by involuntary contraction of the thyroarytenoid muscle, usually report more robust improvements than those with the abductor spasmodic dysphonia, the less frequent type of dysphonia. Although more complicated, BoNT injections into the posterior cricoarytenoid muscle with the EMG needle placed posterior to the thyroid lamina may be used quite effectively in the treatment of the abductor form of spasmodic dysphonia. Adverse experiences include transient breathy hypophonia, hoarseness and rare dysphagia with aspiration. BoNT produces less consistent benefits when spasmodic dysphonia is accompanied by voice tremor.

Cervical Dystonia (CD)

The introduction of BoNT in the treatment of CD has not only improved the quality of life of patients with this most common adult-onset focal dystonia, but has also changed the natural history in that cervical contractures are now much less frequent than they were prior to BoNT. A variety of instruments has been used to assess the response in patients with CD, but the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) is used most commonly. The efficacy and safety of BoNT in the treatment of CD have been demonstrated in several controlled and open trials and the (TTAC-AAC) report concluded that BoNT should be offered as a treatment option for the treatment of CD (Level A evidence). In a first US multicenter, double-blind, randomized, controlled trial assessing the safety and efficacy of Dysport® in CD, 80 patients were randomly assigned to receive one treatment with Dysport (500 U) or placebo. Dysport® was significantly more efficacious than placebo at weeks 4, 8, and 12 as assessed by the TWSTRS. The median duration of response was 18.5 weeks. Side effects were generally similar in the two treatment groups; only blurred vision and weakness occurred significantly more often with Dysport®. These results were confirmed by another pivotal study of Dysport® in CD involving 116 patients. The most common treatment-related adverse events in other studies of BoNT in CD were mild to moderate weakness, dysphagia, neck pain, and injection-site pain. In a prospective, open-label, multicenter study of 333 patients with CD, never previously exposed to BoNT, after a median of 9 of BOTOX® treatments, with mean doses per session ranging from 148.4 to 213.0 over a mean of 2.5 years (range: 3.2 months to 4.2 years), only 1.2% tested positive for blocking antibodies (**Table 2**).

Table 2 Recommended doses of BoNT in patients with CD

Muscle	*BoNT/A (Botox/ Xeomin)*	*BoNT/B (Myobloc/ Neurobloc)*
Trapezius	35–100	1500–5000
Sternocleidomastoid	40–70	2000–3000
Splenius capitis	60–100	2500–5000
Levator scapulae	25–60	1250–2500
Scalene complex	25–60	1250–2500

The most important determinants of a favorable response to BoNT treatments are a proper selection of the involved muscles and an appropriate dosage. Although the treatment must be individualized, the average optimal dose for patients with CD is 200 U of BOTOX® or Xeomin®, 500 U of Dysport®, and 10 000 of Mybloc/Neurobloc®. BOTOX® and Myobloc were directly compared, at 1:40 dose ratio, in 139 patients with CD, the so-called 'ABCD Study,' using a randomized, double-blind parallel arm study design. While the improvement in TWSTRS score at 4 weeks following injection did not differ between the two serotypes, dysphagia and dry mouth were more frequent with Mybloc®. A post hoc comparison of these two groups with respect to EMG use found that the only difference between the two groups was in number of muscles injected and toxin dosage, both being statistically higher in the EMG-guided group. In another study, designed as a noninferiority trial, 111 patients with CD were randomized to receive either Botox (150 U) or Myobloc/Neurobloc® (10 000 U) at a dosing ratio of 66.7. There were no significant differences in the efficacy or occurrence of injection-site pain and dysphagia. Dry mouth has been consistently found to be more frequent with Myobloc/Neurobloc® than with BOTOX®. Also, the risk of immunoresistance seems to be higher with Myobloc/Neurobloc® than with BOTOX®. In one study of 100 patients with CD followed for 42 months over a mean of 5 (up to 12) visits, a third of the patients who were negative for BoNT/B antibodies at baseline became positive for such antibodies at the last visit. Thus although BoNT/B offers a useful alternative to patients with immunoresistance to BoNT/A long-term efficacy is limited by the development of blocking antibodies, probably as a result of the cross-reactivity between the two serotypes.

Writer's Cramps and Other Limb Dystonias

The treatment of hand dystonia with BoNT is more challenging than the other dystonias, because there are more muscles involved in finely coordinated motor function required in the act of writing, dressing, other activities of daily living and in various demanding tasks such as playing musical instruments and sport activities. Using

the Burke–Fahn–Marsden scale, a marked improvement in the severity and disability was achieved with EMG-guided injection of BoNT in 47 patients with writer's cramp, whereas primary writing tremor was little improved. In one study, 69% of 84 musicians reported improvement with EMG-guided BoNT (Dysport) injections, but only 36% reported long-term benefit. Appropriate recognition of overflow and mirror dystonia induced by volitional movement in the unaffected hand may provide clues to the muscles involved in the hand that are primarily affected by the focal hand dystonia.

Several open and double-blind controlled trials have concluded that BoNT injections into selected hand and forearm muscles probably provide the most effective relief in patients with various task-specific and occupational dystonias. Although EMG guidance may be appropriate for BoNT treatment of limb dystonia, supported by the finding that only about a third of needle placement attempts reached the proper hand muscles in the absence of EMG guidance, this does not mean that placement with EMG guidance correlates with better results since the selection of the muscle involved in the hand dystonia is based on clinical examination and not on EMG. Ultrasound-guided EMG techniques are increasingly applied in the treatment of hand and other focal dystonias.

Hemifacial spasm

Hemifacial spasm is defined as a neurologic disorder manifested by involuntary, recurrent twitches of the eyelids, perinasal, perioral, zygomaticus, platysma, and other muscles of only one side of the face. It is an example of a peripherally induced movement disorder (segmental myoclonus) in which the muscular contractions result from an irritative lesion of the ipsilateral facial nerve. While microvascular decompression of the facial nerve has a high success rate, this surgical treatment is associated with certain risks, such as permanent facial paralysis, deafness, stroke, and death. Therefore, local injections of BoNT into involved facial muscles offer a useful alternative to surgical therapy. Nearly all patients improve; the complications are minimal and transient; and the approach can be individualized by injecting only those muscles the contractions of which are most disturbing to the patient. Along with blepharospasm, the FDA approved BoNT injections for hemifacial spasm in 1989.

In our experience with BoNT injections in 110 patients with hemifacial spasm, 84 (76%) of whom had adequate follow-up, the amount of Botox used in each injection varied from 5 to 100 U, with an average of 32.7±12.9 U. The latency from injection to the onset of benefit was 5.4±7.8 days (range: 0–45 days) and the total duration of benefit averaged 18.4±6.1 weeks (range: 0–37). Sixty seven (80%) of the 84 patients had a peak effect of 4 (marked improvement in severity and function) and 13 (15%) had a score of 3 (moderate improvement in severity and function). The side effects included facial weakness ($N = 25$), lid weakness ($N = 22$), ptosis ($N = 17$), teary or dry eyes ($N = 10$), diplopia ($N = 7$), hematoma ($N = 6$), and diverse other side effects ($N = 5$). The average duration of improvement in hemifacial spasm, 5 months, was longer than in any of the dystonic disorders and rare patients have achieved long-lasting remissions. Facial myoclonus associated with Rasmussen encephalitis, similar to hemifacial spasm, but pathophysiologically related to focal cortical seizure, has been also reported to improve with BoNT.

Tremor

Tremor accompanies dystonia in about half of all dystonic patients, and in some patients treated for focal dystonia with BoNT, their dystonic tremor improved. Chemodenervation with BoNT may ameliorate not only dystonic tremor, but also essential tremor involving hands, as demonstrated by at least two double-blind, placebo-controlled studies. Although BoNT is clearly a useful treatment in patients with hand tremor, it has been found particularly effective in patients with head tremor and may even improve primary writing and other task-specific tremors, jaw tremor and voice tremor.

Tics

Motor and phonic tics associated with Tourette's syndrome typically improve with antidopaminergic drugs, but when these drugs do not adequately control the tics or are associated with troublesome side effects, BoNT injections into the affected body parts not only may provide satisfactory control of the tics but also may eliminate the premonitory urge. BoNT treatment is particularly useful in the treatment of focal motor tics and phonic tics, including coprolalia. In a placebo-controlled study of 18 patients with simple motor tics, BoNT treatment was associated with a 39% reduction in the number of tics per minute within 2 weeks after injection as as against a 6% increase in the placebo group ($p = 0.004$). In addition, there was a 0.46 reduction in 'urge scores' with BoNT as against a 0.49 increase in the placebo group ($p = 0.02$). This preliminary study, however, lacked the power to show significant differences in other measured variables, such as severity score, tic suppression, pain, and patient global impression. Other limitations of the study include the following: (1) the full effect of BTX may not have been appreciated at only 2 weeks, (2) a single treatment protocol does not reflect the clinical practice which involves several adjustments in doses and sites of injections over several treatment visits, and (3) the patients were relatively mild as suggested by the statement that they 'did not rate themselves as significantly compromised by their treated tics' at baseline.

Spasticity and other Hypertonic Disorders

In addition to involuntary movement disorders, BoNT has been used effectively to treat disorders of muscle tone, including spasticity associated with cerebral palsy, multiple sclerosis, or following stroke. One double-blind, placebo-controlled study showed that Botox (200–240 U) reduced wrist and finger spasticity in patients following stroke. In another one controlled study, 125 patients with cerebral palsy and dynamic equinus spasticity during walking were randomized to receive 10, 20, or 30 mg kg^{-1} of Dysport®, or placebo to the gastrocnemius of both the legs. There was a statistically significant improvement in all the three dose groups, particularly the 20 mg kg^{-1} group, compared with placebo in the dynamic component of the gastrocnemius muscle. Experienced injectors have recommended the following doses of BoNT/A (BOTOX®) in the treatment of spasticity: for the lower limb 3–6 U kg^{-1} per muscle, for the upper limb above the elbow 2–3 U kg^{-1} per muscle, for the upper limb below the elbow and posterior tibialis 0.5–2 U kg^{-1} per muscle. In children with cerebral palsy, BoNT (2–8, up to 16 U per kg body weight per muscle) is often found effective when injected in calf muscles to correct equinus deformity and toe walking, in the hamstring muscles to correct crouch and scissor gait, to improve sitting and hygiene care, and to reduce pain. In a double-blind, controlled study patients with cerebral palsy receiving 40–80 U of BOTOX® per muscle experienced a significantly greater improvement in Ashworth score and gait measures than the 'low-dose' group (20–40 U per muscle). The results of many of the studies are difficult to interpret and compare, because patients with various forms and etiologies of spasticity were enrolled and different methodologies were used to inject and rate the patients. Although some double-blind trials have demonstrated meaningful functional improvement in patients with spasticity, other controlled studies have failed to demonstrate improvement. Many of the published studies suffer methodological problems, particularly in selecting the appropriate outcome measures that may or may not capture the functional goals of the patients.

Table 3 Clinical applications of botulinum toxin

Dystonia
Blepharospasm (lid 'apraxia')
Oromandibular-facial-lingual dystonia
Cervical dystonia (torticollis)
Laryngeal dystonia (spasmodic dysphonia)
Limb dystonia
Task-specific dystonia (e.g., writer's or other occupational cramps)
Other focal/segmental dystonias (primary, secondary)
Other involuntary movements
Hemifacial spasm
Limb, head, voice, chin tremor
Palatal myoclonus
Motor and phonic tics, including coprolalia
Nystagmus and oscillopsia
Myokymia
Inappropriate contractions
Spasticity (stroke, cerebral palsy, head injury, multiple sclerosis)
Painful rigidity
Strabismus
Bruxism and temporo-mandibular joint syndrome
Stuttering
Muscle contraction headaches
Lumbosacral strain and back spasms
Radiculopathy with secondary muscle spasm
Myofascial pain syndromes
Achalasia (lower esophageal sphincter spasm)
Spasm of the inferior constrictor of the pharynx (cricopharyngeal muscle)
Spasm of the sphincter of Oddi
Spastic bladder, detrusor-sphincter dyssenergia
Anismus
Vaginismus
Other applications
Protective ptosis
Hyperlacrimation
Drooling (sialorrhea)
Hyperhidrosis
Gustatory sweating
Anal fissure
Constipation
Overactive bladder
Prostatic hypertrophy
Obesity (distal stomach)
Diabetic foot ulcers
Cosmetic (wrinkles, brow furrows, frown lines, 'crow's feet,' platysma lines, facial asymmetry)
Tennis elbow and other sports injuries
Debarking dogs

Other Indications

The use of BoNT is continuously expanding as clinicians are becoming more familiar with its therapeutic potential. In addition to treating focal dystonias, such as blepharospasm, oromandibular, cervical, laryngeal, and limb dystonia dystonia, and other movement disorders, such as hemifacial spasm, tics, tremors, palatal myoclonus, and even restless legs syndrome, BoNT is increasingly used in a variety of cosmetic, painful, gastrointenstinal, urological, and autonomic disorders (**Table 3**).

See also: Blepharospasm; Cervical Dystonia; Dystonia; Dystonia, Task-specific; Dystonia, Traumatic; Generalized Primary Torsion Dystonia; Hemifacial Spasm; Tardive Dystonia; Tics; Writer's Cramp.

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Braak Classification

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Introduction

In the clinically recognizable phase of sporadic (idiopathic) Parkinson's disease (PD), patients present with a combination of motor dysfunction signs, such as bradykinesia or hypokinesia, cogwheel rigidity, resting tremor, and postural instability. However, the same clinical phenotype can appear as 'parkinsonism' in other disorders associated with dopamine depletion of the nigrostriatal system. Familial forms of parkinsonism also exist, and the syndrome may result following head trauma, infection, or intoxication. In addition, it may develop as a result of metabolic disease, normal pressure hydrocephalus, or cerebrovascular disease. Finally, parkinsonism accompanies neurodegenerative protein misfolding-related disorders known as 'tauopathies' and 'synucleinopathies.'

For this reason, and because there are currently no biomarkers for the synucleinopathy sporadic PD, an accurate differential diagnosis is difficult and autopsy-based neuropathological assessment is necessary not only to confirm the clinical diagnosis but also to detect the potentially presymptomatic individuals in the broader population at large. To date, the intraneuronal aggregated filamentous inclusion bodies that are the morphological hallmarks of sporadic PD, α-synuclein-immunopositive Lewy neurites (LNs) in axons, and Lewy bodies (LBs) in the somata of host nerve cells are not known to affect the nervous systems of nonhuman vertebrates or to involve organ systems apart from the nervous system.

Vulnerable nerve cell types cannot be distinguished from those that resist the pathological process with respect to neurotransmitter type and functional systems (see **Figure 1**), but all of the neurons that become involved belong to the class of projection neurons. Additionally, the presence of the presynaptic neuronal protein α-synuclein of the somal lipofuscin pigment or neuromelanin granules (see next section below), and a disproportionately long and thin-caliber axon that is sparingly myelinated or unmyelinated appear to be among the prerequisites for the formation of the misfolded and abnormally aggregated α-synuclein (Lewy pathology). All the intrinsic and extrinsic factors that contribute to the induction and maintenance of α-synuclein misfolding and aggregation are presently unknown.

Axons and neurons that contain aggregated α-synuclein can survive for years. For this as well as other reasons, it is hotly debated whether LNs and LBs cause premature neuronal death, and whether they contribute to nerve cell dysfunction or loss at all. Some argue or postulate that LBs are neuroprotective. Neuronal survival, however, is *not* synonymous with *functional integrity*, and there are indications that inclusion-bearing neurons do forfeit some of their functional capacities (e.g., reduced synthesis of tyrosine hydroxylase, loss of dendritic spines) long before cell death occurs. It is also reasonable to surmise that beyond a certain threshold the intraneuronal inclusions ultimately become detrimental to the host neuron's and organism's health.

Sensory centers	Olfactory: early and severe involvement Nociceptive: early involvement Somatosensory: mostly intact Viscerosensory: mostly intact Auditory and visual: mostly intact
Motor centers	Visceromotor: early and severe involvement Somatomotor: partial involvement Limbic: severe involvement
Stage 1	Anterior olfactory nucleus Olfactory bulb, olfactory tract Dorsal motor nucleus of the vagal nerve Intermediate reticular zone
Stage 2	[plexuses of Meissner and Auerbach] Lower raphe nuclei Magnocellular reticular nuclei Coeruleus–subcoeruleus complex
Stage 3	[spinal cord lamina I] Central subnucleus of the amygdala Olfactory tubercle, piriform cortex (olfactory system) Periamygdalear cortex (olfactory system) Medial entorhinal region (olfactory system) Substantia nigra, pars compacta Edinger Westphal nucleus Upper raphe nuclei Tuberomamillary nucleus of the hypothalamus Magnocellular basal forebrain nuclei Tegmental pedunculopontine nucleus
Stage 4	Interstitial nucleus of the terminal stria Cortical and basolateral amygdala Thalamic intralaminar nuclei Thalamic midline nuclei Anteromedial temporal mesocortex Ammon's horn, second sector (CA2) Insular and subgenual cortex Anterior cingulate cortex Claustrum
Stage 5	High-order sensory association neocortex Prefrontal neocortex Entorhinal region, CA1 and CA3 sectors
Stage 6	First-order sensory association neocortex Premotor neocortex Primary sensory areas Primary motor field

Figure 1 A distinctive topographic or temporospatial distribution pattern of Lewy pathology as well as nonrandom neuronal dysfunction and, at some sites, neuronal loss characterize sporadic Parkinson's disease (PD). Sensory components of the human nervous system remain uninvolved or, for the most part, intact, with the exception of olfactory structures and portions of the pain system. The most disease-related damage revolves around motor areas: particularly around superordinate centers of the limbic and visceromotor systems as well as portions of the somatomotor system. Terms in brackets [ ] indicate extracerebral structures where Lewy pathology occurs and the earliest Braak stages *to date* at which the lesions are seen in relation to brain stages. CA, cornu ammonis (hippocampal formation).

The presence of lesions associated with other proteinopathies does not appear to diminish the pathological influence of LNs and LBs in sporadic PD. In fact, there is some evidence for a facilitatory or synergistic effect between Alzheimer-related lesions of the neurofibrillary type and abnormal α-synuclein fibrillization.

Neuropathological Staging

Neuropathological staging is based on the topographic extent of the Lewy pathology, neuroanatomical connectivities between involved sites, and neuronal loss in specific nuclei.

Lewy pathology in immunoreactions against α-synuclein appears as spindle-shaped or thread-like LNs within neuronal processes and, in the somata of vulnerable projection neurons, as punctate (particulate) aggregations, faintly contoured pale bodies, and globular LBs. Voluminous LNs/LBs can be visualized in 6–30 μm paraffin sections stained for general overview with hematoxilin-eosin or in unconventionally thick (≥100 μm) polyethylene glycol-embedded sections with an advanced silver technique. Prior to the era of α-synuclein immunocytochemistry, the punctate aggregations, very thin LNs and smaller LBs could be most effectively visualized using immunoreactions against the heat shock protein ubiquitin.

Deposits of lipofuscin pigment occur in the somata of most nerve cell types in the human adult and are more difficult for macrophages or astrocytes to degrade than LBs and LNs. Structurally, lipofuscin and neuromelanin are so stable that they survive delayed or suboptimal fixation unchanged. It is precisely this asset that can be exploited to assess neuronal loss. Special histochemical techniques stain deposits of neuronal lipofuscin pigment more prominently than granules of the same type in glial or nonneuroectodermal cells. Such aldehyde fuchsin-Darrow red staining enables the viewer to visualize the breakdown of nerve cells in the form of extraneuronal lipofuscin pigment remnants, a phenomenon sometimes termed 'pigment incontinence.' In the adult human brain, neuromelanin is an oxidative byproduct of the biosynthesis of catecholamines and, thus, we utilize it as a marker for catecholamine-synthesizing nerve cells (**Figure 2**). Because neuromelanin can be specifically labeled and its natural brown color is recognizable even in unstained tissue sections, it is easy to diagnose the degradation of all the melanized nerve cell types. Phagocytosing cells take up the neuromelanin granules and stay in place for long periods of time, thereby, marking the sites of lost melanized neurons (**Figure 2(e)**).

In the brain, the distinctive temporospatial distribution pattern of the lesions is despite exceptions, more or less symmetrical and remarkably consistent across cases, thereby permitting the recognition of six neuropathological stages. Staging systems are imperfect because they are artificial constructs requiring validation and revision – ideally within the context of findings from large prospective (longitudinal) autopsy-controlled studies, which include cohorts of 'healthy normals' (controls). The staging systems by Braak et al. and Saito et al. are based on retrospective cross-sectional studies performed on series of nonselected autopsy cases using immunocytochemical and semiquantitative methods. The earlier of the two staging systems proposes assigning symptomatic cases (i.e., individuals with clinically diagnosed PD) to one of four subgroups that differs with respect to the temporospatial distribution of Lewy pathology in the brain. In other words, each subgroup displays additionally involved brain regions together with the lesions at previously involved sites.

Sporadic PD does not develop overnight and, as such, the presymptomatic phase continues to occupy a focal position with respect to the pathogenesis of the disorder. At autopsy, ~5–20% of nonsymptomatic individuals above the age of 60 display mild (incidental) lesions in portions of the nervous system known to be susceptible to PD. In the Braak staging system, such cases were also subdivided into three subgroups using temporospatial criteria. An essentially caudorostral trajectory of the pathological process was observed in the brain (i.e., it probably begins in the lower brainstem and ascends until it reaches the cerebral cortex). Taken together, it was proposed that all six subgroups may reproduce the progressive nature of the disorder. Both sets of subgroups combined may reflect the spectrum of the larger pathological process (presymptomatic or preclinical versus symptomatic or clinical phase) that underlies sporadic PD.

The term 'presymptomatic phase' implies that incidental Lewy pathology in persons without classical motor symptoms is, neuropathologically speaking, equivalent to the incipient PD and the forerunner of the symptomatic phase. The pathological process underlying both the presymptomatic and symptomatic (motor) phases is marked by the presence of the same types of α-synuclein-immunoreactive inclusion bodies in the same susceptible neuronal types in specific regions of not only the brain but also of the peripheral and enteric nervous systems.

It is the topographic distribution and extent of the Lewy pathology *via interconnected anatomical fiber tracts* as well as neuronal dysfunction/loss at specific sites that provide the basis for the Braak classification (staging system). No remarkable nerve cell loss takes place in the earliest stages, but whether mild neuronal loss is negligible or proves functionally deleterious may well depend on comorbidities, neuronal reserve, and the nerve cell types involved. A nonrandom loss of nerve cells probably impairs function, whereas comparable but random neuronal loss may be less likely to do so.

Stage 1: Medullary Autonomic Region and Anterior Olfactory Structures

LNs in the brain are seen in preganglionic cholinergic projection neurons of the dorsal motor nucleus of the vagal nerve, sometimes together with Lewy pathology in the intermediate reticulate zone of the lower medulla, olfactory bulb, anterior olfactory nucleus, and olfactory tract. Cases with incidental Lewy pathology confined to the olfactory bulb and/or anterior olfactory nucleus ('olfactory only' cases) in the absence of medullary and/or nigral Lewy pathology also exist (unpublished findings). From stage 3 onwards, additional olfactory structures (piriform cortex, periamygdalar cortex, medial entorhinal region) become involved. Lewy pathology has not been found in the olfactory epithelium; however,

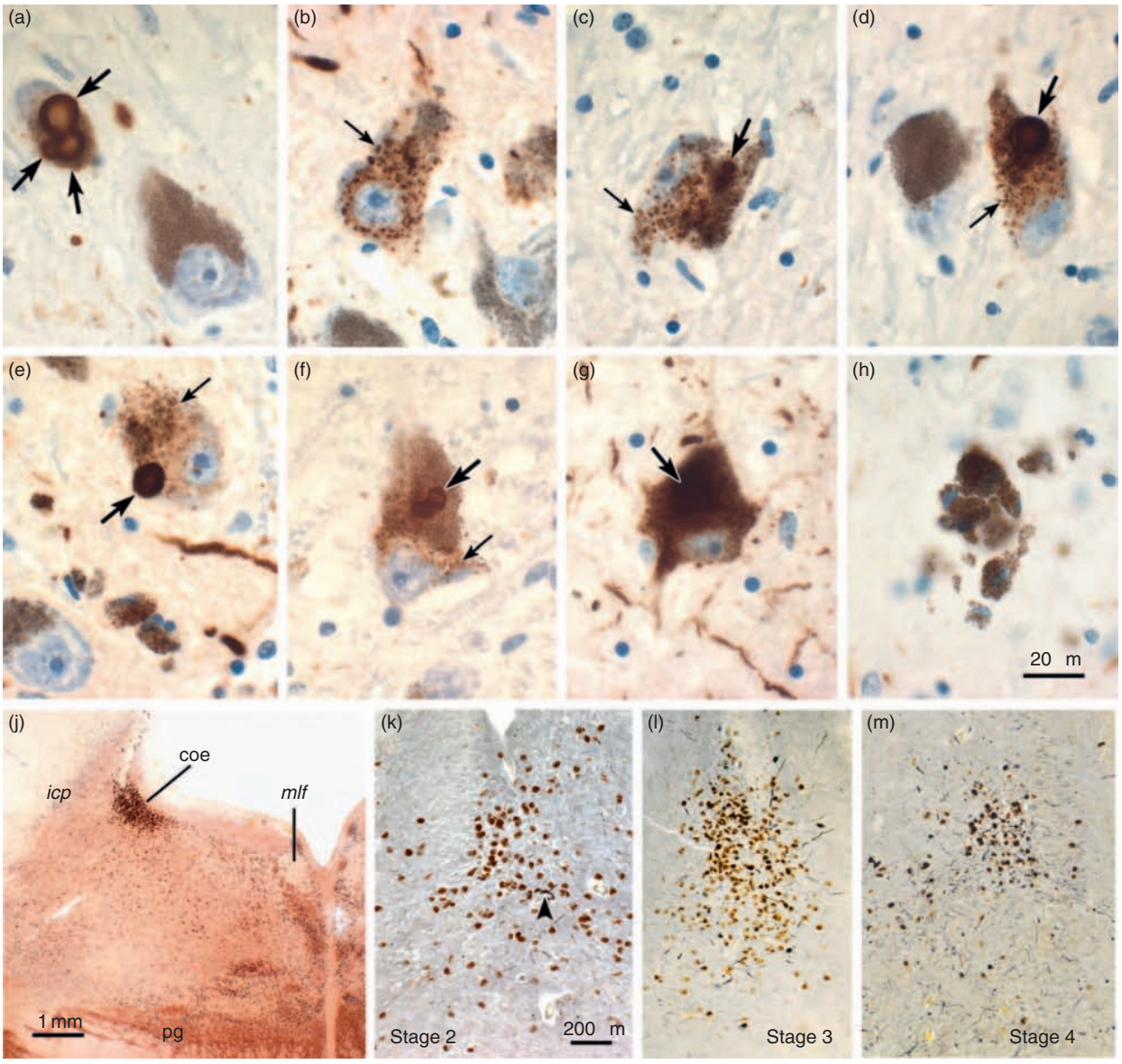

Figure 2 Lewy bodies (LBs) in especially vulnerable melanized (noradrenergic, dopaminergic) projection neurons of the pontine and midbrain tegmentum in sporadic PD. (a)–(h) Micrographs showing dopaminergic nerve cells in the substantia nigra and pars compacta. (a) Multiple mature LBs (arrows) fill a large proportion of the cell body. The adjacent melanized nerve cell is healthy. (b)–(f) Aggregated punctate, that is, particulate, α-synuclein (small arrows) appears to organize into LBs (large arrows). (d) Compare the normal melanized neuron, without α-synuclein particles, with the melanized nerve cell at the right. (e). Two smaller astrocytes (below, directly in the middle) have ingested α-synuclein immunoreactive abnormal material together with neuromelanin. The terms 'extraneuronal' neuromelanin or 'pigment incontinence' apply to such material. (g) In this micrograph, it is difficult to distinguish the LB (arrow) from the immediately surrounding and densely packed particulate α-synuclein. (h) Following cell death, a group of macrophages containing neuromelanin granules and immunoreactive LB remnants mark the shape and site of the former nerve cell. Such 'extraneuronal' LBs are no longer surrounded by a neuronal cell body with a nucleus. They remain visible in the tissue (neuropil), similar to ghost tangles in Alzheimer's disease, but they are more rapidly degraded by macrophages than extraneuronal neurofibrillary tangles. α-Synuclein immunoreactions (Syn-1, BD Bioscience Laboratories, Mountain View, CA, USA) in conventional 6 μm paraffin sections. Scale bar in (h) is valid for (a)–(g). (j) Overview of transverse section through the pontine tegmentum, including the coeruleus–subcoeruleus complex of the level setting system, from a control case. Staining for topographic orientation, lipofuscin pigment, and Nissl material (aldehyde fuchsin-Darrow red) in unconventionally thick 100 μm polyethylene glycol-embedded sections. (k–m) Lewy pathology (arrowhead in (k) indicates a Lewy neurite) without neuronal loss develops in the locus coeruleus during stage 2. The lesions there subsequently worsen (l) accompanied by clear signs of loss of melanized (catecholeminergic) neurons (l, m). α-Synuclein immunoreactions (Syn-1, BD Bioscience Laboratories, Mountain View, CA, USA) in unconventionally thick 100 μm polyethylene glycol-embedded sections. Scale bar in (k) also applies to (l, m). Abbreviations: Coe, coeruleus–subcoerules complex; *icp*, inferior cerebellar peduncle; *mlf*, medial longitudinal fascicle; pg, pontine gray.

the gradient of the olfactory pathology appears to be from more peripherally placed structures (bulbopetal) in the olfactory bulb to the anterior olfactory nucleus and cortical olfactory structures rather than vice versa. The discussion regarding the olfactory vector hypothesis of sporadic PD is still unresolved.

Other components of the medullary autonomic dorsal vagal area (area postrema, gelatinosus nucleus, nuclei of the solitary tract, myelinated motor neurons of the ambiguus nucleus) remain uninvolved. Notably, the catecholaminergic melanized nerve cells (A2 group) in the dorsal vagal area and intermediate reticulate zone (A1 group) are not drawn into the disease process until stage 3.

Stage 2: Level Setting Nuclei of the Lower Brainstem and Pontine Tegmentum

The term 'level setting' (or 'gain setting') system is not widely known in Anglo-American anatomical usage. It encompasses three groups of nuclei: the serotonergic lower raphe nuclei, the magnocellular portions of the adjoining reticular formation, and the noradrenergic coeruleus/subcoeruleus complex (A6, A7 catecholaminergic groups). All three groups are driven by supramedullary centers of the limbic (central subnucleus of the amygdala) and somatomotor (tegmental pedunculopontine nucleus (PPN)) systems. An intact level setting system temporarily inhibits relay nuclei for the conduction of incoming pain signals (somatosensory and viscerosensory) and places the organism's voluntary motor neurons in a heightened state of preparedness in fight-or-flight situations. Normally, the target neurons of these limbic system-moderated level setting nuclei are capable of switching back and forth from a lower to a higher level of activity, and the individual's emotional status determines the appropriate level in any given situation. An intact limbic system is necessary for the maintenance of this adaptive behavior. In the course of PD, patients can experience a dissociation between the voluntary and emotional motor systems.

Stage 2 cases are marked by the presence of Lewy pathology within the cell somata and thinly myelinated axons of the level setting nuclei (**Figure 2(k)–2(m)**). The observation that all of these nuclei, and only these, become involved at stage 2 is consistent with the concept that retrograde axonal and transneuronal transport via anatomical pathways may play an important role in the pathogenesis of sporadic PD.

During the first two neuropathological stages, Lewy pathology routinely occurs in olfactory areas, portions of the lower brainstem, and in lamina I of the spinal cord. Also involved at these early stages are the Auerbach and Meissner plexuses of the enteric (gut) nervous system as well as sympathetic portions of the peripheral nervous system (cardiac nerves, vesicoprostatic plexus). Thus, the pathological process in sporadic PD does not appear to have the substantia nigra as its point of departure. On the contrary, nigral involvement presupposes the existence of Lewy pathology in the lower brainstem and, possibly, in the spinal cord and peripheral nervous system (**Figure 1**).

Stage 3: Nuclear Complex of the Amygdala, Midbrain Tegmentum, Nonthalamic Diffusely Projecting Nuclei, Basal Forebrain, and Cortical Olfactory Structures

Stage 3 cases are characterized by the presence of Lewy pathology in the central subnucleus of the amygdala followed by involvement of the pedunculopontine tegmental nucleus, the pars compacta (A9 catecholaminergic group) of the substantia nigra, and nonthalamic nuclei that project extensively to the cerebellum, subcortical sites, and cerebral cortex. Among the diffusely projecting nonthalamic nuclei that become involved during this stage are the upper raphe (serotonergic) nuclei, the magnocellular (cholinergic) nuclei of the basal forebrain (medial septal nucleus, interstitial nucleus of the diagonal band, basal nucleus of Meynert), the hypothalamic tuberomamillary nucleus with its GABAergic and histaminergic neurons as well as the paranigral and parabrachial pigmented nuclei with their dopaminergic neurons (A10 group) (**Figure 1**). In stage 3, Lewy pathology also appears in the catecholaminergic melanized neurons of the dorsal vagal area (A2 group), intermediate reticulate zone (A1 group), and in nerve cells (A4 group) close to the roof of the fourth ventricle that form the cerebellar portion of the coeruleus nucleus.

The central subnucleus of the amygdala regulates all nonthalamic nuclei with diffuse cortical and subcortical projections. It also exercises limbic influence on subcortical nuclei that regulate autonomic and endocrine functions. From the central subnucleus, the pathological process progresses into the basolateral (mainly basal and accessory) subnuclei of the amygdala in stage 4. The central subnucleus sends thinly myelinated descending projections not only to the level setting nuclei but also to the dorsal motor nucleus of the vagal nerve, and it receives afferents from the substantia nigra and basolateral complex of the amygdala. The latter group has reciprocal connectivities with the hippocampal formation and is fed by afferent projections arriving from the magnocellular nuclei of the basal forebrain and from the temporal mesocortex.

The PPN consists of cholinergic and GABAergic as well as glutamatergic neurons. LNs occur within the nucleus followed by LBs in the somata of its cholinergic projection neurons that connect the PPN with the substantia nigra, subthalamic nucleus, thalamic intralaminar nuclei, and the previously mentioned nonthalamic nuclei with diffuse cortical, cerebellar, and subcortical projections. The PPN probably channels the pathological process into the striatal circuit. Together with the level

setting nuclei, the PPN also belongs to a rhythmogenic complex that initiates and modulates oscillatory patterns of activity, including those of the sleep-waking cycle and states of consciousness (arousal, vigilance, attention).

Macroscopically, the pars compacta of the substantia nigra in stage 3 cases appears to be intact. Thinning and obliteration of melanized neurons set during stage 4 and then persist (**Figure 2(h)**). Stage 3 is marked by the appearance of LNs in the posterolateral subnucleus of the substantia nigra, pars compacta, and by LBs in the dopaminergic melanized neurons there (A9 group) (**Figure 2(a)–2(g)**). By contrast, the nonmelanized projection neurons in the pars reticulata do not become involved in the disease process. Approximately, 450 000 dopaminergic melanized neurons populate the pars compacta in each half of the midbrain and, apparently, a mild loss of these cells accompanies aging. Thus, once the pathological process enters the substantia nigra, a cascade of events presumably follows which accelerates the decline and loss of involved nigral cells. Among the possible factors contributing to portions of the nigra's increased susceptibility are neuromelanin, high iron content, proteasomal dysfunction, free radical formation, and inflammation. In addition, each individual is different. In some, the nigral destruction is fulminant and massive, in others prolonged and milder.

The paranigral nucleus and pigmented parabrachial nucleus display less pronounced pathology than the substantia nigra, whereas the perirubral subnucleus and other dopaminergic neurons of the mesencephalic central gray contain little or no Lewy pathology. To date, no truly plausible explanation exists for the resistance on the part of these dopaminergic neurons.

In addition to the lesions that develop during this stage in many of the nonthalamic nuclei (including those not described here in greater detail), the presence of Lewy pathology within the piriform cortex, periamygdalear cortex, and medial entorhinal region provides evidence that the disease process within the olfactory system is also progressive (**Figure 1**).

Stage 4: Thalamic Midline and Intralaminar Nuclei, Mesocortex, Allocortex

Retrospective study of available clinical records revealed that the clinical course of sporadic PD is subject to considerable interindividual variation with respect to symptoms and severity. Because PD-related motor symptoms were mentioned in the clinical records of some stage 3 individuals and in the majority of those with stage 4 brain pathology, we interpreted these remarks as an indication that the presymptomatic phase may yield to the clinically recognizable phase of the disorder at approximately this time.

From stage 4 onwards, Lewy pathology appears in vulnerable regions of the thalamus, including the glutamatergic neurons of the midline and intralaminar nuclei (**Figure 1**). Notably, the intralaminar nuclei send poorly myelinated diffuse projections to layers I and VI of the neocortex.

The pathological process also progresses during this stage into the cerebral cortex, and its point of entry is the anteromedial temporal mesocortex. The mesocortex creates an interface between the sensory neocortex and centers of the limbic system, including the entorhinal region, hippocampal formation, and amygdala. All vital information passing from neocortical high-order sensory association areas to the prefrontal cortex does so via the temporal mesocortex. LNs can be seen there in cortical layers II and III, whereas LBs occur predominantly in layers V and VI. In the adjacent allocortex, LBs appear in the entorhinal region and LNs in the second sector of the Ammon's horn (CA2 of the hippocampal formation).

Stages 5 and 6: Neocortex

During these last two neuropathological stages, the disease process reaches its widest topographic extent. In the locus coeruleus and in susceptible subnuclei of the substantia nigra, the loss of melanized neurons is recognizable upon macroscopic inspection. Lewy pathology within the Ammon's horn expands into the adjoining CA1 and CA3 sectors. The temporal mesocortex and CA2 sector are among the most severely involved regions in the cerebral cortex.

In stage 5, the temporal mesocortex is the point of departure from which the pathological process goes on to occupy portions of the adjoining mature neocortex, beginning with expansive high-order sensory association and prefrontal areas. At this point, the primary sensory and motor fields as well as the first-order sensory association fields of the neocortex are intact. During stage 6, the lesions progress from the high-order sensory association and prefrontal areas into the neocortical first-order sensory association areas and premotor fields. Mild Lewy pathology is also observable in the primary sensory and motor fields.

Summary Remarks

The pathological process associated with sporadic PD is progressive, does not go into remission, and can last for decades. The definition of sporadic PD as a monosystemic disorder with preferential obliteration of dopaminergic neurons in the nigrostriatal system has been recognized as inadequate because it is too narrow. The pathology is widely distributed throughout parts of the entire nervous system, including the spinal cord, peripheral, and enteric nervous systems as early as stage 2.

It is still unclear why the formation of LNs precedes, as a general rule, the appearance of LBs. Since, in its native state, α-synuclein is localized mainly in presynaptic terminals, one would expect to see the earliest aggregations

there. Nevertheless, the earliest light microscopically detectable accumulations begin proximal to the synaptic terminals, that is, in the axon (**Figure 3**). The aggregations fill extensive portions of the axon, leaving only the presynaptic terminals and the initial axon segment free. Terminal axons of corticostriatal and corticothalamic projections appearing as α-synuclein-immunoreactive 'dots' may be exceptions. It remains to be seen whether the abnormal intraaxonal aggregations are transported retrogradely to the cell soma and, there, contribute to the formation of LBs.

The assumption that the pathological process underlying sporadic PD may not begin (or progress) simultaneously in all susceptible regions of the nervous system (olfactory, peripheral autonomic, sympathetic, or parasympathetic nervous systems) but advances in a uniform sequence from predisposed initiation sites still has to be proved, as does the assumption that Lewy pathology in sporadic PD is pathogenic. Nevertheless, in the brain, the process follows an essentially caudorostral trajectory along the neuraxis and progresses from the lower brainstem through

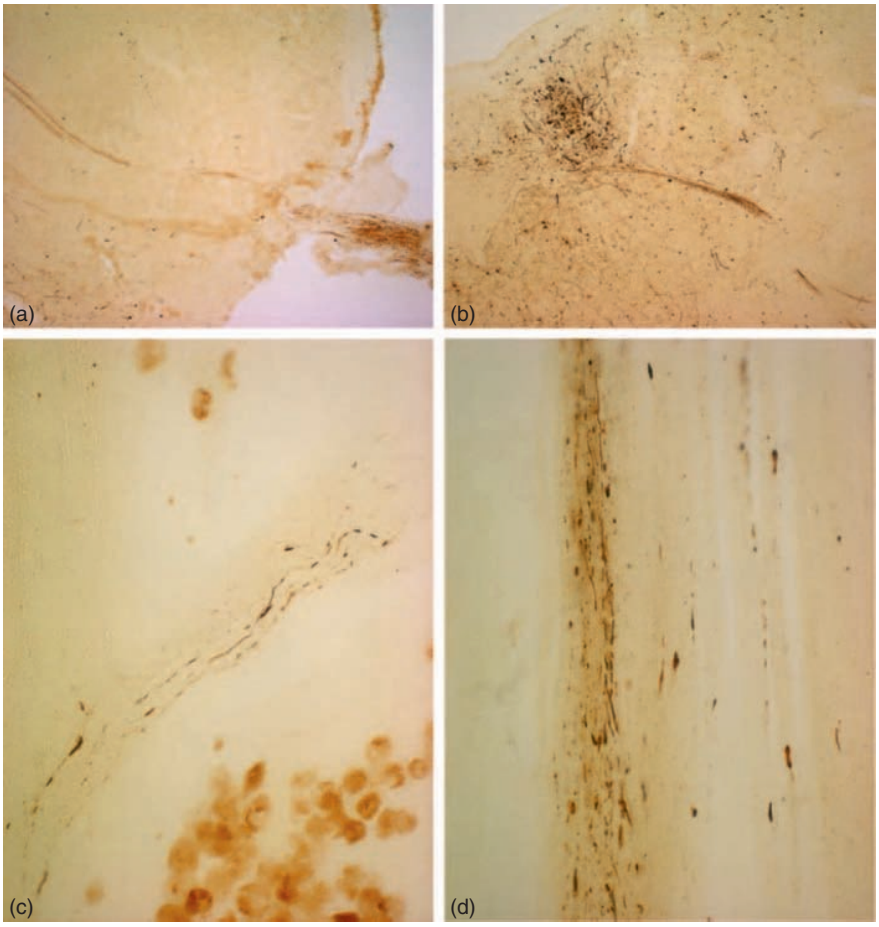

Figure 3 Lewy pathology in the medulla oblongata and peripheral vagus nerve in sporadic PD visualized with α-synuclein immunoreactions (Syn-1, BD Bioscience Laboratories, Mountain View, CA, USA) in unconventionally thick 100 μm polyethylene glycol-embedded sections. (a) Overview of transverse section through the medulla oblongata (intermediate reticular zone) from a 61-year-old male (Hoehn and Yahr stage V, neuropathological stage 5). Note the immunopositive axons (upper left) of the intramedullary vagal nerve and also at the point where they exit the brainstem (lower right). (b, c) Micrographs of a 71-year-old female (Hoehn and Yahr stage V, neuropathological stage 6). (b) Overview of transverse section showing Lewy neurites and LBs in the dorsal motor vagal nucleus (upper left) and in axons of the vagal nerve (lower right). (c) Detail of LNs (intraaxonal Lewy pathology) from a segment of the left peripheral vagus nerve in the mediastinum at the level of the first thoracic vertebra. Fatty tissue appears at the lower right. α-Synuclein aggregations and the extent to which they occur in the peripheral vagus nerve in sporadic PD have not been studied until now because full-body autopsy is not part of the standard routine in neuropathology departments. (d) Detail at higher magnification from another part of the same peripheral nerve. In all probability, such LNs, which in this case were seen in vagal axonal fibers extending from the larynx to the aortic arch, eventually disrupt somatopetal/somatofugal transport and, in doing so, impair the functional capacities of involved nerve cells. Impairment of axonal transport also may induce abnormally high concentrations of α-synuclein within the soma and possibly trigger LB formation within the host neuron.

basal portions of the mid and forebrain until the cerebral cortex becomes involved (**Figure 1**). More caudally located structures are involved early. This trajectory has been confirmed in its essential correctness by independent laboratories. Whereas the Braak staging results originally achieved 88% convergence, other groups have convergence rates between 60% and 94% and include at least one very large prospective study (Honolulu Asia Aging Study). A variable number of cases are not stageable using the systems proposed by Braak et al. or Saito et al. Such individuals often have more than one neurodegenerative disease, for example, Alzheimer-related lesions plus amygdala-predominant Lewy pathology.

The existence of cases with brainstem Lewy pathology in the locus coeruleus but not in the cholinergic neurons of the medullary dorsal motor nucleus of the vagal nerve or in the pigmented neurons of the dorsal vagal area is not incompatible with the proposed caudorostral trajectory, namely, that selectively vulnerable lower brainstem pigmented nerve cells, as well as olfactory structures may become involved prior to the substantia nigra. The caudorostral progression in the lower brainstem does not achieve machine-like precision, but there is also no evidence to indicate that the pathological process begins in all susceptible brain regions at once or that it progresses according to a hit-or-miss principle. It is still open, however, whether the beginnings of the pathological process are mono or multicentric (i.e., brain and spinal cord, brain, and peripheral nervous system), and very large autopsy-controlled prospective studies including healthy 'normals' are required to answer this question.

Presently, much attention is being focused on reversing the impaired somatomotor functions that result from the destruction of nigral dopaminergic nerve cells. However, transplantation of fetal midbrain cells into the putamen of levodopa-refractory patients is fraught with the risk of developing new lesions and does not alleviate nerve cell dysfunction, neuronal loss, or dysfunctional motor neuron responsiveness in other parts of the nervous system as a whole (e.g., limbic system-moderated level setting nuclei, gastrointestinal tract). In addition to the continuing search for biomarkers that can identify individuals who are in the presymptomatic phase of sporadic PD, strategies are needed that can prevent the protein α-synuclein from misfolding or hindering the pathological process from reaching the substantia nigra.

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See also: Alpha-synuclein; Melanin; PARK1, Alpha Synuclein; Parkinson's Disease: Definition, Diagnosis, and Management.

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Bradykinesia

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Glossary

Basal ganglia (BG) – Group of nuclei encompassing the striatum (which includes the caudate, putamen, and accumbens nuclei), globus pallidus, substantia nigra, and subthalamic nucleus that control motor and nonmotor functions through the thalamocortical projections.
Festination – Sudden shortening of stride and quickening of gait usually observed in Parkinson's disease.
Freezing – Sudden loss of mobility usually in initiation of gait or triggered by turning, obstacles and multitasking.
Hypomimia – Reduced facial expression.
Hypophonia – Reduced vocal loudness.
Micrographia – Smaller handwriting, usually characterized by decremental size and speed.
Sialorrhea – Decreased ability to control oral secretion, leading to pooling of saliva and eventually drooling.
UPDRS – Unified Parkinson's disease rating scale, scale used to evaluate the severity of motor symptoms and signs in this disease.

Summary

Bradykinesia is usually used as a broad term to include three different phenomena: slowness (bradykinesia), low amplitude (hypokinesia), and difficulty in initiating movements (akinesia). Although clinical dissociation exists, their differentiation is at present of uncertain value. The common underlying mechanism is basal ganglia (BG) hypofunction interfering with selection and performance of motor programs. The most common and paradigmatic etiology is parkinsonism. Automatic and voluntary movements, including facial expression, handwriting, speech, and gait, are affected. Repetitive and rapid maneuvers of isolated limbs, rising from a chair and gait characteristics, are helpful in clinical practice. Differential diagnosis includes paralysis, fatigue, depression, apraxia, ageing, abulia, and catatonia. Treatment is dependent on the physiopathology and topography of the dysfunction and includes sensory rehabilitation strategies and dopaminergic stimulation when there is an underlying dopaminergic deficit.

Introduction

Bradykinesia is defined as slowness of movements, as stressed by its two Greek roots (*brady* = low; *kinesis* = movement). Frequently the terms bradykinesia, hypokinesia, and akinesia are used interchangeably but their meaning differs. Bradykinesia refers to the decreased velocity with which a movement is performed, while hypokinesia refers to the decreased amplitude of the movement and akinesia means the inability or difficulty to initiate the movement. Although these phenomena are usually related and may coexist, at present there is not enough evidence to support that the differentiation is of value in clinical practice.

Etiology

There are multiple possible etiologies for bradykinesia. In fact, it can occur in both hypokinetic and hyperkinetic syndromes. Bradykinesia, in the broad sense, is a cardinal feature of parkinsonism, the hallmark of BG hypofunction. Parkinsonism is defined by the presence of two of the following features: bradykinesia, rigidity, rest tremor and postural instability, and the paradigm is Parkinson's disease (PD). Bradykinesia, in the strict sense, usually coexists with hypokinesia and akinesia in parkinsonian disorders. Akinesia and bradykinesia can be particularly significant in some of the parkinsonian disorders such as progressive supranuclear palsy and corticobasal degeneration. However, bradykinesia may occur dissociately from the other phenomena in hyperkinetic movement disorders such as Huntington's disease (HD) and dystonia. Also, pure akinetic syndromes, such as pure akinesia and freezing of gait, exist. Other disorders presenting with akinesia include frontal lobe disorders and schizophrenia.

Physiopathology

Physiopathological mechanisms leading to bradykinesia, hypokinesia, and akinesia are not yet clearly defined. The common underlying mechanism is the disruption of the BG circuits. The BG is a complex functional-anatomic unit that has two main output pathways (direct and indirect pathways). Along with the thalamus and cortex, the BG forms multiple segregated, parallel, and reentrant circuits controlling motor and nonmotor behaviors. The motor circuit has an important role in selecting and reinforcing appropriate patterns of cortical activity during the

preparation and execution of motor programs. This role is critically modulated by striatonigral dopaminergic projections. Deficiency of striatal dopaminergic transmission leads to hypoactivity of the direct pathway with increase in the inhibitory output of the thalamus and consequent decreased activation of motor cortex. This inhibition is responsible for underscaled recruitment and later modulation of motor units in the spinal cord, leading to undershooting and slowness of movements. However, the clinical dissociation between bradykinesia and hypokinesia in different clinical disorders suggests that these two phenomena have different underlying pathological mechanisms involving different subcircuits. For example, in early HD, which is characterized by preferential involvement of GABAergic neurons in the indirect pathway with intact dopaminergic projections, presents with chorea and bradykinesia, but not hypokinesia. In contrast, in PD, the characteristic striatonigral dopaminergic dysfunction that affects different thalamocortical pathways leads to bradykinesia, hypokinesia, and akinesia, and other additional cardinal features of parkinsonism. An alternative hypothesis is that hypokinesia may be a direct consequence of rigidity, and this concept would explain why it is not dissociated from other parkinsonian cardinal features. Akinesia on the other hand, might result from impairment of the motor subcircuits that connect with preparatory areas such as the supplementary and mesial cortical motor areas. These subcircuits provide an internally generated cue that triggers a previously learned motor task, allowing the switch between different movements. When impaired, akinesia ensues, as motor function becomes more dependent on external cueing to be triggered. Besides the contribution of BG dysfunction to akinesia, involvement of other structures such as the pedunculopontine nuclei may also probably play a role.

Clinical Manifestations

Individual description of the different clinical expressions of bradykinesia, hypokinesia, and akinesia, although of uncertain clinical value, is an interesting exercise and might prove helpful in future research assessing this theme. **Table 1** shows a simplistic approach of the possible manifestations of these three phenomena in different motor settings.

A frequent complaint suggesting bradykinesia in parkinsonian patients is the progressive slowness in performing the activities of daily living, such as feeding, dressing, bathing or turning in bed, and in other motor activities such as writing, talking, walking, arising from a car seat or chair or houseworking. On the other hand, hypokinesia manifests as decreased arm swing while walking, lagging one shoulder behind when both shoulders are shrugged and frank reduction in amplitude of limb movements. The decreased arm swinging may be one of the first signs of early PD and consequent shoulder pain, due to secondary joint chances, is in fact one of the most common presentations of this disease. Asymmetric bradykinesia and hypokinesia are typical of PD. Akinesia contributes to the loss of automatic movements. All spontaneous movements and gestures are decreased as evident by patients not moving their hands when speaking, not moving in the chair to relief discomfort, nor crossing or uncrossing their legs.

In parkinsonian patients, the face is expressionless with attenuated wrinkling, also known as hypomimia. This is an expression of hypokinesia. In early stages, it may be referred as 'poker face' as it simulates an apparent lack of emotions, occasionally misinterpreted as depression. In severe stages, might be named 'masked face,' as it becomes completely fixed with the lips apart. Akinesia, shown by decreased automatic movements such as blinking, also contributes to the hypomimic face. Decreased swallowing, another impaired automatic movement, in addition to the hypomimia, leads to pooling of saliva (sialorrhea) and drooling.

Changes in handwriting may be the first reported symptom with parkinsonism starting in the dominant upper extremity. Patients usually report that their handwriting becomes smaller and sometimes unintelligible. This hypokinetic hallmark is named micrographia, and is not only characterized by a smaller letter size, but also

Table 1 Clinical expression of bradykinesia, hypokinesia, and akinesia (simplistic approach)

Feature	*Bradykinesia*	*Hypokinesia*	*Akinesia*
Facial expression		Hypomimia	Decreased blinking
Phonation	↓ verbal debit	Soft, breathy monopitch voice	Eyelid apraxia
Articulation		Imprecise consonants	
Swallowing			Drooling
Associated movements		↓ arm swing	Loss of associated movements
Writing	Slow writing	Micrographia	
Voluntary movements	Slow	↓ amplitude	↑ latency to initiate
Gait	↓ cadence (steps/min)	Small steps (↓ stride)	Hesitation Freezing
Repetitive Movements	↑ cycle duration	↓ amplitude	Difficulty initiating the movement and changing patterns

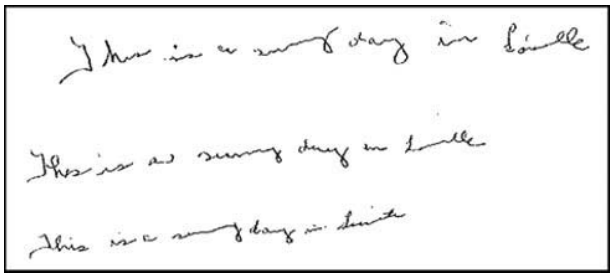

Figure 1 Micrographia. The letters are small and progressively decrease in size, translating the progressive decrease in the amplitude of the movement with repetitive tasks. It is written 'This is a sunny day in Louisville.'

by a progressively decreasing size of the letters as the writing task continues (**Figure 1**). Micrographia is usually associated with slowness and effort in performing this task, which could be phenomenologically described by the neologism 'bradygraphia.' However, the opposite is not always true.

Hypokinesia, contrasting with bradykinesia, has major repercussions in speech. The speech disturbance results from the interaction of multiple factors that include respiratory effort, phonation, and articulation. The decreased amplitude of respiratory movements is at least partially responsible for a soft voice (hypophonia). Phonation may also be impaired by the decreased amplitude of the movements of the vocal cords that leads to glottal incompetence (incomplete adduction) and clinically manifests as breathiness, and decreased variability and low vibration frequencies that explain the monopitch speech. Hypokinesia of the lips, cheek, mandible, and tongue is responsible for the slurred dysarthria with imprecise consonants. The reduction in language flow is a consequence of both bradykinesia and akinesia. Speech disturbances are usually a late feature in PD but can be an early feature of other parkinsonian disorders.

Gait is differently affected by bradykinesia, hypokinesia, and akinesia. Bradykinesia manifests as decreased stride cadence (reduced number of steps per minute), independent of the width or length of the stride. Hypokinesia translates as a decreased stride length (small steps) that is not necessarily slow and in fact can have a normal or compensatory increased cadence. Festination, the increasing speed with progressively shorter steps, is a consequence of hypokinesia that is typical of PD and is not found in other hypokinetic-rigid disorders. The hypokinetic gait can be found in hypokinetic-rigid BG syndromes, usually with coexisting bradykinetic features, and in frontal disorders. The accompanying signs, such as posture and balance, and the distribution of hypokinesia, help to define the etiology. The presence of asymmetric hypokinesia and bradykinesia, a stooped posture and small, slow, narrow-based steps usually suggest PD. In contrast, small slow steps, wider or normal width base, normal or even increased arm swing and less stooped posture, particularly if balance is affected, might indicate atypical parkinsonism, vascular parkinsonism, or normal pressure hydrocephalus.

Freezing or motor blocks are a hallmark of akinesia. Freezing can occur in any motor task, but its major expression is in gait, usually occurring when initiating the gait (start hesitation), turning or approaching an obstacle, or trying to undertake multiple tasks simultaneously. Freezing is a major cause of falls in parkinsonian syndromes.

To assess bradykinesia, hypokinesia, and akinesia, patients are asked to perform rapid and repetitive movements such as finger tapping, fist opening and closing, alternate supination–pronation of the hands and forearms and heel or toe tapping. With these manoeuvers, bradykinesia and hypokinesia can be dissociated. In bradykinesia is evident, with very slow movements of normal amplitude. In the movements are of short amplitude but fast, reflecting hypokinesia without bradykinesia. Decremental amplitude and arrest in ongoing movement characterizes the hypokinesia and akinesia of BG disorders. The unified Parkinson's disease rating scale (UPDRS) is the most common rating scale used to assess these three phenomena in this disorder and includes performance of repetitive tasks with each limb, getting up from a chair and walking. These tasks should be performed individually by each limb, as identical manual tasks facilitate the movement of the most affected side and deteriorates the least affected one. In this scale, bradykinesia, hypokinesia, and akinesia are not rated separately and the score in each individual task does not allow evaluating individualized contributions to the disability.

Differential Diagnosis

Bradykinesia, hypokinesia, and akinesia in movement disorders are specifically related to impairment of the BG and related frontal circuits. Muscle strength is preserved and access to motor programs can be delayed but is possible, making these phenomena distinct from paralysis/weakness or apraxia. The term motor arrest, that in this context is a manifestation of akinesia when intending to initiate or when performing a motor task, should not be confounded with some forms of frontal epilepsy in that the motor arrest is paroxysmal, generalized, independent of a motor task, and usually associated to unconsciousness. Special forms of akinesia, such as catatonia and abulia, should also be distinguished. Although slowness and lack of initiative can be features of depression, hypothyroidism and aging, the underlying physiopathological mechanism is different, and the differentiation must be understood from a complete clinical history and examination.

Treatment

Treatment of bradykinesia, hypokinesia, and akinesia depends on the specific etiology and topography of the disorder.

Nonpharmacological strategies include sensory cues that can significantly improve performance and help to overcome and prevent freezing, when the dysfunction relies in the BG. Cues can be visual, such as striped lines on the walkways, and acoustic, such as the regularly paced beats of a metronome. These external cues substitute for the internally generated cues that are deficiently triggered in BG disorders, and theorically mainly affect akinesia. Their effect in hypokinesia and bradykinesia is different, with visual cues preferentially contributing to the enlargement of the stride, and acoustic cues mostly improving speed and step cadence. They are of no help in hypokinetic frontal gait disorders.

Pharmacological and surgical treatments of bradykinesia, hypokinesia, and akinesia are only available for parkinsonism with a predominant dopaminergic dysfunction of the BG, as in PD. The three phenomena are improved by dopaminergic stimulation, including treatment with levodopa or dopamine agonists. Also in PD, bilateral deep brain stimulation of the subthalamic nucleus has been shown to increase motor UPDRS scores. The differential effect of these therapeutic strategies in the different clinical phenomena is difficult to assess as most studies rely on UPDRS motor subscales that do not differentiate between them.

See also: Akinetic-Rigid Syndrome; Basal Ganglia; Basal Ganglia, Functional Organization; Dysarthria; Freezing of Gait; Gait Disturbances in Parkinsonism; Hypophonia; Micrographia; Parkinson's Disease: Definition, Diagnosis, and Management; Rigidity; Substantia Nigra; Unified Parkinson's Disease Rating Scale (UPDRS) and The Movement-Disorder Society Sponsored-unified Parkinson's Disease Rating Scale (MDS-UPDRS).

Further Reading

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Bradyphrenia

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Glossary

Diffusion tensor imaging – MRI-based imaging that assesses the structural integrity of white matter by measuring the rate and directionality of the displacement distribution of water molecules between tissues.

Information processing speed – The amount of time required to complete a cognitive task that also requires the manipulation of acquired knowledge.
Inspection time – The duration of exposure to a stimulus necessary for an individual to make a simple visual discrimination, for example, determine which of the two lines are longer, with near certain accuracy.

Processing speed – The length of time required to complete a cognitive task or the degree of cognitive output completed in a fixed period of time.
Psychomotor retardation – A visible deceleration of thought and movement.
Reaction time – A measure of duration from stimulus to response that can be classified as either simple (press a button when stimulus appears), recognition (press a button when certain stimuli appear, while ignoring others), or choice (press corresponding button when specific stimulus appears).
Response latency – The amount of time taken to respond after a stimulus, such as a question, is presented.
Subcortical dementia – A syndrome often accompanying movement disorders, consisting of but not limited to mental slowing, retrieval memory difficulties, working memory impairment, personality changes such as loss of motivation, affective changes such as depression and apathy, and marked frontal dysfunction such as loss of ability to initiate and sequence tasks.
Thought blocking – A sudden disruption in an individual's stream of thought interfering with its completion.
Working memory – The ability to sustain attention while manipulating acquired knowledge.

Definition

Bradyphrenia represents a pathological slowing in cognition. Synonymous with the historical term's 'psychic akinesia,' it is a highly sensitive although nonspecific indicator of cerebral dysfunction. Operational definitions depend on the measure used and include impairments in processing speed, information processing speed, complex attention, mental speed, reaction time, and inspection time.

Clinically the patient or caregiver endorses the patient's decreased productivity on timed tasks or the need to take longer time periods to complete mental process. Clinicians may observe increased response latency. Processing speed is a multifactorial construct, comprising speed of perception, processing, and response, the exact definition and objective measurement of which are challenging. The most elementary tasks tap multiple domains and are confounded by sensory and motor dysfunction. Consequently, bradyphrenia is best reported in the presence of cognitive slowing out of proportion to that expected from other contributing impairments.

Historical Context

Empirical measurements of processing speed emerged from the interest in individual intellectual differences suggested by evolutionary theory in the mid-nineteenth century. Sir Francis Galton, with subsequent contributions from Wundt, Cattell, Donders, and Burt, studied individuals' reaction times. They accurately hypothesized but failed to demonstrate intelligence correlating with processing speed. When their data were unable to predict students' grades, enthusiasm for the field waned.

In 1882, Ball first noted slowing of perception, movement, and ideas in parkinsonism. Following the encephalitis lethargica pandemic in the 1920s, Naville coined the term 'bradyphrenia,' known as 'bradypsyche' to German authors, to describe slowed intellectual processing in 40% of the patients. A lack of will and other psychological explanations for the psychiatric sequelae of parkinsonism dominated theories for the next 30 years.

The 1960s represented a renewed effort by experimental psychologists to uncover the heritability and neurophysiological underpinnings of the cerebral basis of 'psychic akinesia' as Hassler termed bradyphrenia. In 1964, Steele reported cognitive deficits in a series of patients with progressive supranuclear palsy. Albert later confirmed bradyphrenia in this population. Significant efforts ensued to characterize slowing in other disorders. In 1981, a processing speed index appeared in the Wechsler Adult Intelligence Scale demonstrating the importance of this measure to overall cognitive–intellectual functioning. However, working models of speed and intelligence as well as bedside and lab measures of bradyphrenia remain elusive.

Pathogenesis

Lesions of the medial neuraxis from frontal pole to pons, specifically the mesocortical pathway and reticular formation, were postulated as the injury site for psychic akinesia in the 1960s. However, no single brain lesion causes bradyphrenia. Its manifestation in subcortical dementias implicates a subcortical focus. However, it also occurs in cortical disease. Potential neurobiological correlates are suggested below.

White Matter Integrity

In multiple sclerosis, total lesion volume directly and independently predicts bradyphrenia. Patients with temporal lobe epilepsy with white matter volume reduction, survivors of severe traumatic brain injuries with quantitative corpus callosum deficiencies, and elderly subjects with more numerous white matter hyperintensities detected on MRI demonstrate clinically significant reductions in

processing speed. Recent diffusion tensor imaging data relate disruption of white matter pathways carrying efferent thalamocortical fibers to age-related cognitive slowing.

Frontal–Subcortical Dysfunction

Both hypokinetic and hyperkinetic basal ganglia disorders are associated with bradyphrenia. Frontally impaired individuals with Parkinson's disease (PD), nondemented subjects with caudate and thalamic lesions, and elderly patients with loss of the D_2 (dopamine)-receptor binding sites in the caudate and putamen manifest disproportionate processing speed deficiencies.

Neurotransmitter Changes

Reduced processing speed in various conditions has been linked to cholinergic deficits, hypodopaminergic states, and altered glutamate activity.

Clinical Assessment

Epidemiology

Factors such as age, baseline intelligence, cerebrovascular risk factors, and genetics modestly predispose individuals to cognitive slowing.

Presentation

The course of bradyphrenia may fluctuate or progress insidiously depending on the associated condition. Sudden arrests of movement in patients with parkinsonism may coincide with thought blocking. Clinical reports consistently associate thought blocking and response latency with reduced motivation, hypophonia, fatigue, apathy, poverty of speech and content, distractibility, perseveration, lack of awareness, and memory disturbance. Cognitive slowing impacts mobility, gait, balance, transitions from sitting to standing, driving competency, and functional reach. Processing speed correlates with functional and quality of life measures.

Bradyphrenia amplifies deficits in other cognitive functions including working memory, episodic memory, executive functioning, reasoning, verbal abilities, problem-solving, reading, arithmetic, and visuospatial skills. Inaccuracies from impairments in these domains in turn contribute to slowing. Despite these interactions, bradyphrenia independently affects performance even in patients with preserved overall intellectual functioning.

Associated Disorders

Table 1 lists some of the many clinical conditions in which bradyphrenia is present. The majority of research

Table 1 Conditions listed by etiology reporting bradyphrenia as a clinical characteristic

Congenital/genetic
Adrenoleukodystrophy
Choreoacanthocytosis
Fragile X tremor–ataxia syndrome
Metachromatic leukodystrophy
Myotonic dystrophy
Pediatric myelomeningocele with shunted hydrocephalus
Williams syndrome
Degenerative
Alzheimer's disease
Corticobasal degeneration
Guamanian parkinsonism–dementia complex
Hallervorden–Spatz disease
Huntington's disease
Mild cognitive impairment
Multiple system atrophy
Parkinson's disease
Progressive supranuclear palsy
Spinocerebellar atrophy
Developmental
Autism
Neurodevelopmental disorder
Iatrogenic
Electroconvulsive therapy, postictal
Idiopathic
Attention deficit and hyperactivity disorder
Bipolar affective disorder
Chronic fatigue syndrome
Epilepsy
Idiopathic basal ganglia calcification
Neuro-Behcet's disease
Normal pressure hydrocephalus
Reading disability
Schizophrenia
Infectious
Postencephalitis
AIDS dementia complex
Inflammatory
Central nervous system vasculitis
Multiple sclerosis
Sarcoidosis (subcortical)
Systemic lupus erythematosus
Metabolic/endocrine/nutritional
Diabetes
Hypoglycemia
Hypothyroidism
Hypoparathyroidism
Korsakoff's
Wilson's disease
Toxic
Substance use disorders (subacute)
Traumatic
Dementia pugilistica
Traumatic brain injury
Vascular
Binswanger's
Cardiovascular disease
Lacunar state
Thalamic infarction
Vascular dementia

studies focus on psychiatric syndromes, movement disorders, multiple sclerosis, and traumatic brain injury.

Conflicting evidence exists over the presence of generalized bradyphrenia in PD patients without dementia. Those with little or no dementia manifest disproportionately slower complex reaction times compared to Alzheimer's patients and elderly controls. The presence of dementia and increased task complexity predict processing speed impairments in the Parkinson's population. Disease duration and severity are not associated. Age, depression, and motor infirmity amplify bradyphrenia. Cognitive slowing contributes to disruptions in speech, mobility, sentence comprehension, executive function, and working memory.

Confounding Conditions

When assessing illnesses characterized by bradyphrenia in the elderly, age-related declines in processing speed require consideration. Cognitive slowing with age also mediates changes in memory, spatial ability, and executive function.

The overlap between psychomotor retardation in depression and bradyphrenia has long been appreciated. A common pathophysiological substrate appears likely. However, slowing in depression reflects more of an abulic or amotivational state, varying less as a function of task complexity compared to bradyphrenia. Phenomenological differences including tearfulness, guilt, suicidal thoughts, and hypochondriasis point to an affective etiology. Bradyphrenia is less likely to improve with antidepressant treatment when the conditions coexist.

Attempts to dissociate bradykinesia and bradyphrenia are long-standing, but have yielded conflictual results. Electrophysiological markers uncontaminated by patients' motor responses show slowing in mid and long-latency auditory evoked potentials delaying further with task complexity. Findings of motor but not cognitive speed improvements after dopamine replacement, and changes in processing speed on tasks requiring similar motor output but more complex decision-making also demonstrate that bradykinesia and bradyphrenia are dissociable phenomena.

Other variables masquerading as reduced processing speed include working memory impairments, apathetic frontal lobe symptomatology with delays in initiating self-generated responses, pathological indecisiveness in obsessive–compulsive disorder, and medication effects, especially due to anticholinergics.

Testing

No gold standard exists for the assessment of processing speed. Principles to guide accurate approximation include use of data from a wide variety of tests, interpretation of findings of processing speed in conjunction with performance on other measures, and minimizing confounding variables such as impairments in sensorimotor functioning, anxiety, impaired arousal, language, education or cultural biases, and practice effects. **Table 2** lists various techniques of eliciting bradyphrenia.

Table 2 Tests for assessing processing speed

Bedside examination
Alphabet backwards
Alphanumeric sequencing: alternate counting with letters of alphabet
Letter fluency: name words beginning with certain letter in given time limit
Serial 7s: consecutively subtract seven from 100
Trail making test: draw line from numbers one through 25 (A) then alternate letters and numbers (B)
Psychomotor and psychophysical speed measures
Simple reaction time: press button in response to stimulus, for example, light
Recognition reaction time: respond to certain stimuli, for example, symbols by pressing button; ignore others
Choice reaction time: respond to identified stimuli, for example, letter on corresponding side
Inspection time: briefest target stimulation duration to score near-perfect recognition of stimulus, for example, which leg of Greek letter π (pi) is longer
Neuropsychological measures[a]
Adult memory and information processing battery: cross out second highest number in each row, timed
Paced auditory serial addition test: single digits presented serially must be summed to previous digit, interstimulus interval varied
Stroop: name color written in incongruous ink
Symbol digit modalities test (SDMT): write target number that matches one of nine geometric figures
Wechsler Adult Intelligence Scale-III digit symbol coding: SDMT but with symbols not figures
Wechsler Adult Intelligence Scale-III symbol search: scan search group of five symbols for presence of target group of two symbols
Computerized measures[b]
Auditory or visual threshold serial addition test: PASAT but report sum aloud while computer determines rate of stimulus presentation producing 50% success rate
Sternberg memory scanning test: memory set of one, two, or four digits, press one of two keys if digits on screen match digits in set
Electrophysiological measures[c]
P300 latency: oddball task – parietally distributed peak on EEG when low probability target stimulus easily discriminated from frequent nontarget stimuli
Alpha peak EEG frequency: fourier transformation performed on EEG time series may demonstrate slowing of alpha peak frequency

[a]When administered together a factor/index of processing speed may be formed.
[b]Most specific measures of processing speed.
[c]Experimental.

Management

Additional time to complete tasks and a greater focus on existing abilities such as verbal skills help compensate for

cognitive slowing. Processing speed training with computer-based target identification, detection, discrimination, and localization improves test measures, driving performance, and timed activities of daily living.

Confounding conditions including apathy and depression require treatment. Elimination of offending medications, minimization of cerebrovascular risk factors, and normalization of blood sugar and cobalamin levels are recommended. The underlying disorder demands optimum management. Empirical trials of psychostimulants and cholinomimetics may attenuate the profound functional impact of bradyphrenia.

See also: Anticholinergics and Movement Disorders; Binswanger's Subcortical Arteriosclerotic Encephalopathy; Bradykinesia; Chorea–acanthocytosis; Choreiform Disorders; Depression and Parkinsonism; Diffusion Tensor Imaging in Parkinson's Disease; Dopamine Receptors; Electroencephalography (EEG); Encephalitis Lethargica and Postencephalitic Parkinsonism; Executive Dysfunction; Hallervorden–Spatz Syndrome (PKAN); Huntington's Disease; Lupus Chorea; Metachromatic Leukodystrophy; Multiple System Atrophy; Normal Pressure Hydrocephalus; Obsessive-Compulsive Disorder; Parkinson's Disease: Definition, Diagnosis, and Management; Progressive Supranuclear Palsy; Reaction Time; Spinocerebellar Ataxias Genetics; Wilson's Disease.

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Brainstem Reticular Myoclonus

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Clinical Syndromes and Definitions

Myoclonus is defined as 'quick movement of muscle.' The resulting brief jerks are shock-like involuntary movements due to either a muscle contraction (positive myoclonus) or a brief interruption of contraction of active muscles (negative myoclonus). The term myoclonus initially included a variety of involuntary movements including tics. In 1903, Lundborg proposed the first classification to help specify this entity. Today, myoclonus can be classified based on clinical features, pathophysiology, or cause. On the basis of the clinical characteristics and electrodiagnostic studies, a relatively accurate site of origin in the nervous system can be predicted. Myoclonus can arise from the cortex, brainstem, spinal cord, and rarely from peripheral nerves. Those arising from the brainstem include exaggerated startle, reticular reflex myoclonus, and palatal myoclonus/tremor.

Exaggerated startle diseases or hyperekplexias (Greek for 'to startle excessively') refer to the brief, explosive, and overblown response to unexpected, mainly auditory stimuli but less frequently to visual or somesthetic stimuli. They were first described in 1958 by Kirstein and Silfverskiold; the definitive description in a large Dutch family occurred in 1966. Clinically, the hyperekplexias are characterized by three major features. A generalized

stiffness in response to handling occurs after birth and disappears by 1 year of age. With time, an exaggerated response to sound stimulation becomes evident especially when the patient is anxious, tired, or frightened. An inconsistent generalized stiffness lasting a few seconds follows the startle and frequently leads to falls and injury. Periodic limb movements during sleep, hypnagogic myoclonus, hernias (umbilical, inguinal, and epigastric), epilepsy, swallowing, and respiratory problems in children, and sudden infant death syndrome may also be concomitantly present. Intelligence is usually normal, but mild mental retardation may be observed. On examination, affected infants may exhibit head retraction reflex, increased muscle tone, and hypokinesia. Adults have wide-based gait without ataxia with an exaggerated head retraction reflex.

The hyperekplexias are largely thought to be familial, but sporadic forms are known to occur. The major autosomal dominant forms are mapped to chromosome 5q33–35; a variety of missense mutations have also been identified in the glycine receptor (GLRA1) gene. Glycine is the most common inhibitory neurotransmitter in the nervous system and its receptor consists of five subunits (3α and 2β); mutations located on the $\alpha 1$ subunit are associated with these diseases. Normally glycine receptors are linked to chloride channels and oppose depolarization. Abnormalities in the receptor lead to decreased inhibition of neuronal activity. Genetic associations are not known to occur with sporadic hyperekplexias, which can result from brainstem infarct, hemorrhage, and encephalitis. Although clonazepam is considered the drug of choice, other benzodiazepines, phenobarbital, vigabatrin, phenytoin, carbamazepine, chlorodiazepoxide, propofol, fluoxetine, 5-hydroxytryptophan, and piracetam can be tried.

Reticular reflex myoclonus was first described in 1977 by Hallet et al. and is thought by some to be a fragment of a generalized form of epilepsy originating in the brainstem. Rat models with urea-induced myoclonus have been well studied, and extensive electrodiagnostic studies including intracellular recordings implicate the nucleus reticularis gigantocellularis of the brainstem. Paroxysmal depolarization shifts (PDS), the most elemental component of a seizure discharge, are found in these regions. Reticular reflex myoclonus appears to be the human version of the brainstem myoclonus in rats. Some experts assert that seizures are a cortical phenomenon, and reticular reflex myoclonus should be considered nonepileptic.

Clinically, these patients have generalized jerks affecting mainly the proximal and flexor regions but are found all over the body. They can be elicited by voluntary movements or by sensory stimulation. Reticular reflex myoclonus was initially described in a patient with post-hypoxic myoclonus (Lance–Adams syndrome) and has been described with renal insufficiency. Single cases were reported in a patient with parkinsonism plus myoclonus, Lyme disease, procarbazine therapy, and neck trauma.

Diagnosis

Reticular reflex myoclonus can be differentiated from the hyperekplexias by several features. Although both appear to need a sensory stimulus to evoke the myoclonus, auditory stimulation is paramount in the startle syndromes. Hyperekplexia patients have the greatest sensitivity to taps in the mantle regions (head, upper chest, and back), while the reticular reflex myoclonus patients greatest sensitivity to taps is in the distal limbs. Presence of spontaneous and action-induced jerks characterize the reticular reflex myoclonus, which have an electromyographic (EMG) burst duration of 10–30 ms. EMG burst duration of more than 75 ms is characteristic of the startle syndromes. When cranial nerves are involved in the reticular reflex myoclonus, the sternocleidomastoid muscle is activated first. Thyrotropin-releasing hormone is thought to have stimulatory effect on the reticular neurons in the medulla and may exaggerate this type of myoclonus. This may be helpful diagnostically in patients with reticular reflex myoclonus. Like exaggerated startle, reticular reflex myoclonus is usually treated with clonazepam. 5-Hydroxytryptophan can be beneficial in patients with reticular reflex myoclonus as well.

Other forms of startle syndromes have been described worldwide for more than 100 years. The startle syndromes, including reticular reflex myoclonus, share a characteristic rostrocaudal progression of muscle contraction and lack of habituation. These syndromes exhibit some variability in excessive startle. The jumping Frenchmen of Maine was first described in the family of French–Canadian lumberjacks in Moosehead, Maine in 1878. In Indonesia and Yemen, the afflicted are referred to as 'latah' and are usually women. In Siberia, these individuals are referred to as Myriachit and in Louisiana, as 'ragin Cajun.' There is some debate that these disorders may be psychogenic or functional in nature but should be distinguished from startle epilepsy.

Palatal tremor is the currently accepted term for what used to be called palatal myoclonus. In the past, this condition was referred to as rhythmic palatal myoclonus, oculopalatal myoclonus, palatal nystagmus, brainstem myorhythmia, and palatal myorhythmia. It is a rhythmic involuntary tremor of the soft palate and can be unilateral or bilateral. It is classified into symptomatic or essential palatal tremor (SPT or EPT, respectively). SPT results from the rhythmic contraction of the levator veli palatini muscle and EPT from tensor veli palatini. Nucleus ambiguus may be the site of origin for SPT and the trigeminal

nucleus for EPT. While other brainstem findings may be evident in patients with SPT, EPT patients have rhythmic clicking in the ear with no other brainstem findings. Pathologic evaluation consistently reveals contralateral hypertrophic degeneration of the inferior olive in SPT patients but not in EPT patients. Magnetic resonance imaging reveals a similar enlargement of the inferior olive and a T2 hyperintensity in the same region. The initial assumption that the lesion had to be within the triangle of Guillain–Mollaret is no longer considered to be completely accurate. Disruptions in other connections may lead to this type of clinical phenomenon also.

Treatment

Surgical and medical treatments for palatal tremor are frustrating. Antiepileptics and sedatives like benzodiazepines can provide some benefit. Botulinum toxin injections can be tried, but administration is difficult and the results are not reliable. Frequent injections are needed with unpredictable results.

See also: Jumping Frenchmen of Maine; Latah; Myoclonus; Myoclonus, Animal Models; Myoclonus, Epileptic; Palatal Myoclonus.

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Relevant Websites

www.movementdisorders.org – Movement Disorder Society.
www.myoclonus.com

Bruxism

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Glossary

Bruxism – From the Greek word *brychein*, 'gnashing of teeth.' The condition distinguishes wakeful from sleep bruxism.
Cyclic alternating pattern – Periodic, synchronous, widely diffuse EEG activity of nonrapid eye movement (REM) sleep characterized by stereotyped phasic patterns lasting <60 s and separated by time-equivalent intervals of background activity. It is an EEG marker of arousal instability during non-REM sleep and is associated with changes in vigilance, muscle tone, and autonomic activity.
Occlusal device (splint) – Any removable artificial intraoral occlusal surface used for diagnosis or therapy affecting the relationship of the mandible to the maxillae. It may be used for occlusal stabilization, for treatment of temporomandibular disorders, or to prevent wear of the dentition. Its mechanism of action has not been fully elucidated.
Occlusion – The static relationship between the incising or masticating surfaces of the maxillary or mandibular teeth or tooth analogs.
Oculomasticatory myorhythmia – Concurrence of pendular vergence oscillations of the eyes along with contractions of the masticatory muscles, suggested as a unique involuntary movement disorder in Whipple's disease, a rare multisystem infectious disease caused by the soil-borne Gram-positive bacillus *Tropheryma whipplei* (Actinomyces family).
Rhythmic masticatory muscle activity (RMMA) – Cocontraction of opening and closing jaw muscles, either in a phasic pattern with single bursts lasting up to 2 s, or in a tonic pattern lasting 3 s and more, or both (mixed episode), occurring mainly in light sleep about once per hour in normal subjects, and up to 2–12 times per hour in those with sleep bruxism. It is the most characteristic electromyographic event associated with tooth-grinding noise during sleep. It is preceded by autonomic and cortical activation.

Definition

First described by Marie and Pietkiewicz, in 1907, this condition consists of an involuntary oral activity characterized by frequent, stereotyped teeth clenching or grinding. If moderate to severe in intensity, the disorder often causes some degree of physical or social discomfort. The condition distinguishes wakeful from sleep bruxism.

Diagnosis

In normal individuals, wakeful bruxism consists of repetitive, aimless, and more or less conscious teeth clenching. In pathological cases, teeth clenching and grinding occur in a variety of psychological, neurological, and orodental conditions. It is often more severe than its sleep counterpart. The clinical diagnosis of sleep bruxism is based on the criteria of the American Academy of Sleep Medicine (**Table 1**). Polygraphic and audio–video recording in the sleep laboratory is the gold standard tool for diagnosis, with moderate-to-severe cases characterized by the presence of more than four (two in mild cases) episodes or 'events' of sleep bruxism or 25 bursts of rhythmic masticatory muscle activity (RMMA) per hour of sleep, and at least two episodes associated with tooth-grinding noise during sleep. The episodes can occur during all stages of sleep but are most common during stages 1 and 2 of light sleep. This method allows the distinction from physiological sources and other types of masticatory muscle activity, such as facio-mandibular myoclonus, tooth tapping, and epilepsy. It can also best document the co-occurrence of a parasomnia (sleep talking, in particular) or a sleep breathing disorder (snoring, apnea).

Epidemiology

Most prevalence studies rely on self account or on a reporting housemate. Wakeful bruxism is a common disorder, particularly in women, with prevalence estimates ranging between 5% and 96% in the adult population (20% on average), reflecting the inaccuracy of self reporting and wide discrepancies in the study design and diagnostic criteria used. The prevalence of bruxism during normal sleep decreases with age based on self report, from 14% to 17% in childhood to 8% in the general adult population, and down to 3% in the elderly, without clear gender predominance.

Table 1 Clinical diagnosis of sleep bruxism (American Academy of Sleep Medicine, 2005)

Criteria
1. Report or awareness of tooth-grinding sounds or clenching during sleep
2. At least one of the following associated feature: (1) abnormal tooth wear; (2) jaw muscle discomfort, fatigue, or pain and jaw lock upon awakening; (3) masseter muscle hypertrophy upon voluntary forceful clenching
3. No other explanation for the disorder (another sleep disorder, medical or neurological condition, medication use, substance use)

Complications

Bruxism activity exerts extremely powerful forces on teeth, periodontal structures, temporomandibular joint, and masticatory muscles. It is often associated with tooth wear and destruction, stress on periodontal tissues, fractures/failures of restorations or dental implants, cheek biting, jaw lock, and tender masticatory muscles hypertrophy causing a characteristic 'square jaw' appearance. Pathological wakeful bruxism may also interfere with normal activities, such as food intake, chewing, swallowing, retention of dental prostheses and bridges, and cause speech impairment.

In sleep bruxism, chronic temporomandibular joint and muscle pain as well as tension-type headache may occur in adolescents as well as in adults, but the pain intensity does not correlate with the intensity of bruxism. Although the sleeper is unaware of the jaw activity, the grinding noise, most conspicuous in severe cases, can disrupt the sleep of the bedroom partner and cause social embarrassment.

Pathophysiology

Pathological wakeful bruxism is a heterogeneous condition (**Table 2**). It has been ascribed to psychological disturbances in individuals with clenching habits. Neurological disorders associated with wakeful bruxism are extremely varied, including mental retardation, dementia, certain neurodegenerative conditions (Rett syndrome, in particular), and subcortical infarcts, supporting the existence of a cerebral origin. Wakeful bruxism has been argued to represent a focal form of dystonia in some cases. It can arise alone or with other dyskinetic manifestations during exposure to medications and amphetamines that directly or indirectly alter the brain dopamine levels, perhaps linking dopamine neurotransmission and abnormal basal ganglia neural processing in the development of some forms of wakeful bruxism. Peripheral factors such as edentulism, denture condition, occlusal disturbances, and overbite, may also contribute to clenching and other parafunctional orofacial activities during wakefulness in otherwise normal individuals, and these factors should not be neglected even in those suffering from a neurological condition that readily provides an obvious 'central' explanation for the disorder. A distinct form of persistent

Table 2 Causes of bruxism

Subtype	*Cause*
Wakeful bruxism	Anxious habit
	Drug-induced
	Antipsychotics
	Antidepressants
	Levodopa
	Anticholinergics
	Acute toxic exposure (ecstasy, amphetamines)
	Mental retardation (Down syndrome)
	Form of focal dystonia, regardless of etiology
	Gilles-de-La-Tourette syndrome
	Neurodegenerative disorders
	Alzheimer disease
	Amyotrophic lateral sclerosis
	Huntington disease
	Neuroacanthocytosis (with 'eating dystonia')
	Wilson disease
	Rett syndrome
	Head trauma
	Subcortical infarcts
	Anoxic encephalopathy
	Cerebellar hemorrhage
	Coma
	Infections
	Whipple disease
	Syphilis
	Temporal lobe epilepsy (rare)
	Peripherally induced
	Malocclusion
	Edentulism
	Ill-fitting dental prosthesis
Sleep bruxism	Idiopathic
	Psychological disturbance
	Emotional stress
	Occlusal factors (limited evidence)
	Drug-induced (antidepressants)
	Oculomasticatory myorhythmia (Whipple's disease)
	Temporal lobe epilepsy (rare)

bruxism can also arise in Whipple's disease as part of a picture of 'oculomasticatory myorhythmia.'

The prime generator of sleep bruxism is still debated. A yet undefined genetic predisposition may contribute. Peripheral biomechanical factors, such as changes in dental occlusion or craniomandibular dysmorphology, proposed for decades as key mechanisms, are now thought to play a minor role, if any. As in other movement disorders, psychological factors, emotional or work-related stress, and personality traits may enhance the expression of sleep bruxism. A basal ganglia contribution has been suggested on the basis of the bruxogenic effect of certain drugs, and the results of a neuroimaging study, which showed an asymmetric distribution of iodobenzamide-labeled dopamine D2 receptors in the striatum in subjects with sleep bruxism relative to controls, a finding of unknown significance awaiting replication. Recent evidence suggests that bruxism episodes are associated with the so-called cyclic alternating pattern (CAP) and are generated in the brainstem as part of a cerebral and autonomic microarousal reactivation state, increasing trigeminal neuron activity. A few minutes prior to bruxism, an increase in central sympathetic drive is apparent, followed by acceleration in brain wave activity and a change in some physiological parameters (rise in suprahyoid muscle tone, faster heart rate, deep breath), which occur ~4 s and 1 s, respectively, prior to the actual occurrence of tooth grinding. A strong swallowing ensues in over one-half of the episodes. This central mechanism better explains the enhancing influence of various factors such as anxiety, smoking, alcohol, caffeine, illicit drugs, and medications.

Management

There is a paucity of consistent evidence-based recommendations regarding the management of unremitting, moderate-to-severe bruxism. The enhancing factors described should be systematically inquired and stopped if possible before any treatment plan is proposed. The orodental condition of bruxers should be monitored periodically and treatment provided accordingly. In general, dental treatments are restricted to oral hygiene maintenance, preservation of chewing function, replacement of ill-fitting dentures, and acute pain management. Children with sleep bruxism are usually managed conservatively with observation and reassurance. The traditional treatment for sleep bruxism, offered whenever the damage is deemed significant, has included occlusal (intraoral devices in many versions), psychological (stress reduction therapy), and behavioral feedback (sound alarms) approaches. Occlusal splints (nightguards) made of hard acrylic are the oral appliances primarily used, designed not to correct the causative mechanisms but to prevent and treat the consequences of bruxism and protect the teeth, with variable and transient results on bruxism activity itself. A different protrusive mandibular splint designed to clear the upper airways has also shown benefit on bruxism. There is no evidence to support the use of irreversible restructuring approaches such as occlusal equilibration, and extensive orthodontic treatment is best avoided. A wide variety of behavioral approaches of questionable value have been tried, including biofeedback, psychoanalysis, autosuggestion, progressive relaxation, hypnosis, meditation, lifestyle improvement, sleep hygiene, self-monitoring, or habit awareness.

Finally, several medications have been reported to be efficacious mainly in open pilot studies, including GABA-enhancing drugs such as gabapentin, tiagabine, and clonazepam. Unlike propranolol, the α_2 adrenergic agonist clonidine was found to reduce RMMA in an acute single-dose study, supporting the view of a sympathetic

drive contributing to sleep bruxism. The practicability of this approach as a long-term treatment has not been addressed. In contrast, dopaminergic drugs have produced only modest or insignificant effects. Magnesium supplements have provided symptomatic relief, but controlled large-scale studies are needed to confirm the benefit and the optimal dosage. Intramuscular botulinum toxin is an increasingly popular option in severe bruxism, but its efficacy has not been tested in a controlled trial.

See also: Drug-induced Movement Disorders; Oculomasticatory Myorhythmia; Rett Syndrome; Tardive Syndromes; Whipple's Disease.

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C

Caenorhabditis Elegans

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Glossary

Hermaphrodite – An organism that is able to produce self-fertilized progeny by having both male and female reproductive organs.
High-throughput screening – Possibility to perform scientific experiments quickly and in a large scale in order to test, for example, pharmacological compounds, automated data handling, and robotics are often used in high-throughput screens.
Molting – The shedding of the cuticle in order to allow growth.
Nematode – A roundworm, an unsegmented worm from the phylum nematoda, mostly free-living but parasitic forms exist.
RNA interference (RNAi) – Silencing of an endogenous gene by administrating double-stranded RNA, the microRNA controlled gene expression is not discussed.

Definition and History

The free-living soil nematode *Caenorhabditis elegans*, also referred to as the worm, has gained increasing amounts of attention during the last decades. At the moment the worm is the simplest multicellular model organism still able to produce a variety of behavioral patterns. Its other qualities, such as transparency, ease of genetic manipulations and rapid generation time, make the *C. elegans* an ideal tool for various research purposes. The research on *C. elegans* was originated in 1960s and it was first focused on studying the cell divisions in the developing worm. The following mutagenesis screens revealed genes which induced abnormal movement, but to study the human diseases in a worm model the evidence for the genomic similarity between man and a worm was needed. The genome sequencing projects in 1990s provided us with the information that 65% of human disease genes have a counterpart in *C. elegans* and ever since the worm has been utilized to study a variety of human disorders.

Basic Worm Biology

Adult *C. elegans* hermaphrodite is 1 mm in length and its body consists of 959 cells, 302 of these being neurons. A newly laid egg develops into an adult worm in 3 days. *C. elegans* has four larval stages and the worm transits from one stage to another through molting. The normal lifespan of a worm is ~3 weeks, but the lifespan as well as the developmental time depends greatly on ambient temperature. There are two sexes in *C. elegans*; hermaphrodite and male. The hermaphrodites are self-fertile organisms usually populating most of the worm cultures. Occurrence of males in self-fertilized progeny is a rare result of spontaneous nondisjunction of the X chromosome. This gives the male a genotype of five autosomes and only one X chromosome while the hermaphrodites have two X chromosomes. By self-fertilization hermaphrodites produce 300 eggs during their lifespan and approximately one out of thousand in this progeny will be a male. With the appearance of the male worm the population dynamics change rapidly. The hermaphrodites fertilized by males not only produce over 3 times more eggs but also the portion of males in the offspring rises to 50%. Most of the research results discussed below comes from hermaphrodites. The male behavior is somewhat comparable to the hermaphrodites', but males have also many specific additional behavioral patterns.

Different Movement Behaviors in *C. elegans*

The worm feeds on bacteria both in nature and in the laboratory. In the laboratory the most common habitat for

a worm is a petri dish with agar and bacterial lawn. There the *C. elegans* moves by alternating the contraction and relaxation of its bilateral body wall muscles thus resulting into a movement which is composed of ventral and dorsal turns of the body. The muscles are innervated with excitatory motor neurons that use acetylcholine as a neurotransmitter and with inhibitory γ-butyric acid (GABA) utilizing neurons. The firing of these neurons with opposite activities is coordinated by neuronal interactions. The result of this neuron–muscle interplay is seen in the typical worm tracks, that is, balanced sine waves on a bacterial lawn (**Figure 1**).

In normal conditions the worms are more or less in constant movement. The movement slows down when the worms are foraging on the bacterial lawn and speeds up when they are on areas with no food available. This behavior originates from mechanosensory stimulus and it is mediated by the neurotransmitter dopamine. Other stimuli that result into change in movement in *C. elegans* include touch, odorants, and temperature. When a normal *C. elegans* is touched on the nose it moves quickly backwards to avoid collision. Touch to the posterior part of the body induces faster forward movement. Harsh touches to other parts of the body are followed by movement to avoid the source of sensation. The movement responses to different stimuli are modified by the worm's earlier experiences. An example of this is habituation, the decreased response after repeated stimulation such as touch.

Worm phenotypes that commonly arise from genetic manipulations have been organized into several classes in Wormbase, an online database for worm genetics. The phenotype class *movement abnormal* is a subgroup of *organism behavioral abnormalities* which also include abnormalities in body posture and/or mechanosensation. *Uncoordinated* (*unc*) is a short version of class *locomotion abnormal*. There are hundreds of gene mutants with different uncoordinated phenotypes. Some of the *unc* phenotypes are self-explanatory, such as *shrinker* or *twitcher*, whereas others, such as *rollers* which rotate around their longitudinal body axis as they move forward, are less clear. There are various methods for analyzing worm locomotive behavior; the preferred method depending on which kind of abnormality is being studied. Many of the movement impairments can simply be seen as changes in the worm trail on bacterial lawn. The worm tracks may be irregular in shape, have marks of worm stopping frequently or have only very small waves. The basic test for *C. elegans*' motor performance is the thrashing assay. In the thrashing assay a worm is placed in an isotonic liquid droplet and as it tries to reach solid ground it makes fast sinusoidal movements that can be counted. One thrash is determined as the movement of the head from dorsal to ventral side. Test times up to 2 min have been used but usually thrashes are counted for 30 s and during that time a normal worm can perform ∼90–100 thrashes. The method for analyzing velocity of the movement and/or coordination of the worm is called radial locomotion assay. In the assay a few worms are placed in the middle of the petri dish and the distance they have moved from the centre is measured at certain time points.

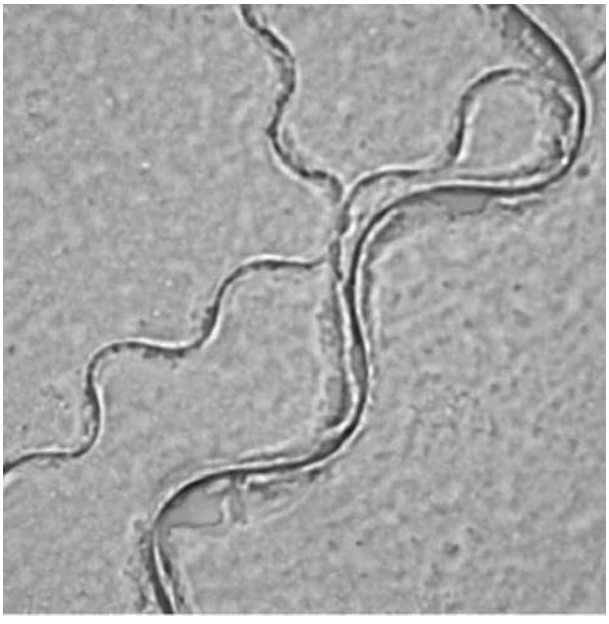

Figure 1 Normal *C. elegans* tracks on bacterial lawn.

Tests assessing functions other than locomotion are also available and they may be applicable when analyzing the effects of gene manipulations. The pharyngeal pumping rate is used to quantify the amount of food taken in by the animal. The pumping rate is analyzed from rhythmic forward–backward movement of the pharyngeal pump as the animal forages. A low pumping rate in *eat-2* mutants is linked to caloric restriction and thus extended life span. Egg-laying and defecation are worm behaviors controlled by neurons and muscles and assays for analyzing them are available. Similarly, tests for monitoring learning have been developed. Worms can be taught to avoid odorants or temperatures by starving them and a failure in avoiding these circumstances refers to a problem either in learning or in perception.

Usage of *C. elegans* in Modeling Human Disorders

The ease of genetic manipulations in *C. elegans* is one of its greatest advantages. Expressions of certain human disease genes, such as β-amyloid peptide, huntingtin, tau, and α-synuclein, have provided both behavioral and morphological phenotypes (**Table 1**). These transgenic worms have thereafter been available for further genetic manipulations or high-throughput drug screens. Different high-throughput analyses in order to break down the pathway

Table 1 Selected *C. elegans* models of abnormal movement

Type	*Description*	*Trashing rate compared to controls*	*Reference*
Drug	1.5 mM muscimol	70%	*EMBO Journal* 2005;24(14):2566–2578
Genetic mutant	Mutations in the *unc-2* gene	25–65%	*Journal of Neuroscience* 2003;23(16):6537–6545
Genetic mutant	Mutation in gene *nid-1*	80%	*Journal of Neuroscience* 2003;23(9):3577–3587
Genetic mutant	Mutation in gene *cle-1*	76%	*Journal of Neuroscience* 2003;23(9):3577–3587
RNAi treatment	Down-regulation of ceGAT-1	124%	*Journal of Biological Chemistry* 2005;280 (3):2065–2077
Transgenic	Pan neuronal expression of human MAPT gene	60–95%	*Proceedings of the National Academy of Sciences USA* 2003;100(17):9980–985
Transgenic	Pan neuronal expression of human α-synuclein	50–60%	*Journal of Neurochemistry* 2003;86(1):165–172

of disease pathogenesis are the forte of *C. elegans* research. With *C. elegans* it is possible to study effects of various treatments on whole animal in 96- or 384-well format with computerized analysis systems. However, it must be kept in mind that the more subtle changes in *C. elegans* behavior still require the expertise of a skilled worm behaviorist.

The discovery of RNA interference (RNAi) has provided a grand tool for *C. elegans* researchers. With no other multicellular animal administration of double-stranded RNA (dsRNA) is as simple as it is in *C. elegans*. Feeding the worms with dsRNA-producing bacteria, injecting the worms with dsRNA or soaking the worms in dsRNA media generates a similar gene silencing phenotype. Full genome RNAi screens have been performed and the data are available. The screens have revealed many uncoordinated and other behavioral phenotypes which can be used to model movement disorders. Especially when the etiology of the disease is known, the simple worm model can significantly help in resolving the cause and effect chain of a gene mutation.

See also: Acetylcholine; Alpha-synuclein; *Drosophila* Models of Parkinson's Disease; Drug-induced Movement Disorders; Dyskinesias: Animal Models; Dystonia: Animal Models; Essential Tremor: Animal Models; GABA and Movement Disorders; Huntington's Disease; PARK1, Alpha Synuclein; Parkinson's Disease: Animal Models; RNA Interference; Synucleinopathies; Tauopathies.

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Camptocormia

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Glossary

Dystonia – A neurologic syndrome characterized by sustained muscle contractions, producing twisting and repetitive movements or abnormal postures or positions.
Myopathy – A muscular disorder in which the primary symptom is muscle weakness due to dysfunction of muscle fibers. Other symptoms of myopathy can include muscle cramps, stiffness, and spasms. Myopathies can be inherited or acquired.
Myositis – The general term for an inflammation of the skeletal muscles. The most common causes are injuries, infections, or autoimmune diseases.

Definition and History

The term camptocormia (CC) was coined in 1914 by Souques and Rosanoff-Saloff. Derived from the greek 'kampto' or to bend and 'kormos' or trunk, it means a pathological bending over of the trunk. During World War I and II, CC was used to describe psychogenic conversion reactions of the soldiers. Later on, French rheumatologists, best represented by the works of Laroche and colleagues and Delcey and colleagues, have linked CC with various, mostly axial myopathies. Recently, there has been a renewed interest for CC as a levodopa-refractory and late-stage parkinsonian syndrome.

Pathophysiology

There is no unitarian pathophysiological concept of CC. As proposed by Djaldetti and Melamed, two schools of thought can be distinguished. The first connects CC to peripheral mechanisms, in particular to myopathy of the antigravity muscles. The latter considers CC as a central disorder, in particular an extreme form of rigidity, or an action dystonia of the spine. The two mechanisms are not mutually exclusive but may add up in the individual patient, leading to a cascade of CC mechanisms (see **Table 1**).

Peripheral Causes

Axial and, more rarely, generalized myopathy have been reported in well-documented case reports and a few small case series. Mostly, the myopathic changes have been unspecific. In some patients, myositic changes were predominant. Two objections against a myopathic cause have been advanced. First, the association of a rare myopathic condition with the even rarer syndrome of CC raises the question of whether there is causal link or just coincidental appearance. Second, most myopathies, with the exception of inclusion body myositis, cause pelvic girdle weakness and thus lumbar kyphosis. However, CC is associated with lumbar kyphosis. The contributive roles of spondylarthrosis and other arthrogenic changes have been questioned because CC is not immutable and disappears in the recumbent position. Cumulative age-dependent factors such as loss of muscle tone, tissue elasticity, chronic stretch, and partial denervation of the paraspinal muscles from degenerative spinal disease have been proposed as contributive peripheral causes.

Central Causes

Three possibilities have been discussed: first, a focal action dystonia of the spine; second, an extreme form of rigidity primarily due to dysfunction of nondopaminergic pathways in the basal ganglia and the brainstem (i.e., the reticulospinal pathway); and third, an imbalance between excessive central motor drive to the abdominal wall muscles and reduced motor drive to the paraspinal muscles. In one series of 16 CC patients reported by movement disorder specialists, two thirds of the subjects were suffering from PD, while four patients had dystonia and one patient had Tourette syndrome. According to Lepoutre, only a quarter of PD patients show some mild improvement of CC after levodopa. CC has also been described in Parkin-gene mutation PD and multiple system atrophy (MSA). Finally, the acute onset of CC has been described in a few patients with vascular lacunar lesions of the putamen or the caudate nucleus.

Cascade from Central to Peripheral Causes

It is possible that in Parkinsonian patients, dystonia of the trunk, possibly triggered by initial high dosage of levodopa, causes continuous straining of the erector trunci, resulting in secondary myositis. Such a pathophysiological cascade could explain the localized delineation of the myositic changes, and the only focal muscle atrophy and replacement by fat tissue. In analogy, excessive load on the paraspinal musculature has been proposed as the cause of myopathy seen in the dropped head syndrome. Theoretically, a

Table 1 Etiology of camptocormia

Parkinsonism
Idiopathic Parkinson's disease
Often end-stage disease
Predominant axial symptoms
Poor or no levodopa response
Possibly myopathic or myositic changes in muscle biopsy
Parkin-related Parkinsonism
Multiple system atrophy
Possibly myositic changes in muscle biopsy
Dystonia
Primary axial dystonia
Secondary
Medication-induced
Tourette syndrome
Neuromuscular
Amyotrphic lateral sclerosis
Unspecific myopathy of the erector trunci
Inclusion body myositis
Proximal myotonic myopathy
Mitochondrial myopathy
Nemaline myopathy
Amyloid myopathy
Stroke
Lacunar lesions
Putamen
Caudate nucleus
Psychogenic
Conversion reaction secondary to wounding during war
Malingering

spreading of a mitochondriopathy or a synucleinopathy from the central nervous system to muscle neurons or paravertebral muscles is also conceivable, but has not been demonstrated so far.

Epidemiology and Risk Factors

CC is a rare condition. Prevalence studies have not been published. Most series have been published by specialized movement disorder or neuromuscular clinics. Thus, the distribution in the general population is unknown. Mild CC, expressed by an anteroflexion angle of less than 45° may be overlooked. Old age, male gender, and in patients with Parkinsonism, long disease duration and predominant axial involvement have been proposed as risk factors for CC. Indeed in the study by Lepoutre and colleagues, most PD patients had severe other axial symptoms such as dysarthria, freezing, and postural instability. A genetic predisposition has been discussed because in the study by Laroche and colleagues, 20 out of 27 patients with myopathy-linked CC had a positive family history for CC.

Clinical Features

CC is characterized by hyperflexion of the thoracolumbar spine that manifests while standing and walking and that, typically, vanishes in both the sitting and the supine position. The angle of the hyperflexion has been differently defined by various authors, ranging from 15° to 90°. Mostly, an inclination of at least 45° is required to establish the diagnosis. CC may worsen during ambulation, throughout the diurnal cycle, or due to stress and fatigue. 'Sensory tricks', as used in dystonia, can rarely help to overcome the flexion posture. CC is associated with back pain in some patients, while it is painless in others. In PD patients, rapid appearance of CC (in $<$1 year) is not unusual. According to three larger case series (Laroche et al., 1995; Azher and Jankovic, 2005; and Lepoutre et al., 2006), the mean age of patients with CC is 65–69 years. In PD patients, the mean duration from onset of the neurologic symptoms to manifestation of CC is 6–7 years.

Allied Conditions

The drop head or anterocollis syndrome, the Pisa syndrome (see the corresponding chapter), and CC represent all axial involvement and may thus represent a continuum of the same underlying condition. Focal myopathy has most convincingly been demonstrated in the drop head syndrome. CC and Pisa syndrome can be concomitant features of an axial dystonia. Anterocollis is considered to be a 'red flag' for the possibility of MSA, while CC has only rarely been described in MSA. Other late manifestations of end-stage PD such as bent-knee posture or tiptoeing have been linked to CC as well, and, similarly, are apparent during ambulation but not in the recumbent position.

Diagnostic Work-Up

CC is a clinical diagnosis. In PD patients, the abatement of the marked anteroflexion of the trunk in the recumbent position and the lack of response to levodopa are pathognomonic signs (see **Figure 1**).

Laboratory investigations include inflammation markers and muscle enzymes. *Electromyography* is often not interpretable, because patients cannot sufficiently relax and extend their trunk in a sitting position. In contrast, two other diagnostic procedures involving the thoracolumbar spine can be very helpful. *MRI of the erector trunci* can demonstrate fatty involution and focal patchy hyperintensities with gadolinium enhancement of the paraspinal muscles. The high signal intensity lesions are best visualized on the T2-weighted, fat-suppressive, short inversion time inversion recovery (STIR) sequence (see **Figure 2**). *Paraspinal muscle biopsy* can evidence an increase of fibrous tissue, focal myopathy, or myositis. Interestingly (see **Figure 3**), such changes have also been found in patients with PD or MSA, thus suggesting that the muscle

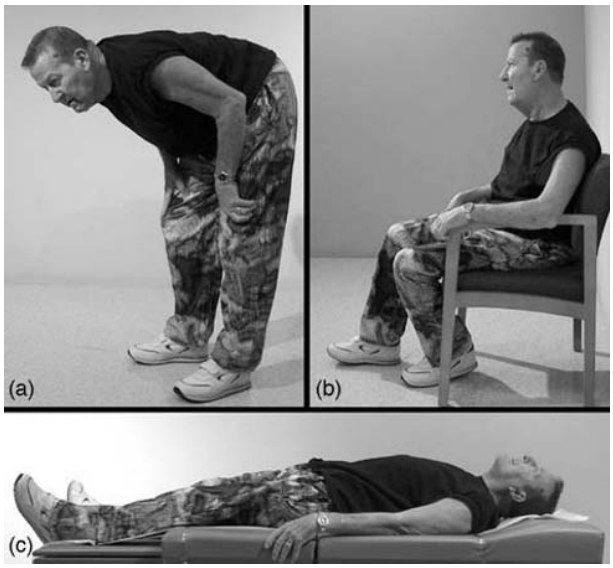

Figure 1 Patient with CC in different positions: (a) While standing, (b) markedly improved on sitting, and (c) markedly improved in the supine position. Reproduced from Azher SN and Jankovic J (2005) Camptocormia: Pathogenesis, classification, and response to treatment. *Neurology* 65: 355–359, with permission from ● ● ●.

pathology may be either the primary cause of CC, a focal reaction to the CC posture, or a coincident syndrome of old age. In PD patients with CC, conventional MRI of the brain and single-photon emission computed tomography with dopamine transporters have not evidenced significant differences between PD patients with or without CC, although in one study, a negative correlation between the severity of CC and the normalized brain volume and sagittal pons area has been demonstrated.

Management

Treatment of CC is mostly unsatisfactory. The treatment responsiveness probably depends on the underlying pathophysiological mechanism. However, as shown above, this mechanism remains mostly elusive. Furthermore, secondary and irreversible mechanical damage to overstretched muscle fibers may preclude substantial effect of any causal treatment strategies. Symptomatic or palliative treatment regimens, however, deserve a 'trial and error approach' in patients with the most disabling syndromes.

Dopaminergic Drugs

CC is mostly insensitive to adjustment of the dopaminergic medication in both directions (increasing dosages and complete withdrawal). Similarly, in PD patients, the severity of CC remains mostly unchanged during 'on' or 'off' phases, although a minority of patients show a temporary deterioration during the 'off' periods.

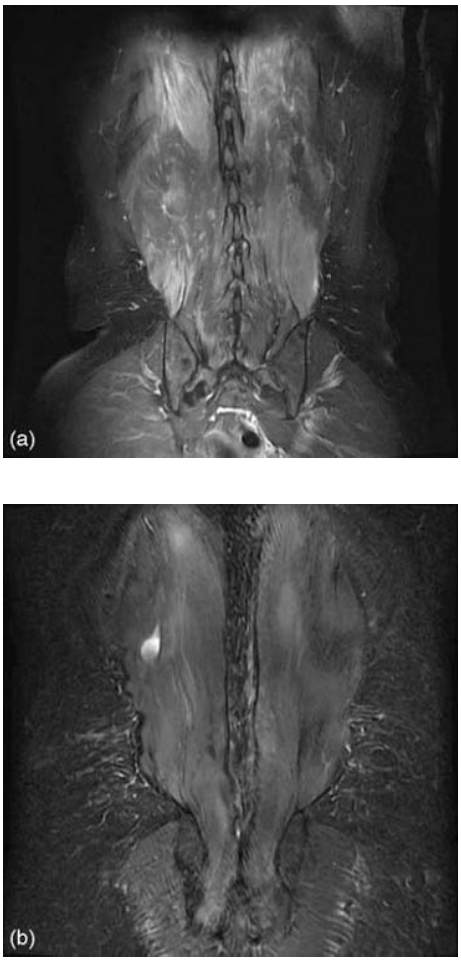

Figure 2 MRI of the erector trunci. (a) Fast T1 spin echo coronal section with fat suppression and after contrast medium injection. Heterogeneous gadolinium enhancement and patchy hyperintensities of the posterior bilateral paraspinal muscles, (b) Fast T2 spin echo coronal section with fat suppression. Same findings, plus swelling of the muscles and right-sided liquid necrosis zone. Reproduced from Diederich NJ, Goebel HH, Dooms G, et al. (2006) Camptocormia associated with focal myositis in multiple-system atrophy. *Movement Disorders* 21: 390–394, with permission from ● ● ●.

Deep Brain Stimulation

In the presence of axial dystonia, bilateral stimulation of the globus pallidum internum or the nucleus subthalamicus has been reported to produce persistent alleviation of CC in a few patients. However, there has been no systematic study, and publication bias is possible.

Botulinum Toxin (BT)

In one study, four out of nine patients receiving BT injections in the rectus abdominus showed notable improvement of the CC, while in another study with BT injections in the iliopsoas muscle, performed under ultrasound guidance, there was no beneficial effect

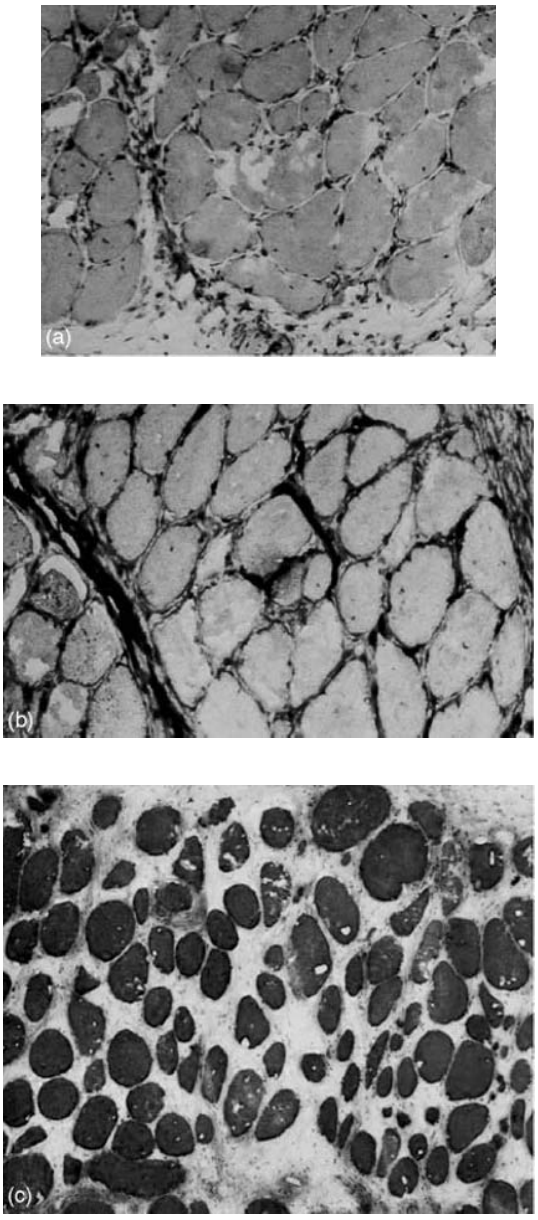

Figure 3 Biopsy results. (a) Numerous T lymphocytes among muscle fibers. Immunohistochemistry. Magnification: 465×. (b) Partial expression of the major histocompatibility complex I on numerous muscle fibers. Immunohistochemistry. Magnification: 450×. (c) Considerable variation in muscle fiber diameters with atrophic and hypertrophic fibers, indicating a myopathic spectrum. Modified Gomori trichrome stain. Magnification: 400×. Reproduced from Diederich NJ, Goebel HH, Dooms G, et al. (2006) Camptocormia associated with focal myositis in multiple-system atrophy. *Movement Disorders* 21: 390–394, with permission from ● ● ●.

Immunomodulation

Corticosteroids, applied in patients with myositic changes, occasionally and temporarily relieve the forward flexion and produce some pain relief. In rare cases, immunoglobulins and cyclosporine have produced the same effect.

Physical Therapy

Pardessus and coworkers have published a retrospective study on the use of flexible leather corsets (LC) in patients with CC of various origins. Prescribed in 27 patients, LC was used by 20 patients, and 19 answered a questionnaire after a mean treatment time of 33 months. Three quarters of these patients responded positively to five of the seven functional areas assessed and two-thirds wore the LC at least 9 h a day.

Prognosis

The prognosis is poor, with CC being mostly progressive and patients ending up in a crippling condition and wheelchair-bound. In some patients, a plateau phase can be maintained with constant physiotherapy.

See also: Dystonia; Dystonia, Secondary; Multiple System Atrophy; Parkinson's Disease: Definition, Diagnosis, and Management; Pisa Syndrome.

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Cannabinoids

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Glossary

Cannabinoid – A compound that is structurally related to compounds derived from the *Cannabis sativa* plant.
Inverse agonist – A compound that binds to a receptor but reverses the constituent activity of the receptor.
Long term depression – Synaptic plasticity resulting in the release of endocannabinoids and long-lasting inhibition of neurotransmitter release.
Psychoactive – Having properties that induce psychotic symptoms such as altered perceptions, hallucinations, and delusions.

Definitions

Cannabinoids are C_{21}compounds that are present in *Cannabis sativa* as well as structurally related to the main psychoactive component, delta-9-tetrahydrocannabinol (Δ^9-THC).

History

Medicinal properties of the exogenous cannabinoid *C. sativa* (marijuana) have been known for millennia. The proposed uses included antinausea, pain control, muscle spasms, and epileptic seizures. Until recently, however, most uses were generally unsubstantiated, and there was a lack of scientific rationale or clinical trial evidence to support these claims. In addition, concerns regarding cognitive and psychotropic effects of cannabinoids have generally limited clinical development of these drugs. *C. sativa* is made up of over 60 naturally occurring cannabinoids. The main psychoactive component is Δ^9-THC. Several other components have been identified, and they include cannabidiol and cannabinol. Following the discovery of these components, several closely related cannabinoid drugs were synthesized (**Table 1**).

Cannabinomimetic Effects

Acute effects of cannabinoids in human may include euphoria, relaxation, perceptual alterations, time distortion, and intensive sensory experiences, as well as impaired short-term memory, motor skills, and reaction times. In animal studies, cannabinoids produce four classical cannabinomimetic effects including antinociception (analgesia) without respiratory suppression: reduced spontaneous activity, catalepsy, and hypothermia. The effect on motor activity depends on the dose of agent; thus low doses will induce hyperactivity but higher doses, catalepsy. These behavioral properties have now been confirmed using cannabinoid receptor knockout mice models.

Cannabinoid Receptors

The biological effects of cannabinoids are now known to be mediated by two cannabinoid receptors, CB_1 (cloned in 1990) and CB_2 (cloned in 1993) (**Table 2**). Cannabinoid receptors are members of the G-protein-coupled receptor superfamily and inhibit Gi/o resulting in inhibition of adenylyl cyclase. In addition, CB_1 receptors activate potassium and N-type and P/Q-type calcium channels. The cannabinoid system is unusual in that despite the wide distribution of cannabinoid receptors, to date; only two types of receptors are present. Thus, all actions of cannabinoids are mediated through these two receptors, mainly the CB_1 receptor, and as such, therapeutic potential for cannabinoid agonists is potentially limited by unwanted actions and side effects.

Table 1 Clinically available cannabinoid drugs

Name of drug	*Type of cannabinoid*	*Licensed indication*
Nabilone (Cesamet ®)	Mixture of Δ^9-THC, cannabinol, cannabidiol, and other cannabinoids	Treatment of chemotherapy-induced nausea and vomiting that has not responded to conventional antiemetics. Treatment of anorexia and weight loss in patients with AIDS
Dronabinol (Marinol®)	Δ^9-THC	Treatment of severe nausea and vomiting with chemotherapy that has not responded to conventional antiemetics and AIDS-related anorexia
Sativex®	Buccal spray of *cannabis sativa* extract containing Δ^9-THC (2.7 mg) and cannabidiol (2.5 mg)	Symptomatic relief of neuropathic pain and adjunctive analgesic treatment in advanced cancer for pain control despite opioid therapy Approved in Canada as adjunctive treatment for the symptomatic relief of neuropathic pain in multiple sclerosis
Cannador®	Oral cannabis extract of *cannabis sativa* containing Δ^9 THC (2.5 mg) and cannabidiol (1.25 mg)	
Rimonabant	CB_1 receptor antagonist	Treatment of obesity (licensed in European union)

Table 2 Relative affinity of exogenous and endogenous cannabinoids at cannabinoid CB_1 and cannabinoid CB_2 receptors

Cannabinoid	*Name*	*CB_1*	*CB_2*
Exogenous cannabinoids	Δ^9-THC	++	+
	Δ^8-THC	++	+
	Cannabinol	(+)	(+)
	Cannabidiol	0	0
Synthetic cannabinoids	11-hydroxy-Δ^8-THC (HU 210)	+++	+++
	CP55,940	+++	+++
	WIN55,212-2	+++	+++
	Arachindonyl-2-chloroethylamide (ACEA)	+++	0
	Arachindonylcyclopropylamide (ACPA)	+++	(+)
	Methandamide	++	+
	O-1812	+++	0
	AM 1241	+	+++
	JWH 133	+	+++
	HU 308	0	+++
	GW 405833	(+)	+++
	JWH 015	(+)	++
Endocannabinoids	Anandamide	+	(+)
	2-AG	+	+
	Noladin ether	++	0

0 = no affinity; (+) = very low; + = low, ++ = moderate, +++ = high affinity for the receptor.
Δ^9-THC = Δ^9-tetrahydrocannabinol; Δ^8-THC = Δ^8-tetrahydrocannabinol.
Source: Pertwee R (2005) In: Pertwee R (ed.) *Cannabinoids. Handbook of Experimental Pharmacology*, vol. 168. Heidelberg, Germany: Springer-Verlag.

Cannabinoid CB1 Receptors

CB_1 receptors are widely distributed in both the peripheral and central nervous system. Cannabinomimetic effects are related to CB_1 receptors within particular brain regions.

Memory

CB_1 receptors are located in the hippocampus, particularly in CA3 field of Ammon's horn and the molecular layer of the dendate gyrus.

Analgesia

CB_1 receptors are located on the peripheral terminals of primary sensory neurons and in the dorsal horn of the spinal cord, in addition to the central sites that may mediate pain including amygdala, thalamus, superior colliculus, and rostral ventromedial medulla.

Thermoregulation

CB_1 receptors are located within the hypothalamus.

Antiemetic

CB_1 receptors are located in the dorsal vagal complex, consisting of the area postrema (the chemoreceptor trigger zone for emetic reflexes), nucleus of the solitary tract, and the dorsal motor nucleus of the vagus in the brainstem.

Motor functions

The basal ganglia have one of the highest concentrations of CB_1 receptors in brain. CB_1 receptors are located on the presynaptic terminals of the GABAergic striatopallidal pathways in the globus pallidus (GP) (both internal (GPi) and external (GPe) segments) and the substantia nigra pars reticulata (SNpr). In addition, CB_1 receptors are found on the corticostriatal glutamatergic projection neurons as well as paravalbumin positive interneurons of the striatum. In the cerebellum, CB_1 receptors are located in the molecular layer, which contains the fibers and dendritic processes from Purkinje cells.

Other locations

CB_1 receptors are also found in the periphery in vasculature, heart, bladder, and small intestine and vas deferens.

Several synthetic cannabinoids are now available (**Table 1** and **Table 2**).

Cannabinoid CB_2 Receptor

The CB_2 receptor is principally located in the immune system both in the brain and periphery. The receptor was initially derived from a human promyelolocytic leukaemia (HL60) cell line and is found in high amounts in B-cells and natural killer cells. In addition, CB_2 receptors are located in microglia and blood vessels. Until recently, CB_2 receptors were not thought to be located in neuronal tissue, but they have been demonstrated in the brainstem as well as in the hippocampus and cerebellum. The function of CB_2 receptors in the brain is currently unknown, but a role in neuroprotective mechanisms has been implied. The CB_2 receptor shares 68% homology with the CB_1 receptor.

Non-CB Receptors that Mediate Cannabinomimetic Effects

Several actions of cannabinoids appear to be mediated by non-CB_1 or CB_2 receptors. Thus, vasodilatory and some analgesic properties of cannabinoids appear to be due to an action at capsaicin (vanilloid VR-1 or TRPV1) receptors. Other targets of cannabinoids include N-type and T-type calcium channels, sodium channels, voltage gated potassium channels, nicotinic receptors, glycine receptors, and 5-HT_2 and 5-HT_3 receptors.

Endocannabinoid System

The discovery of the cannabinoid receptors led to the discovery of the endogenous ligands called endocannabinoids for these receptors. Several endocannabinoids have now been described, but arachydonoyl ethanolamide (anandamide) and 2-arachidonylglycerol (2-AG) are the best characterized. These are ecosanoid phospholipids produced on receptor-mediated demand in response to elevated intracellular calcium and immediately released. This is in contrast to the classical neurotransmitters that are synthesized and stored in vesicles in presynaptic terminals. Anandamide is produced from hydrolysis of membrane phosphatidylethanolamine, and is released and removed by active reuptake, via an anandamide transporter and hydrolyzed by fatty acid aminohydrolase (FAAH). 2-AG is produced from sequential hydrolysis of phosphatidylinositol (4,5)-biphosphate, and the effects are terminated by active uptake into cells and hydrolysis.

Function of Endocannabinoids

The function of the endocannabinoids system is to modulate neurotransmission. Thus, depolarization of the postsynaptic membrane results in release of the endocannabinoids that diffuse to the presynaptic membrane and inhibit GABA and glutamate activity. In addition, endocannabinoids function as retrograde messengers and are implicated in synaptic plasticity in the hippocampus, thus potentially having a role in memory and learning. Within the striatum, endocannabinoids also act as retrograde messengers and mediate long term depression by interacting with dopamine D_2 receptors in the indirect striatopallidal pathway.

Cannabinoid Receptor Antagonists

All cannabinoid receptor antagonists currently available are competitive antagonists at CB_1 or CB_2 receptors of endogenously released endocannabinoids. However, these compounds also have inverse agonist properties by negative, possibly allosteric, modulation of the constitutive activity of CB receptors and by shifting the receptor from a constitutively active to an inactive state. In addition, these compounds may also block non-CB-mediated effects, for example antagonism of endogenously released adenosine at A_1 receptors.

Cannabinoids in Movement Disorders

The potential role of the endocannabinoid system in movement disorders stems from the high concentration of CB_1 receptors found within the basal ganglia as well as elevated levels of endocannabinoids. To date, there is no consensus on changes in CB_1 receptors in Parkinson's disease (PD). Investigating the localization of cannabinoid receptors has been difficult due to the highly lipophilic nature of their ligands and has been restricted to in vitro studies with inconsistent results. A recent cannabinoid ligand [^{18}F]MK-9470 has been developed for in vivo use in PET imaging that will potentially enhance the understanding of these receptors in disease states.

Endocannabinoid System in Parkinson Disease

FAAH inhibitors

Increased endocannabinoids are found in untreated PD patients (in CSF) and in the striatum of animal models of untreated PD. This may be a compensatory effect for the loss of dopamine. Stimulation of CB_1 receptors decreases corticostriatal glutamatergic transmission, and enhanced

endocannabinoids may thus be an attempt to decrease the enhanced glutamate input in PD. Further enhancing endocannabinoids may therefore result in the alleviation of the PD motor symptoms. Inhibition of FAAH, prevents breakdown of endocannabinoids and reduces excitatory striatal glutamate activity in 6-OHDA lesioned rats. In addition, in PD, overactivity of the indirect striatopallidal pathway may be in part due to loss of long-term depression (LTD), an effect mediated by both dopamine D_2 receptors and endocannabinoids. Thus, combined treatment of 6-OHDA-lesioned rat or reserpine-lesioned rat models of PD with a dopamine D_2 agonist and a selective FAAH inhibitor URB597 reversed parkinsonism. To date, no studies using FAAH inhibitors have been reported in primate models of PD and none are clinically available.

CB_1 Cannabinoid receptor antagonists

Alternatively, enhanced endocannabinoids within other regions of the basal ganglia may be mediating parkinsonian symptoms. Thus, in reserpine treated rats and untreated MPTP-lesioned primates, increased levels of endocannabinoids in the GPe are found. These endocannabinoids, by stimulating CB_1 receptors within the GPe, and reducing GABA reuptake may lead to reduced activity of the GPe, a key abnormality in PD. Thus, CB_1 antagonists may have an antiparkinsonian action. The CB_1 selective antagonist, rimonabant, had a mild effect on reversal of motor symptoms in the 6-OHDA-lesioned rat and MPTP-lesioned primate, while another CB_1 antagonist carboxylic acid amide benzenesulfonate (CE) had no antiparkinsonian action alone but enhanced the antiparkinsonian actions of levodopa in the MPTP-lesioned primate. In clinical studies, in four advanced PD patients, there was no effect on PD motor symptoms using rimonabant (20 mg d^{-1}) compared to placebo as add-on therapy, but no adverse effects were noticed. To date, no further clinical studies have been performed.

Endocannabinoid System in Levodopa-Induced Dyskinesia (LID)

CB1 receptor agonists

In PD patients following long term treatment with levodopa, involuntary movements (dyskinesia) may develop. The neural mechanism underlying levodopa-induced dyskinesia (LID) involves overactive corticostriatal glutamate activity; CB_1 receptor stimulation reduces glutamate release from corticostriatal inputs in the striatum, and thus, CB_1 receptor agonists may be useful in reducing LID. An alternative site of action may be via stimulation of CB_1 receptors on the striatopallidal terminals of the indirect GABAergic pathway which reduces GABA reuptake and thus reduces the firing of the GPe. In preclinical studies, the CB_1 agonist WIN55,212 reduced LID in the reserpine and 6-OHDA-lesioned rat. An alternative action of cannabinoids may be on TRPV1 (vanilloid) receptors and the TRPV1 agonist, capsaicin, reduces levodopa-induced hyperkinesia in the reserpine treated rat. In the MPTP-lesioned marmoset model of LID, nabilone reduced dyskinesia without affecting the antiparkinsonian action of levodopa. In clinical studies, nabilone was shown to have a mild effect on reducing dyskinesia in a Phase IIa trial using a cross-over acute challenge study design in seven PD patients. There was no effect on parkinsonian disability, and all patients had a nonsignificant fall in systolic blood pressure and experienced side effects of mild sedation and dizziness. Another Phase II randomized controlled trial (RCT) study using Cannador®, showed no significant effect on LID or any significant adverse effects in 19 PD patients when treated over 4 weeks. The variable effects may relate to the different cannabinoid agents used as well as to the differences in trial design. To date, no further studies have been performed in PD patients to assess the effects of cannabinoids on LID.

CB_1 receptor antagonists

Cannabinoid antagonists have also been proposed to reduce dyskinesia as increased levels of anandamide are found in the striatum in MPTP-primates after long term levodopa. CB_1 receptor stimulation on corticostriatal inputs may reduce overactive glutamate transmission, a key abnormality underlying dyskinesia. Preclinical studies in rodents and MPTP-lesioned primates have suggested that the CB_1 cannabinoid receptor antagonist rimonabant and another CB_1 receptor antagonist AVE1625 may reduce dyskinesia, without affecting parkinsonian disability and PD activity. As discussed, rimonabant has been assessed in a single study and also had no significant effect on dyskinesia.

Endocannabinoids in Dystonia

The neural mechanism underlying idiopathic dystonia is less well-defined but probably involves reduced output from the GPi and SNpr, an effect that may be driven by increased activity of the GPe. Animal models of the phenomenology of idiopathic dystonia are limited, but a genetic model of paroxysmal dystonia has been used for pharmacological investigation into potential therapies for dystonia. In this model, the CB_1 agonist WIN55,212 reduced dystonia, an effect blocked by the CB_1 antagonist rimonanbant. Several case reports have suggested potential for cannabinoids in focal dystonia. An RCT of acute treatment with nabilone in idiopathic generalized dystonia failed to show benefit (Fox et al., 2002). Further investigation of cannabinoids in dystonia is ongoing.

See also: Acetylcholine; Basal Ganglia, Functional Organization; GABA and Movement Disorders.

Further Reading

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Relevant Websites

www.clinicaltrials.org

CAPIT, CAPSIT

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Introduction

The core evaluation program for intracerebral transplantation, the CAPIT, was created in response to the plethora of evaluation tests various groups within the neural tissue transplantation field presented at a Conference in Sweden in 1990. When trying to deduce any communality of the effects of the procedures, it became clear to all the participants at the meeting that a common evaluation program was essential, and a committee was appointed with members from various ongoing and planned transplantation programs. The CAPIT aimed at defining a minimal set of criteria for how a patient should be evaluated in an experimental transplantation study and defined diagnostic criteria, inclusions, exclusions, and the many issues around when and how to observe and evaluate patients. The CAPIT quickly became a standard for how to perform neurosurgical studies for Parkinson's disease in general, but it also soon became clear that what was sought to be a minimal common program was regarded as too cumbersome to manage larger patients groups. As some of the recommendations were clearly limited to the transplantation field and objections to some items were raised in the scientific literature, a new version was worked on by a working group within a EU-sponsored scientific project. The aim of the new version was to be applicable also to other neurosurgical techniques such as deep brain stimulation, DBS, and hence the new acronym CAPSIT, Core Assessment for Surgical Interventions and Transplantation. It was also added a tail – PD for Parkinson's disease, as a parallel EU-sponsored project, that worked toward the same end for transplantations and interventions in Huntington's Disease, resulting in a CAPSIT-HD. The original members of the CAPIT committee, along with the critics, were consulted prior to the completion of the CAPSIT-PD, and all have endorsed the newer version along with the EU-project participants. The CAPSIT should be regarded as the 2nd generation generic evaluation program.

The Core Evaluation and Suggested Protocol

The CAPIT/CAPSIT protocols aim at defining a minimal common evaluation program, allowing for comparisons between studies. It sets the criteria for how and when patients are to be assessed and is meant to be "inclusive," that is, allowing for the exchange of various items tested, bearing in mind that evaluation protocols also evolve

but that investigators should keep in mind the ability to compare back in time keeping also the "old versions" around for this purpose. The protocol is meant to be open in order to allow for specific study designs as needed (see **Figures 1** and **2**). There is a list of suggested terms and definitions that is very helpful and also a time chart.

Core Inclusion Criteria

Clinical Diagnostic Criteria

To secure as much as possible the diagnosis of idiopathic PD for the patients selected for surgery, a disease duration of a minimum of 5 years should be considered. The use of

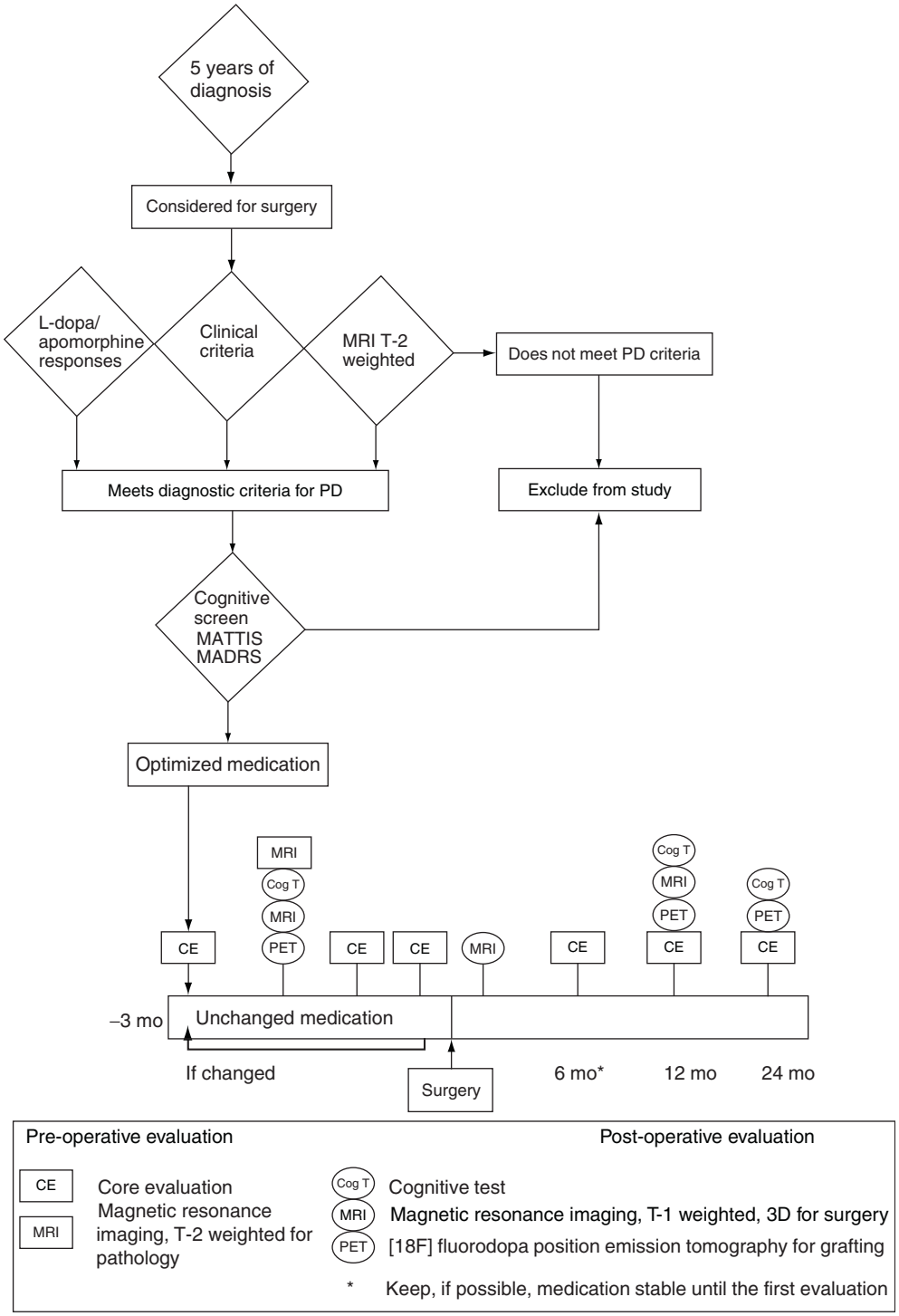

Figure 1 Schematic outline and proposed flow chart of the Core Assessment Program for Surgical Interventional Therapies. The time points for the different items in the program are indicated by symbols.

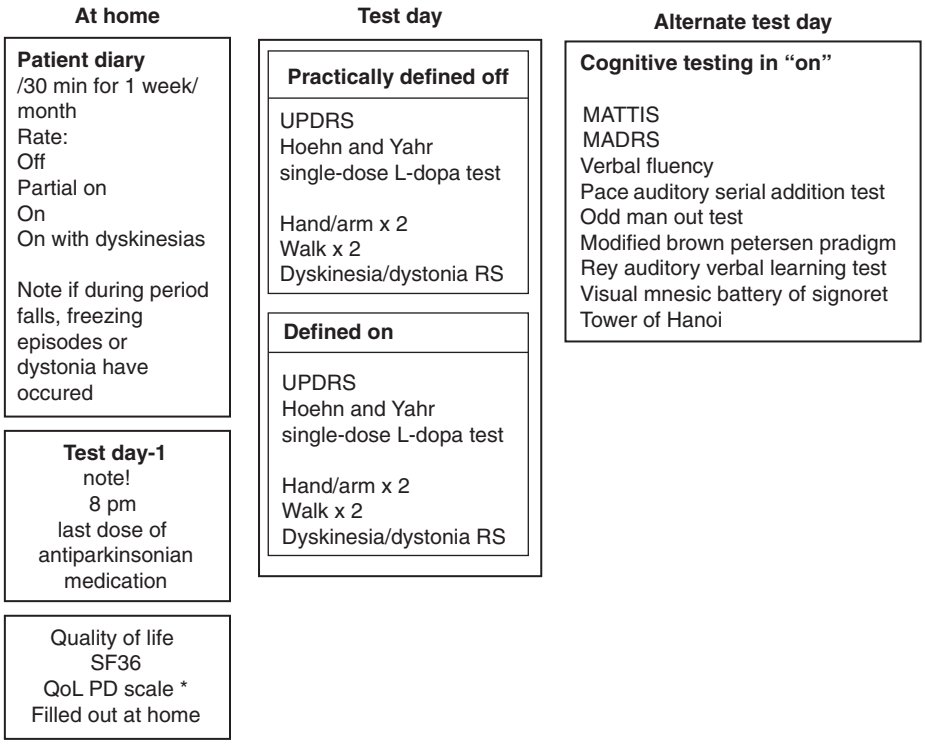

Figure 2 Outline of the contents of the Core Evaluation and a suggestion of the cognitive evaluation.

published consensus guidelines for PD with dementia, Multiple System Atrophy (MSA), dementia with Lewy bodies, and Progresive Supranuclear Palsy (PSP) is recommended to exclude patients with atypical parkinsonism.

Dopaminergic Responsiveness

The term dopaminergic responsiveness was intentionally chosen in place of L-dopa responsiveness in order to allow selection of patients treated and evaluated with dopamine agonists only. The dopaminergic responsiveness should be confirmed by a pharmacological test using L-dopa, or apomorphine for patients who cannot take, tolerate, or be correctly evaluated using L-dopa at the time of the selection for surgery. The test should induce at least a 33% decrease of the UPDRS part III score.

Cognitive and Behavioral Criteria

Two levels of evaluation are defined: the first level consists of a screening process in order to exclude patients with cognitive deterioration and/or having severe depression, with predetermined cutoff-scores defined and/or having major behavioral disorder.

The second level consists of standardized cognitive assessments in order to evaluate the impact of surgery on cognitive functions.

Definitions

Defined-off=the off condition observed after a patient has received no antiparkinsonian medication for 12 h.

Defined-on=the condition during the pharmacological test; the patient and the investigator both agree that the functional benefits are the most beneficial.

Core Methodology

Clinical Rating Scales

Unified Parkinson's Disease Rating Scale version (3.0) as a primary scale for the motor score (Part III) for evaluating dopaminergic responsiveness evaluation, and Hoehn and Yahr Staging are recommend.

Quality of Life Scale

The use of the SF 36 scale is highly recommended to assess the patient's quality of life. In addition, a PD-specific QoL scale is strongly encouraged. The patient should complete the scale forms before starting the preoperative evaluation, and thereafter, at the time of subsequent assessments, that is, 6 months, 1 and 2 years, and then once a year if the evaluation is continued.

Dyskinesia/Dystonia Rating Scale

There are different patterns of hyperkinesias, and the amount of dyskinesias varies over the day. There is no simple way of quantifying dyskinesias. Ratings are performed at least once in conjunction with the Core Evaluation with the patient in "defined-Off" and in "defined-On" conditions, as defined previously. For quantification, the patient is made to sit in a chair and observed at rest. The patient is then asked to perform the tests in the UPDRS motor part (III), that is, speaking, hand grips, finger taps, hand pronation/supination, leg ability test, raising from chair, and the timed tests, the hand–arm and the walking test as defined in the following section. The highest score of the dyskinesias observed during these tasks is recorded.

Self-Reporting

The use of a diary (over the day, waking hours, 30 min fractions) divided into four conditions is recommended: complete Off, partial Off, complete On, On with dyskinesias. The committee recommends that the patient perform the self-reporting as regular as possible at 1 week per month during the 3 preoperative months and then for 12 or, if possible, 24 months after surgery. Additional but optional items during each week of self-reporting are number of falls, number of freezing episodes, number of off episodes with dystonia.

Timed-Tests

Two timed tests are recommended for the motor evaluation:

- A hand–arm movement between two points 30 cm apart, for example, using a simple device for a defined fixed time (20 s). Each hand is tested twice and the mean time is reported.
- A walking-test, with the patient walking as fast as possible 7 m back and forth, including turning. The time and the number of steps are recorded. As an option, if freezing episodes occur, these can be noted.

These tests should be performed during the drug challenge in the defined-Off and defined-On conditions. In the case of a test failure, an a priori defined maximal value should be given.

Pharmacological Testing

A drug challenge using the patient's regular morning dose of L-dopa or apomorphine should be performed after a 12 h washout of antiparkinsonian drugs. If a patient fails to tolerate the washout, one should determine the longest tolerable washout and to keep this period for all subsequent assessments. The evaluations should include UPDRS and HY staging, timed-tests, and dyskinesia/dystonia rating. The dose (and the drug) used for the pharmacological test should be kept unchanged before and after surgery and should be the dose used to define the dopaminergic responsiveness. Other parameters of the test should be consistent, that is, patient fasted from midnight, gastrointestinal protection prior to apomorphine test, test started at the same time in the day.

Dopaminergic response parameters should be obtained for the defined-Off and the defined-On conditions respectively. Principally, DBS might be assessed in different conditions depending on the activity of the device (on or off) and the administration of the drug (with or without). It is recommended to perform the test in the following two conditions:

- device on, off medication;
- device on, on medication

In all cases, the stimulator should be maintained on during the washout period.

Timing and Numbers of Evaluations

The preoperative period should be at least 3 months and include three core evaluations.
The postoperative period should have three major end-points: 6 months, 1 year, and 2 years.
The assessment must be repeated on a yearly-basis if the evaluation is continued.

Medication Adjustment

The relatively short preoperative run-in period should not constitute any hindrance for a stable medication during this period. It is stressed that if the medication is changed at any time during the preoperative period, the latter should be restarted. It was further suggested that an assessment of the degree of medication changes at the last end-point of the evaluation (2 years) should be made.

Preoperative Period

During the 3 month preoperative period, medication should be kept unchanged. If not, a new evaluation period of 3 months should be started again.

Postoperative Period

For the postoperative period, the committee recommends to keep medication unchanged until the first end-point (6 months), provided there are no alteration of the clinical state and no negative interaction with the surgical procedure. The evaluation of a therapeutic end-point at 2 years (i.e., the % decrease of L-dopa and of other antiparkinsonian drugs) is recommended.

Imaging Criteria

Morphological Imaging

Preoperative period

MRI imaging (0–3 months prior to surgery) using T2-weighted coronal slices centered on the basal ganglia, and T1-weighted 3D images are strongly recommended. T2-weighted abnormalities should lead to exclusion of the patient from the study.

Postoperative period

MRI should be performed before stimulator implantation in deep brain stimulation surgery. For lesioning surgery, MRI might be performed in the first postoperative week, but an additional MRI 1 year after surgery is also recommended. The use of T1-weighted 3D images is again recommended.

In addition, the coordinates of the lesion/electrode position should be calculated. The use of Talairach's atlas for calculation of coordinates is recommended.

Functional Imaging

The use of PET in the evaluation of grafting procedure of parkinsonian patients has proved useful for the evaluation of survival and function of the grafted neuronal cells. If available, PET studies are recommended for neuronal graft procedures. [18F] Fluorodopa PET-scanning should be performed before and 1 and 2 years after surgery. The patients should be scanned ~10–12 hours after drug withdrawal (defined off). Carbidopa (100–150 mg) or benserazide (50 mg) should be given one hour before injection of the tracer. Measures of brain metabolism with [18F] Fluoro-deoxyglucose, or motor activation studies using H2[15O]-cerebral blood flow measurements, have evidenced functional changes.

Cognitive and Behavioral Assessment

The goal of the CAPSIT evaluation was to add neuropsychological inclusion/exclusion criteria as well as a test battery for pre- and postoperative assessments. Pre- and postoperative cognitive evaluations should incorporate tests sensitive to frontal lobe function in order to detect possible alterations by the surgical manipulations and should be selected according to the following considerations:

(a) the tests need to be especially sensitive for executive tasks, including working memory, episodic memory tasks, and procedural memory tasks;
(b) retest effect should be minimal or parallel forms must be available;
(c) the tests have to be sensitive enough in order to assess the preoperative patient status and to detect changes induced by the surgical procedure (positive or negative effect);
(d) completion of the test battery should not require more than 90 min.

To reduce psychiatric abnormalities that could interfere with the neurological assessment, patients with major behavioral disorders or severe psychiatric illness should be excluded. A psychiatric evaluation including the Minnesota Multiphasic Personality Inventory (MMPI) and the Montgomery and Åsberg depression rating scale (MADRS) in order to exclude patients with a high risk of psychiatric complications after surgery.

Exclusion–Inclusion Criteria

Mattis Dementia rating scale (MDRS) with a suggested cutoff score=130 or 120. Montgomery and Åsberg depression rating scale (MADRS); suggested cutoff score: 7–19. Minnesota Multiphasic Personality Inventory (MMPI).

Preoperative Evaluations and Follow-up

General and behavioral evaluation: Mattis Dementia rating scale and the Montgomery and Åsberg depression rating scale (MADRS).

Executive functions: Verbal fluency: letters F, A, and S (set maintenance with external cue). Paced Auditory Serial Addition Test (shifting ability). Odd-Man-Out Test (set maintenance with internal cue). Modified Brown Peterson Paradigm (MBPP: working memory).

Explicit memory: Rey auditory verbal learning test (RAVLT) and Visual mnesic battery of Signoret (BEM 144, only learning phase of graphic signs).

Procedural memory: Short Version of Tower of Hanoi.

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See also: Deep Brain stimulation; Levodopa; Parkinson's Disease: Definition, Diagnosis, and Management; Surgery for Movement Disorders, Overview, Including History; Transplantation.

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Carbon Monoxide Poisoning

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Glossary

Carbon monoxide – A colorless, odorless, tasteless yet highly toxic gas, primarily produced by a partial combustion of carbon-containing compounds. Its molecule consists of one carbon atom covalently bonded to one oxygen atom.

Carbon monoxide poisoning – A leading cause of fatal poisoning worldwide, primarily caused by the inhalation of carbon monoxide gas. It mainly affects the brain and the heart.

Hemoglobin – The iron-containing, oxygen-transport metalloprotein in the red blood cells of vertebrates.

Hyperbaric oxygen therapy – The medical use of oxygen at a higher than atmospheric pressure.

Hypoxia – A pathological condition in which the body as a whole or region of the body is deprived of adequate oxygen supply.

Definition and History

Carbon monoxide (CO) is a colorless, tasteless, odorless, nonirritating but highly toxic gas, primarily produced by an incomplete combustion of hydrocarbons. CO was first described by the Spanish doctor Amaldus de Villa Nova in the eleventh century, and its toxic properties were first investigated by the French physiologist Claude Bernard around 1846.

Epidemiology/Pathophysiology

CO poisoning is a leading cause of poisoning mortality in the world and may account for more than half of all fatal poisonings. CO binds rapidly to hemoglobin with an affinity more than 200 times that of oxygen, leading to the formation of carboxyhemoglobin (COHb) that significantly decreases the oxygen-carrying capacity of the blood, causing tissue hypoxia. Reperfusion injury can be caused by CO-induced tissue hypoxia. Hyperoxygenation promotes the production of partially reduced oxygen species, which in turn can oxidize essential proteins and nucleic acids, resulting in typical reperfusion injury to the central nervous system (CNS). CO exposure also causes lipid peroxygenation producing demyelination of CNS lipids.

Diagnosis

The clinical symptoms and signs of CO poisoning are often nonspecific and may mimic various common disorders. Mild poisoning may cause flu-like symptoms, while severe poisoning can cause coma or even death. Thus, CO poisoning is often difficult to detect unless the attending physician has a high level of suspicion. CO poisoning can be suspected when more than one person or pet is affected, particularly if there are combustion appliances or a fireplace, or an environment with occupational exposure. Diagnosis of CO poisoning usually depends on a patient's serum COHb level. A nonsmoker would be expected to have a baseline level of less than 3% from the endogenous production of CO and background environmental exposure, whereas smokers may have levels of up to 10%, particularly immediately after smoking. Thus,

CO poisoning should be suspected if someone shows serum COHb higher than these levels. Relatively low COHb levels, between 10 and 20%, usually produce mild symptoms of CO poisoning such as nausea and headache, while levels greater than 60–70% are highly fatal. The half-life of serum COHb is about 4–5 h; the measurement of serum COHb level should be performed as soon as possible, and the interval between CO exposure and serum testing should be taken into account for the diagnosis of CO poisoning based on serum COHb levels.

Acute Intoxication

The brain and the heart, because of their high metabolic rates, are the organs most susceptible to CO toxicity. The clinical symptoms and signs associated with acute CO poisoning are listed in **Table 1**. Early neurologic manifestations include headache, dizziness, and nausea. More exposure may cause altered mental status, confusion, seizure, and coma. Early cardiovascular effects of CO poisoning present as tachycardia and tachypnea in response to hypoxia. Increasing exposure may result in hypotension, dysrhythmia, ischemia, infarction, and rarely cardiac arrest. CO poisoning also exacerbates the underlying cardiovascular diseases; even low-level exposure may produce dysrhythmia in patients with coronary artery disease. CO poisoning may also cause rhabdomyolysis as a direct toxic effect of CO on skeletal muscles and results in acute renal failure.

Table 1 Clinical signs and symptoms of CO poisoning

Acute poisoning	*Delayed sequele*
Mild	*Neurological deficits*
Headache	Parkinsonism/other motor disturbances
Dizziness	Ataxia/gait disturbance
Nausea/vomiting	Urinary and fecal incontinence
	Cortical blindness
	Seizure
	Mutism
Moderate	*Psychiatric deficits*
Confusion/memory loss	Memory loss
Irritability/disorientation	Emotional lability
Incoordination/weakness	Confusion/disorientation
Dyspnea/tachypnea	Psychosis/hallucinations
Chest pain/tachycardia	
Severe	
Hypotension/syncope	
Convulsions/seizures	
Myocardial ischemia/ cardiac arrest	
Coma	
Death	

Delayed Sequelae

The effects of CO poisoning are not confined to the acute period after exposure. There are two types of chronic sequelae of CO poisoning: the persistently progressive type and the delayed relapsing type. The persistently progressive type is diagnosed when the patient's neuropsychiatric deficits are progressively deteriorating without any sign of recovery from acute intoxication, while the delayed relapsing type, often referred to as 'delayed neurological sequelae (DNS),' is diagnosed when the patient apparently recovers from acute intoxication and then develops behavioral and neurological deterioration after a latency period of 2–40 days, the so-called 'lucid interval.' DNS may manifest itself as memory loss, confusion, ataxia, seizures, urinary and fecal incontinence, disorientation, hallucinations, parkinsonism, mutism, psychosis, and gait or other motor disturbances (**Table 1**). DNS occurs in about 10% of hospitalized patients with acute CO poisoning. The risk of developing DNS is particularly high in patients with more severe initial deficits such as loss of consciousness and/or older age. Once DNS develops, about 70% of the patients may recover within 1 year, while the others relentlessly deteriorate to become bedridden or even die. The mechanisms underlying DNS remain to be elucidated, but recent reports suggest that diffuse white matter changes, either demyelination or axonal damage, are mainly responsible for DNS.

Pathology

Pathological findings in the brains of CO-poisoned patients include white matter changes such as demyelination and axonal damage and necrosis of the globus pallidus. Accordingly, brain MRI often shows diffuse white matter hyperintensities and hemorrhagic necroses of the pallidum (**Figure 1**). Although the patients with DNS often have accompanying symptoms of severe parkinsonism, pathological studies rarely show substantia nigra damage. Dopamine transporter imaging of DNS patients has demonstrated a significant dopamine neuronal loss, but the degree of loss is much less than that observed in patients with Parkinson's disease. Recent reports suggest that white matter changes are more likely related to DNS than either pallidal necrosis or dopamine neuronal loss. Reversible DNS cases are usually thought to be associated with pure demyelination, while those with progressive deterioration presumably have additional axon damage. Routine brain MRI cannot distinguish pure demyelination from axonal damage, but MR spectroscopy may help to determine the severity of white matter damage and decide the prognosis of DNS patients.

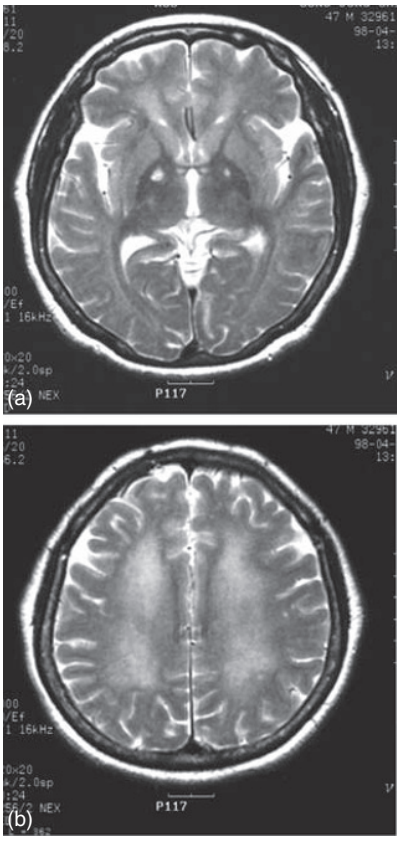

Figure 1 T2-weighted MRI obtained one month after CO poisoning in a patient shows (a) necroses of the bilateral globus pallidus and (b) diffuse high signal lesions in the white matter.

Management

Treatment of acute CO poisoning should begin with supplemental oxygen and aggressive supportive care that includes airway maintenance, blood pressure support, and cardiovascular stabilization. High-flow oxygen therapy helps in reducing damage from CO-induced hypoxia, as well as in promoting the elimination of CO from the body. Since the clinical signs and symptoms of CO poisoning are nonspecific, patients under suspicion of CO poisoning should be treated with oxygen inhalation immediately after blood is drawn for COHb measurements. Increasing the partial pressure of oxygen decreases the half-life of COHb: approximately 40–80 min with 100% oxygen under ambient pressure, and approximately 20 min with 100% oxygen at 2.5–3.0 atm absolute (ATA), also known as 'hyperbaric oxygen therapy' (HBOT). HBOT accelerates the dissociation of CO from hemoglobin and other heme-containing proteins such as cytochromes. However, animal experiments have demonstrated that HBOT does not prevent neuronal injury following CO poisoning and has the potential to increase oxidative damage because of increased production of free radicals. Randomized controlled trials, although they have failed to show consistent results, demonstrate that HBOT can promote recovery from acute CO poisoning and reduce the development of DNS better than oxygen under ambient pressure. Thus, HBOT may be indicated for patients of older age who present with severe CO poisoning.

See also: Dopamine.

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Caspases and Neuronal Cell Death

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Glossary

Amyotrophic lateral sclerosis (ALS) – Lou Gehrig's disease is caused by the death of motor neurons in the spinal cord resulting in progressive paralysis.
Apoptosis – A form of programmed cell death that is useful during development, to remove excess cells, but harmful when irreplaceable motor neurons are lost. It is characterized by DNA fragmentation, chromatin condensation, and membrane blebbing.
Caspase – Cysteine aspartic acid proteases digest and cleave other proteins, including other caspases, frequently inducing apoptosis.
Motor neuron – Large nerve cells predominantly populating the ventral horns of the spinal cord that communicate impulses to muscles.
Necrosis – Accidental cell death involving rapid cell lysis.
Parkinson's disease – A relatively common neurodegenerative condition leading to muscular rigidity and tremor.
Programmed cell death – Genetically dictated, active cell death requiring transcription and protein synthesis.
Transcription factor – An intracellular molecule that, as an early step in gene regulation, recognizes specific DNA sites and controls whether, and how often, messenger RNA is synthesized from particular genes.

Definition and History of Caspases

Apoptotic programmed cell death is a normal process in the developing central nervous system (CNS); however, it may also be induced by a variety of stimuli including toxins, pharmacologic agents, viral infections, and other biochemical upsets in a variety of disorders resulting in the loss of neurons and motor function. More than 50 genes have been identified as promoting apoptosis with more than one-fourth of these being proteases. The key proteases involved are termed caspases, for cysteine aspartic acid proteases, originally defined as members of the nematode, *Caenorhabditis elegans* cell death (CED-3) family of proteases by the Nobel Prize winning work of Sydney Brenner, Robert Horvitz, and John Sulston. Caspase-1 was originally identified as interleukin converting enzyme (ICE), and caspase-3 has been termed Yama (after the Hindu God of death), CPP32β, and apopain. Caspase-3 cleaves poly(ADP-ribose) polymerase (PARP), an enzyme involved in DNA maintenance.

Apoptosis was first used in a modern, cell biology context by Kerr, Wylie, and Currie in 1972. The term apoptosis is, of Greek origin, referring to dropping off of petals and leaves, and Hippocrates used the term medically in ~400 BC, followed by Galen in ~175 AD. In the 1800s, the process was described by Carl Vogt studying tadpoles and later by Walter Flemming. Various alternative programmed cell death mechanisms have also been reported, for example paraptosis, identified in 2000, has been observed in some instances and does not involve the same protease activations or apoptotic bodies. The other common form of cell death is necrosis which involves rapid lysis. Discriminating characteristics of apoptosis versus necrosis are listed in **Table 1**. After the first three papers in 1972, publications addressing apoptosis reached 100 in 1990, and these have since increased exponentially to over 19 000 in 2008.

The primary caspase mediated cell death mode, apoptosis, is a positive process during development, when vestigial organs and excess neurons are removed. Later, apoptosis is involved in the removal of harmful cells and regulation of the immune system. Dysregulation of apoptosis is harmful in certain disorders of the immune system, cancer, and neurodegenerative diseases. Caspase triggered cell death can be induced through starvation, hypoxia, viral infection, or stress. Signaling through death receptors, involving tumor necrosis factor receptors (TNFR) and tumor necrosis factor associated death domain proteins (TRADD, FADD) can lead to conversion of procaspase-8 to activated caspase-8 which in turn activates caspase-3 by removal of its N-terminal prodomain. Caspase-3 cleaves cell survival (repair) proteins in an irreversible process resulting in apoptotic bodies and cell death. Positive regulators of caspases include bax, bak, bid, and bad and negative regulators include bcl-2, bcl-xl, and bcl-W. These factors generally involve response mechanisms for cellular damage.

Caspase Functions

When caspase-3 is knocked out in mice, they do not survive longer than about 2 weeks. In these mice, there are obvious brain abnormalities including disorganization, duplicate

structures, and overall brain size 2–3 times larger than normal.

There are probably several hundred caspase substrates, and these include regulatory proteins (e.g., DNA fragmentation factor (DFF/ICAD), PKCδ), cytoskeletal proteins (Actin, Fodrin), nuclear proteins (PARP, 70 kD U1 small nuclear ribonucleoprotein (SNRP)), and molecules for triplet repeat neuromuscular disorders (e.g., Huntingtin) (see **Table 2**).

Apoptosis is measured by directly counting changes in cell numbers, viability assays, staining with cell impermeant dyes, observing chromatin condensation with nucleic acid stains like Hoechst 33342, examining DNA fragmentation by TUNEL, ISEL, or electrophoresis on agarose gels, staining for external phosphatidyl serine with Annexin V, and electron microscopy which early on was considered the standard to define apoptotic cells.

Table 1 The major forms of neuronal cell death

Apoptosis	*Necrosis*
Mild insult	Major insult
Nuclear chromatin condensation and margination	Degradation
Cytoplasmic shrinking, endoplasmic reticulum dilation	Swelling
Membrane blebbing	Early membrane disruption
Intact mitochondria, some swelling	Swollen mitochondria
Apoptotic bodies	Lysis
Caspase activation	Not programmed

Table 2 Caspase categories

Category	*Caspases*	*Target*	*Known substrates*
Group I	1, 4, 5, 11, 12, 13	WEHD	Inflammatory processes, pro-IL-1β, procaspases-1,-3,-4
Group II	2, 3*, 7, CED-3	DEXD	Maintenance and repair proteins during apoptosis, CED-3 sterol regulatory binding proteins, PARP, procaspases-6,-9, DNA dependent protein kinase, kinase Cδ
Group III	6, 8, 9, 10	(L/V) EXD	Caspases-3 and-7, poly(ADP-ribose) polymerase, lamins
*Caspase-3, (CPP32, Yama, apopain)		DEVD	Poly(ADP-ribose) polymerase, huntingtin, sterol regulatory element binding proteins, D4G-protein dissociation inhibitor, 70 kDa subunit of U1 SNRP

Regulation of Caspases

Caspases are central to a variety of pathways important to the health of neurons and some of these are shown in **Figure 1**.

In the mid-1990s, apoptosis was identified in spinal cords and brains after traumatic injury. It was shown that caspase-3 was activated and that inhibition of caspase-3 could result in improved recovery in animal models. Importantly, the peak of apoptosis occurs in neurons, microglia, and astrocytes about 3 days after the impact injury providing a window of therapeutic opportunity.

Dysregulated genes fall into categories generally consistent with functional and morphological changes in the motor system. Certain proapoptotic genes, like death-associated protein kinase 1, are upregulated while some antiapoptotic genes, such as peroxiredoxin 2, are downregulated. In injured rat spinal cords, proapoptotic p53 mRNA was upregulated more than twofold. At 24 h after moderate injury, mRNA for the Bcl-2 antagonist of cell death, Bad, increased 60%. Bad inhibits the apoptosis repression activity of Bcl-x(L) and hence promotes apoptosis. This might counter the increased expression of the antiapoptotic factor, bcl-2, after cord injury. A similar increase was seen in a neuronal cell death related gene, DN-7, also known as the TATA box binding protein-associated factor 9 (TAF9) which interacts with p53 to induce transcription of target genes, such as bax. A moderate upregulation of the death effector domain containing protein, DEDD, was also seen. These observations of pathways involved in motor neuron loss in vitro and in vivo may help us understand how we may preserve neurons.

Transcription Factors

Sp1, p53, NF-κB, Atf3, Atf5, Atf6, c-Jun, CREB, HSF1, and C/EBP and several other transcription factors are involved to varying extents in cell death pathways. NF-κB is one transcription factor that plays a significant role in inflammatory responses. NF-κB is activated by a variety of intercellular signals that can both induce and prevent apoptosis. Controversy currently exists, as to whether NF-κB is primarily a pro- or antiapoptotic signal. Experiments testing NF-κB involvement have been aided by parthenolide, a sesquiterpene lactone, that can inhibit NF-κB activity either by alkylating the p65 subunit and/or by inhibiting the degradation of IκBs. The ability to directly and specifically inhibit transcription factors provides tests as to their

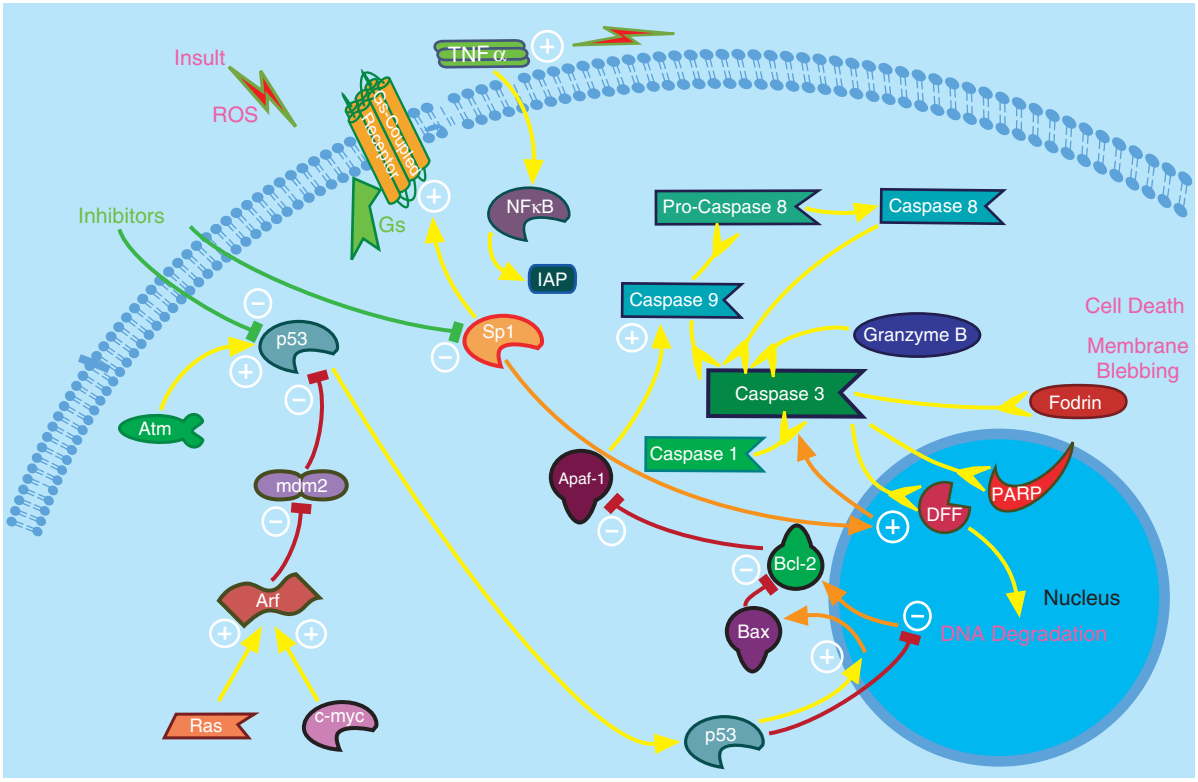

Figure 1 Caspases are among many factors involved in neuronal survival. Several pathways important to neuronal health have been drawn with BioCarta icons and symbology (www.biocarta.com). Insults can result in increased proteases which trigger protease activated receptors (PARs) coupled to G-proteins. Transcription factors such as NF-κB, Atf5, and Sp1 participate in regulatory choices important to survival although the extent of this regulation is not understood in motor neurons or in the degenerating spinal cord. Reactive oxygen species (ROS) also trigger cell death. Many other pathways are not shown. For example, tissue transglutaminase (tTG) is cleaved by proteases or its RNA is alternatively processed to produce a potentially hyperactive protein. tTG can crosslink proteins into aggregates and inclusions (e.g., Lewy bodies). Calcium influx (Ca^{2+}) affects enzymes requiring calcium for activity (e.g., transglutaminase). Also, the proteinase complex, regulated by Parkin and other factors, processes many proteins involved in neurodegeneration including Tau, neurofilament, β-amyloid, synuclein, huntingtin, and p53. Two mechanisms naturally regulating p53 are illustrated in the diagram. The oncogenes Ras and c-myc can induce Arf which promotes the degradation of the mouse double minute 2 homolog, mdm2. Mdm2 could otherwise complex p53 inhibiting its gene transactivation. The ataxia telangiectasia mutated protein (Atm) activates p53 by phophorylation, in response to damage. Examples of genes regulated by p53 include induction of proapoptotic Bax and downregulation of antiapoptotic B-cell lymphoma oncogene, Bcl-2. Bcl-2 would block Apaf-1 initiation of the caspase cascade through caspase-9, caspase-8, and Granzyme B activation of caspase-3 leading to cell death. Caspase substrates include DNA fragmentation factor (DFF), poly (ADP-ribose) polymerase (PARP), and Fodrin (nonerythroid spectin). Their cleavages are the terminal biochemical events leading to membrane blebbing and cell death.

roles in cellular responses and suggests a role in future treatments of disorders associated with transcription factor activation.

Motor neurons may also become susceptible to cell death by early upregulation of the transcription factor, p53. Supporting this, we have determined that p53 levels increase twofold in mouse spinal cords when motor neurons are programmed to die. In a major motor neuron loss disease, Lou Geherig's disease (also known as amyotrophic lateral sclerosis, ALS), p53 is prominently involved.

Although caspases are predominantly constitutively expressed and activated by proteolysis, the central apoptotic caspase-3 is also regulated at the level of gene expression. Differential mRNA display and other measures of mRNA levels demonstrated upregulation of caspase-3 during motor neuron loss in neurodegenerative mouse models and after traumatic CNS injury. Caspase-3 is regulated by the transcription factor Sp1, based on consensus sequences in the promoter and biochemical analysis of caspase-3 regulation in cultured cells and inhibition with the Sp1 inhibitor, mithramycin A.

Therapeutic Prospects

Many neurodegenerative disorders, including spinal cord injuries, have no cure. From a molecular standpoint, there is no reason to doubt that there can be an effective

Table 3 Drugs reducing apoptosis

Compound	*Target*	*Compound*	*Target*
Nerve growth factor (NGF)	Tumor necrosis factor (TNF) superfamily receptors	Glial cell-line derived neurotrophic factor	Neurotrophic factor receptors
Progesterone	Hormone receptors	E-64-d	Calpain
Fibroblast growth factor (FGF)	Tyrosine kinase receptors	Antiinflammatory agents	TNF-α
Indolcarbazole derivatives	c-Jun N-teminal kinase 1 (JNK1)	Fasudil HCl	Protein kinase (PK) inhibition
Dihydroxytestosterone	Androgen receptors	Deprenyl, diphenylpiperazines	Monoamine oxidase (MAO) inhibition
Minocycline, Boc-D-FMK	Caspases	MK-801, *N*-methyl-D-aspartate (NMDA) receptor antagonists, glutamate antagonists	Glutamate excitotoxicity
Pifithrin-α	p53	Granulocyte colony stimulating factor	Induces antiapoptotic pathways
Ac-DEVD-CHO	Caspase-3	Tirilazad mesylate, α-tocopherol	Reactive oxygen species (ROS)

treatment for spinal cord injury. Although regeneration or replacement via stem cells will likely prove fruitful, an earlier intervention aimed at preventing the initial loss of neurons should benefit many patients. There are early indications that portend well for the future. Several studies have provided evidence that tetrapeptide caspase inhibitors reduce cavitation and enhance functional recovery after spinal cord injury in rodent models.

It is likely that effective prevention of irrecoverable motor neuron loss will involve multiple pharmaceuticals targeting several processes. Since apoptosis is a major process in the death of neurons in the CNS, inhibition of different apoptotic pathways should prove to be beneficial and several inhibitors that have been tested are shown in **Table 3**.

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See also: Amyotrophic Lateral Sclerosis/Parkinsonism-Dementia Complex of Three Pacific Isolates; ATM Gene; *Caenorhabditis Elegans*; Parkinson's Disease: Definition, Diagnosis, and Management.

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Cayman Ataxia

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Glossary

Ataxia – Incoordination of movement.
Cerebellum – Major brain region mediating coordination.
Dystonia – Involuntary movements characterized by abnormal posture of the affected body part, often with a torsional component.

Epidemiology

Cayman ataxia (OMIM #601238) is a rare, autosomal recessive disorder found solely in the Cayman Islands. Founder effects and an isolated population with a high rate of consanguineous marriage resulted in a relatively high prevalence of Cayman ataxia and at least two other rare recessive disorders, Mucopolysaccharidosis III/A (Sanfilippo syndrome) and Usher syndrome. In 2006, there were an estimated living 24 individuals with Cayman ataxia, out of a total population of approximately 48,000 Cayman Islanders: an approximate prevalence of 50/100,000, greatly exceeding the prevalence of any ataxic disorder in the United States. The increasing diversity of the Cayman Islands' population and a drop in consanguineous marriages have caused a decline in the incidence and prevalence of Cayman ataxia.

Clinical Features

There is little published literature on the phenotype of Cayman ataxia. Available descriptions indicate the presence of hypotonia in early childhood, variable mental retardation, extraocular muscle paralysis, pes planus, and scoliosis. Cerebellar dysfunction, including limb dystaxia, dysarthria, nystagmus, dystaxic gait, and tremor, is prominent. There is no reported pathology of Cayman ataxia. One anecdotal report describes cerebellar hypoplasia on neuroimaging. Those with Cayman ataxia require special education. The overall impression is of a congenital static encephalopathy of variable severity. Cayman ataxia is compatible with a normal lifespan.

Genetics

In 2003, Bomar et al. established that Cayman ataxia was due to mutations in the *ATCAY* locus, which produces the caytaxin protein. Bomar et al. found two homozygous sequence variants in the DNA of Cayman ataxia subjects: a C-to-G change in exon 9, predicting a serine to arginine substitution at amino acid 301, and a G-to-T substitution in the third base of intron 9. The serine to arginine substitution is not predicted to alter caytaxin protein structure, but the intronic G-to-T substitution disrupts RNA splicing, producing a significantly truncated transcript and resulting in a marked but probably not complete deficit of mature caytaxin mRNA.

Rodent Homologs

The search for the ATCAY locus was paralleled and facilitated by the identification of 3 relevant, spontaneously occurring murine mutations. Jittery (*ji*), hesitant (ji^{hes}), and sidewinder (ji^{swd}) are allelic mutations of varying severity. Jittery and sidewinder mice have a severe phenotype with marked ataxia, dystonic limb postures, and death prior to 1 month of age. Hesitant mice have a milder phenotype with milder ataxia, dystonia, and normal lifespan and fertility. Bomar et al. discovered jittery, hesitant, and sidewinder result from different mutations in the murine homolog of *ATCAY*. Jittery has a B1 element insertion in exon 4 and hesitant has an IAP insertion in intron 1. Both mutations produce aberrant transcripts, but the hesitant mutation allows production of a small amount of normal message, accounting for the milder phenotype. The sidewinder mutation is a 2 base pair deletion in exon 5, resulting in a significantly truncated transcript.

Mutation of the rat homolog of *ATCAY* was identified subsequently as the defect underlying the phenotype of the recessive genetically dystonic rat. Homozygotes of this line exhibit marked generalized dystonia, which can be detected as early as postnatal day 12. Dystonia worsens and mice die by about postnatal day 40. The mutation is an IAP insertion in exon 1, resulting in abnormal transcripts. The phenotype can be largely ameliorated by cerebellectomy. Careful histologic analysis of genetically dystonic rats reveals only subtle changes. Cerebellar physiology, particularly the function of the olivocerebellar system, is markedly abnormal. Interestingly, routine histology of the jittery mouse is unrevealing as well.

The presence of apparent dystonia in these rats has led to the suggestion that cerebellar function abnormalities could underlie dystonia in humans.

Caytaxin Biology

Caytaxin is a 371 amino acid, 42 kD protein of unknown function. Caytaxin is suggested to have a CRAL-TRIO domain, which is responsible for binding small lipophilic molecules. Caytaxin has also been named BNIP-H (for BNIP-2 homology), because it has 69% amino acid sequence similarity to the BNIP-2 protein. BNIP-2 and related proteins may possess a novel protein–protein binding domain called BCH (BNIP-2 and Cdc42GAP homology). Caytaxin is expressed solely by neurons and is expressed widely in the CNS. Caytaxin expression is regulated in the course of development. Subcellular fractionation experiments indicate that caytaxin in localized to the presynaptic cytosol. In cerebellar cortex, caytaxin may be expressed by granule cell terminals synapsing on purkinje cells. Buschdorf et al. suggest that caytaxin binds to and regulates the glutaminase responsible for producing neurotransmitter glutamate. The phenotypes of Cayman ataxia and of rat and mouse *ATCAY* homolog mutants suggest that caytaxin plays an important role in cerebellar development and cerebellar function.

See also: Ataxia; SCA1; SCA2; SCA3, Machado–Joseph Disease; SCA4; SCA5; SCA6; SCA7, Spinocerebellar Ataxia with Macular Dystrophy; SCA8; SCA10; SCA11; SCA12; SCA13, 14, 15, and 16; SCA17; SCA27; Scale for the Assessment and Rating of Ataxia (SARA); Spinocerebellar Ataxias Genetics.

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Central Nervous System Stimulants and Movement Disorders

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Glossary

Choreoathetosis – A movement disorder causing random movements with jerky, writhing qualities.
Dystonia – A movement disorder causing abnormal postures.
Stereotypy – A movement disorder in which similar movements are repeatedly exhibited. Tongue thrusting, chewing, lip licking, and lip protrusion are the most typical symptoms.
Substituted amphetamines – Drugs with an amphetamine structure in which additional molecules (usually a methyl group) have been added to the phenyl ring. They have mixed amphetamine and hallucinogenic properties.

Definition and History

Amphetamines are a class of compounds with a relatively simple chemical structure that is shared by catecholamine neurotransmitters (dopamine, epinephrine, norepinephrine) and some aromatic amino acids. They are old drugs; amphetamine was originally synthesized in the late 1800s and methamphetamine in 1919. First used as nasal decongestants and for asthma, amphetamines had become widely used as stimulants, for weight loss, to promote vigilance, and to improve concentration and memory before their abuse potential was recognized and their use restricted. Although both amphetamine and methamphetamine induce euphoria, methamphetamine is more potent, and when used parenterally, induces a strong 'rush' of euphoria that is very similar to cocaine but longer lasting.

Substituted amphetamines, most notably 3,4-methylenedioxymethamphetamine (MDMA) ('ecstasy'), have mixed stimulant and hallucinogenic properties; psychic effects include a feeling of increased energy as well as a sense of well being and empathy and visual hallucinations. More typical amphetamine effects such as increased body temperature, hypertension, tachycardia, and increased respirations also occur. Many of the substituted amphetamines have been poorly characterized and their toxicities are largely unknown.

Methylphenidate and pemoline (which has been withdrawn from use because of hepatotoxicity) are CNS stimulants that are structurally unrelated but have effects similar to amphetamine.

Cocaine, an alkaloid derived from the coca plant, has been used since antiquity as a stimulant and to suppress appetite. It became very popular in the 1800s and was widely available in tea and soft drinks, and was used medicinally for depression and as a patent medicine for nasal congestion and toothaches before being reclassified as a narcotic. A nonionized, basic form of cocaine ('free-base' or 'crack'), which is able to be vaporized by heat, has also become a widely abused form of the drug.

Pharmacology

Amphetamines are readily absorbed when administered orally; peak plasma concentrations occur in 2–3 h after immediate release and 4–7 h after sustained release formulations. Peak levels occur within minutes of parenteral administration.

Amphetamine and methylphenidate stimulate release of monoamine neurotransmitters from nerve terminals; in the peripheral nervous system, this results in sympathetic effects including tachycardia, hypertension, increased respiration, and temperature.

Substituted amphetamines have similar effects, but have a higher affinity for serotonergic nerve terminals.

Cocaine acts by a mechanism slightly different from that of amphetamines; rather than stimulating release of monoamine neurotransmitters, cocaine blocks their reuptake in presynaptic nerve terminals. The net effects are similar to amphetamine, though; the effects of an intravenous dose of cocaine are nearly indistinguishable from the effects of methamphetamine.

The increase in dopaminergic neurotransmission in the ventral striatum and nucleus accumbens is thought to account for most of the psychic effects and abuse potential of CNS stimulants. In addition, a major factor that likely leads to some of the movement disorders and psychosis induced by CNS stimulants is drug-induced sensitization.

With repeated administration of many drugs of abuse, an increase in their behavioral effects occurs. A simple example is locomotor activity induced by amphetamine or cocaine in rodents. With repeated administration of these drugs, a marked increase in the duration and peak behavioral effects is seen at doses lower than in previously untreated animals. In addition, more complex and novel behaviors develop with repeated drug administration; rodents may develop chewing behaviors that are not seen with initial drug exposure. This mechanism is probably the basis for the development of levodopa-induced dyskinesia in patients with Parkinson's disease.

The neuroanatomy and neurochemistry of sensitization is complex. Acetylcholine, adenosine, and serotonin are important in modulating the effects of amphetamine, MDMA, and cocaine in affecting firing rates and dopamine turnover in striatal or dopaminergic neurons, and each can be affected differently with repeated drug administration.

Tremor

The most common movement disorder induced by CNS stimulants is probably tremor, particularly at higher doses and with more potent drugs. Methamphetamine, cocaine, and MDMA are well recognized by the lay public, drug counselors, and emergency physicians to cause tremor, usually accompanied by other signs of adrenergic effects such as tachycardia and hypertension.

Similar to a number of other drug-induced tremors, the tremor is usually a postural and action tremor, chiefly affecting the upper extremities. Although it is similar to essential tremor, drug-induced action tremor rarely affects cranial muscles, the trunk, or lower extremities.

In individuals who already have essential tremor or another drug-induced tremor, CNS stimulants can significantly exacerbate tremor.

Tic Disorders

Tic disorders are also commonly seen with the use of amphetamines and cocaine, as well as other CNS stimulants used in attention deficit hyperactivity disorder (ADHD) such as methylphenidate (and formerly pemoline).

Although tics can occur de novo with stimulant use, it is more common for these drugs to produce tics in individuals with a current or previous history of a tic disorder. This is especially common in children treated with stimulants for ADHD. When stimulants became commonly used in children, a number of case reports were published that described either emergence or worsening of a tic disorder, and these drugs were then felt to be injurious if a child developed a tic during treatment. More recent studies, though, indicate that these risks were

overestimated. Although ~5–10% of children treated with CNS stimulants may either develop tics de novo or may experience exacerbation of tics, it has also been seen that tics may improve or remit with continued stimulant treatment, and these drugs are now viewed to be relatively safe in most patients.

The tics that occur with cocaine or methamphetamine use in adults are similar to those seen in Tourette syndrome; the most common tics are simple motor tics such as forceful blinking, nose wrinking, or head jerking, but a wide variety of simple and complex motor and phonic tics can occur. They are sometimes admixed with psychosis and other, complex stereotypic movements during acute drug intoxication. As in children, tics generally remit after drug discontinuation in most adults who exhibit tics during use of amphetamine or cocaine use. However, there have been some case reports of individuals who have developed long-lasting tic disorders after brief exposures to cocaine and methamphetamine, although it would be hard to prove that the tic disorder was caused rather than having been unmasked by the stimulants.

Stereotypies and Complex Repetitive Motor Behavior (Punding)

A third group of movement disorders that are seen with amphetamines are repetitive motor behaviors. Adventitious jaw movements are a particularly common motor effect of methamphetamine and MDMA; trismus (jaw clenching), bruxism (tooth grinding), and chewing movements may be prominent effects seen with acute and chronic use of these drugs.

Other, more complex repetitive behaviors, termed 'punding' are seen with chronic use of methamphetamine. This may include compulsive disassembling and reassembling or manipulating objects, playing cards, searching drawers, etc. and is known colloquially by drug users as 'tweaking.' With +chronic use, a delusion that insects are crawling under the skin (formication) develops and leads to repetitive, compulsive picking at the skin. This behavior has characteristics of both punding and a compulsion.

Although complex repetitive behaviors are best known with methamphetamine use, it is not uncommon with cocaine use; one series estimated that 10–40% of cocaine-addicted individuals may experience punding.

Chorea and Dystonia

Choreoathetotic and akathisia-like movements are seen with chronic cocaine abuse. Case reports have described patients in whom a number of movements are seen; these include facial grimacing, lip smacking, blinking, choreoathetoid movements of the extremities, slow athetoid writhing of the trunk and extremities, hand wringing and foot stomping, semipurposeful movements of the hands, and sustained jaw opening movements.

The prevalence is largely unknown, but it is notable that there are English ('crack dancing') and Spanish ('twisted mouth') colloquialisms for movements seen with cocaine addiction, and it is probable that these movements are relatively common.

The effects are generally transitory but have been described by some cocaine addicts as lasting a few days. On rare occasions, more persistent movements can occur; one case report described a young woman with choreiform dyskinesias that persisted over 20 months after abstention from cocaine.

Although quite uncommon, there have been case reports of oromandibular dyskinesias and generalized choreoathetosis induced by amphetamines and pemoline.

There is also evidence that cocaine use may increase the sensitivity of an individual to develop an acute dystonic reaction when receiving a neuroleptic. On very rare occasions, withdrawal from acute cocaine use may also trigger an acute dystonic reaction.

Differential Diagnosis

In most cases in which movement disorders present acutely and there is a known history of stimulant use, the diagnosis is clear. In young adults or children with an acute presentation of a hyperkinetic movement disorder, drug use should be strongly suspected until ruled out.

A number of other signs and symptoms of acute and chronic stimulant abuse may aid in the clinical suspicion. For most stimulants, common autonomic manifestations may include tachycardia, hypertension, increased respiratory rate, mydriasis, dry mouth, and urinary retention. Psychiatric symptoms and signs, especially seen with cocaine and amphetamine addiction, may include agitation, anxiety, restlessness, or paranoia or overt psychosis, and violent behavior; in contrast, MDMA-intoxicated individuals may appear calm or euphoric.

Even in the setting of known or proven stimulant use, a preexisting or concomitant neurological disorder should also be suspected. Although tremors, tic disorders, chorea, and other movement disorders may occur in previously healthy individuals, it is far more common for these conditions to be worsened by CNS stimulants. Mild essential tremor or a prior history of a transient tic disorder, for example, may become obvious only to a patient in the setting of acute or chronic stimulant use.

A medical cause of chorea or tremor, such as a recent streptococcal infection or thyrotoxicosis, should be considered in the setting of severe tremor, tics, or chorea.

Drug interactions may also be a major factor in the acute presentation of a movement disorder associated with stimulant use. Recent or concomitant cocaine use, for example, increases the sensitivity to developing an acute dystonic reaction following administration of a neuroleptic or antiemetic, and a drug screen to rule out recent use of cocaine or amphetamines should be considered in patients with an acute dystonic reaction.

One serious disease that can present similar to an acute dystonic reaction is tetanus. Approximately 50–75% of patients with generalized tetanus present with trismus secondary to masseter muscle spasm, which is commonly accompanied by nuchal rigidity and facial grimacing. Tonic contractions, triggered by noise or touch may cause opisthotonus and look very similar to an acute dystonic reaction. A history of a recent laceration or puncture wound, a recent sore throat accompanied by dysphagia, or a chronic wound may be present but up to 10% of patients have no antecedent, known cause.

Although generalized chorea would be an unusual presentation, structural lesions in the basal ganglia or nearby structures can present with acute hemichorea or hemiballismus, and cranial imaging should considered.

Diagnostic Workup

Depending on the clinical presentation, blood tests for recent streptococcal infection and screening tests for hyperthyroidism should be considered in most patients with an acute presentation of tremors, tic disorders, or chorea. An acute dystonic reaction to health care professionals who are not used to this condition can appear similar to a seizure. In contrast to seizures, though, the level of consciousness is maintained during an acute dystonic reaction. Extensor posturing due to brainstem disease can also appear somewhat similar but is accompanied by a number of other neurological signs that would not be expected in acute dystonia.

In most patients, the movement disorders associated with stimulant use should disappear over a few hours, and persistent movement disorders, lasting more than 48 h after known drug ingestion, should prompt a search for other etiologies.

Treatment and Prognosis

In most cases, no specific treatments are needed to eliminate or reduce hyperkinetic movements, although dopamine antagonists, such as haloperidol, can be used to antagonize severe choreoathetosis or parenteral benzodiazepines or antihistamines for acute dystonic reactions.

In most individuals, the hyperkinetic movements disappear within 24–28 h. In some patients, tic disorder may be more persistent and may require treatment with dopamine antagonists.

In severely affected individuals or in patients with cardiovascular or hemodynamic instability, admission to the hospital and supportive care may be needed. Patients with MDMA poisoning may need aggressive care for treatment of seizures, hyperthermia, and hypotension.

In the short term, there are no medical complications immediately following discontinuation of chronic use of methamphetamine or cocaine. However, patients addicted to these agents typically have protracted depression after abstinence and may require intensive counseling, antidepressants, and anxiolytics.

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Cerebrotendinous Xanthomatosis

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Glossary

Ataxia – From Greek, 'lack of order.' Incoordination of muscle contractions during voluntary movements or sustained postures. Ataxia might be sensory (secondary to posterior column or peripheral nerve damage) or motor (secondary to cerebellar, cerebral, thalamic, basal ganglia, or brain stem dysfunction). The condition may affect the limbs, trunk, eyes, pharynx, or larynx. Patients most commonly present with unsteady gait, postural imbalance, speech, and gaze disturbances.
Extrapyramidal signs – A group of neurological signs indicating disturbed function of the extrapyramidal motor system. The extrapyramidal system includes substructures of the basal ganglia and brain stem and interconnections with certain regions of the cerebellum, cerebrum, and other areas of the central nervous system. It has a major role in modulation and regulation of motor activity, and when damaged can cause postural and muscle tone abnormalities as well as involuntary movements such as tremor, dystonia, chorea, athetosis, and tics.
Pyramidal signs – A group of neurological signs indicating the presence of damage to the upper motor neuron (cell bodies or corticospinal tracts). These include: spastic paresis/paralysis, hyperreflexia, clonus, pathological reflexes (extensor plantar responses (e.g., Babinski sign), Tromner's and Hoffmann's signs), and loss of superficial skin reflexes (abdominal, cremasteric).
Xanthoma – A lesion characterized by abnormal accumulation of lipid-laden macrophages secondary to disturbed lipid metabolism or a local cell dysfunction. Xanthomas usually occur in the skin and subcutaneous tissues but may rarely involve deep soft tissues such as the gastrointestinal tract, lung, and brain.

Cerebrotendinous Xanthomatosis

Cerebrotendinous xanthomatosis (CTX; MIM 213700) is a recessively inherited lipid-storage disease caused by a deficiency of the mitochondrial enzyme, sterol 27-hydroxylase (CYP27A1). The metabolic defect results in impaired bile acid synthesis and the accumulation of cholesterol and its 5α-dihydro derivative *cholestanol* in numerous tissues. Clinically, CTX is characterized by diarrhea, cataracts, tendon xanthomas, and progressive neurological dysfunction. The first patients were described by van Bogaert, Scherer, and Epstein in 1937. About 30 years later, it was suggested that CTX is caused by deposition of cholestanol in the affected tissues. *CYP27A1* gene was identified in 1991 and was mapped to the long arm of chromosome 2 where the first mutations were detected. CTX is considered to be rare, though its actual prevalence rate is not well-established. The disease is reported worldwide, but is more prevalent in Japan, the Netherlands, and among Moroccan Jews in Israel.

Pathogenesis

CYP27A1 is a key enzyme in bile acid synthesis; it catalyzes the first step in the normal oxidation of the steroid side chain, converting cholesterol as well as other 7α-hydroxylated cholesterol metabolites into 27-oxygenated steroids (**Figure 1**). In its absence, biosynthesis of bile acids (especially chenodeoxycholic acid (CDCA)) is reduced. The negative feedback of bile acids on 7α-hydroxylase, a rate-limiting enzyme in bile acid synthesis, is impaired, and bile precursors are overproduced. Consequently, alternative pathways are activated leading to increased formation of cholestanol and 25-hydroxylated bile alcohols. Deposition of cholestanol was reported in CTX in almost all tissues, particularly the Achilles tendons, brain, and lungs.

CYP27A1 gene was mapped to 2q35 between markers D2S1371 and D2S424. It consists of nine exons and eight introns and spans 18.6 kb of DNA. The transcript is 1966 bp in size, and it encodes a 531 amino acid protein. So far, 49 different mutations of the *CYP27A1* gene have been reported worldwide. About 50% of these mutations were found in the region of exons 6–8, which is known to encode an adrenodoxin-binding site and a heme-binding site. No correlation was found between specific *CYP27A1* mutations and particular CTX phenotypes.

Clinical Features

CTX typically presents as infantile-onset diarrhea, childhood-onset cataracts, and/or adolescent- to young adult-onset tendon xanthomas. Adult-onset progressive

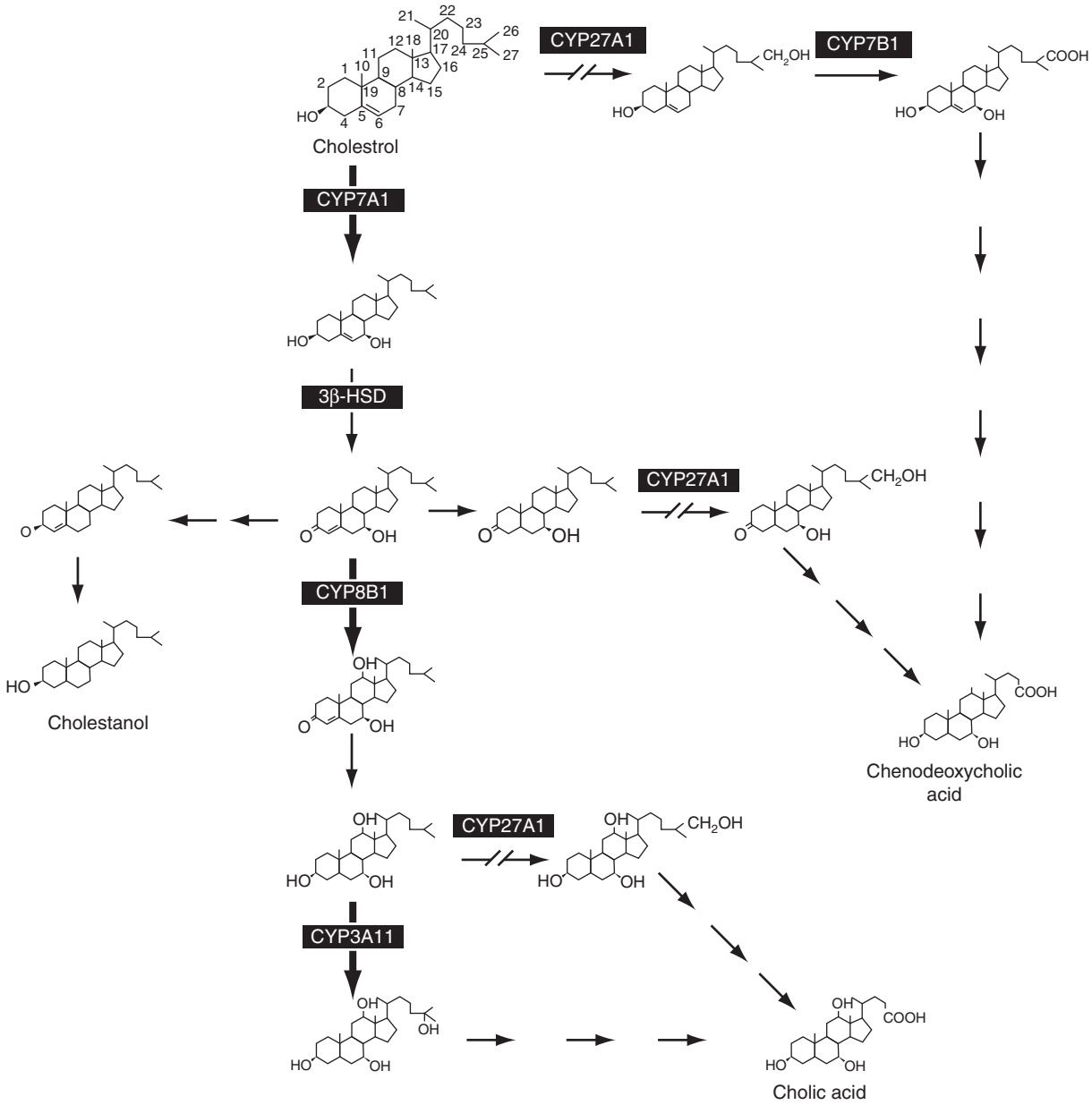

Figure 1 Bile acid synthesis pathways. 3β-HSD, 3β-hydroxysteroid oxidoreductase; CYP3A11, cytochrome P450 3A11; CYP7A1, cholesterol 7α-hydroxylase; CYP7B1, oxysterol 7α-hydroxylase; CYP8B1, sterol 12α-hydroxylase; CYP27A1, sterol 27-hydroxylase. Adapted from Goodwin B et al. (2003) Identification of bile acid precursors as endogenous ligands for the nuclear xenobiotic pregnane X receptor. *Proceedings of the National Academy of Sciences* 100: 223–228, with permission from the National Academy of Sciences, USA.

neurological syndrome usually follows. The chronic diarrhea is thought to be secondary to the excessive amounts of bile alcohols in the gut. Cataracts can be visually significant or insignificant, and additional ocular findings such as optic disc paleness/atrophy, retinal vessel sclerosis, drusen, and pigment changes may also be present. Tendon xanthomas commonly involve the Achilles tendons (**Figures 2** and **3**), but may occur on the extensor tendons of the elbow and hand, the patellar tendon, and the neck tendons. Xanthomas have also been reported in the lung, bones, and the central nervous system (CNS). Other systemic manifestations include premature atherosclerosis and coronary artery disease, lipomatous hypertrophy of the atrial septum, pulmonary insufficiency, osteopenia with frequent bone fractures, hypothyroidism, cholelithiasis, nephrolithiasis, and palpebral xanthelasmas.

Accumulation of cholestanol in the nervous system leads to progressive and broad neurological dysfunction. Some individuals show mental impairment from early infancy, whereas the majority shows normal or slightly

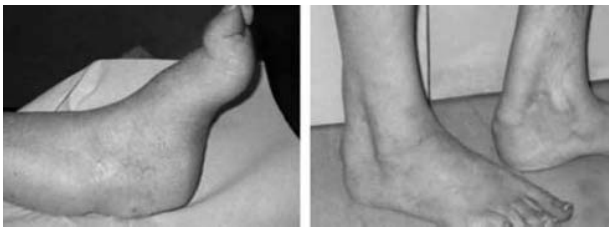

Figure 2 Achilles tendon xanthomas. Adapted from Gallus GN, Dotti MT, and Federico A (2006) *Neurological Sciences* 27: 143–149, with permission from Springer Science and Business Media.

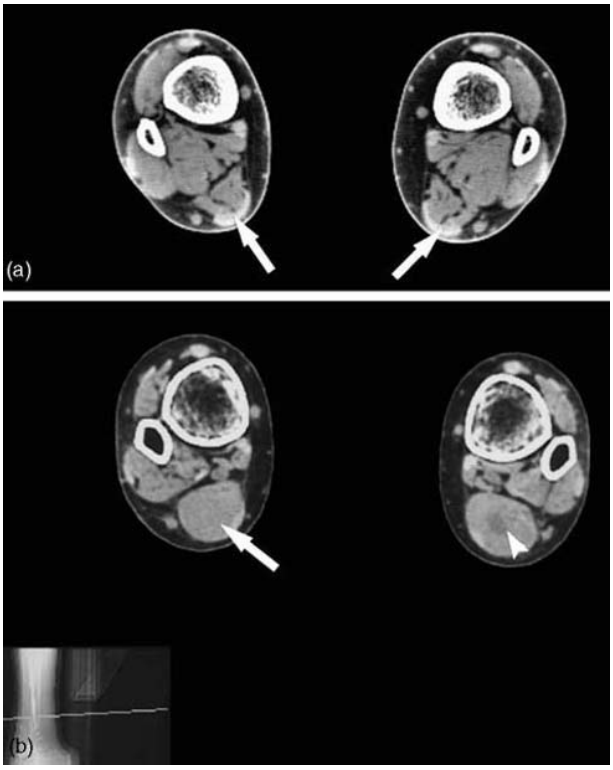

Figure 3 Cross-sectional CT images of Achilles tendon: (a) the normal appearance of the narrow crescent-shaped tendon (arrows). (b) The abnormal markedly thickened tendons of a CTX patient (arrow). Note the central hypodense area representing lipid accumulation (arrowhead).

subnormal intelligence during adolescence. Dementia with slow deterioration in intellectual abilities occurs in the twenties in over 50% of individuals. Neuropsychiatric symptoms such as behavioral changes, hallucinations, agitation, aggression, depression, and suicide attempts may be prominent. Pyramidal signs (spasticity, hyperreflexia, and extensor plantar responses) and/or cerebellar signs (ataxia, dysmetria, and dysarthria) are almost invariably present. A spinal form in which spastic paraparesis is the main clinical symptom was also described. Extrapyramidal manifestations may include atypical parkinsonism (resting tremor, rigidity, bradykinesia), dystonia, and palatal tremor. Epileptic seizures are reported in ~50% of patients. Peripheral neuropathy usually involves motor more than sensory fibers, and might lead to distal muscle atrophy and pes cavus. The combination of early onset cataract, premature atherosclerosis and ischemic heart disease, osteoporosis, dementia, and parkinsonism may mimic premature aging.

Diagnosis and Laboratory Work-up

CTX diagnosis is based on the typical clinical picture (especially the triad of cataract, tendon xanthomas, and progressive neurological disturbance) and typical laboratory findings as follows:

1. *Electrophysiological studies:* The electroencephalogram typically shows diffuse slow-wave activity with paroxysmal discharges. Evoked potentials studies may reveal delayed central conduction time. Electromyography (EMG) typically shows predominantly axonal sensorimotor neuropathy. Controversy still exists regarding the extent of the demyelinating component and the presence of myopathic EMG changes.
2. *Neuroimaging:* Magnetic resonance imaging shows cerebral and cerebellar atrophy, and usually includes regions of increased T2-signal intensity in the cerebellar and periventricular white matter, basal ganglia, brain stem, and more typically around the dentate nuclei. Magnetic resonance spectroscopy shows significant decrease in the *N*-acetylaspartate peak which may represent widespread axonal damage. In addition, an increased peak within the lactate region (0.9–1.3 ppm) is typically present and may represent cerebral mitochondrial dysfunction or increased lipid signal if the peak does not invert at an echo time of 135–144 ms.
3. *Neuropathology:* Classic CNS pathology findings include granulomatous and xanthomatous lesions in the cerebellar hemispheres, globus pallidus, and brain stem. Extensive demyelination and gliosis were reported in the cerebellar white matter and long tracts of the spinal cord, with multiple dispersed lipid crystal clefts. Accumulation of foamy cells and homogeneous myelin-like material was also described, especially around vessels. Nerve biopsy reveals primary axonal degeneration accompanied by a variable amount of demyelination. Muscle biopsy frequently shows neurogenic changes. Mild myopathic changes with some mitochondrial abnormalities were also reported.
4. *Biochemistry:* The biochemical hallmark and the key for laboratory diagnosis of CTX is high serum cholestanol in the presence of low to normal plasma cholesterol level. Large amounts of bile alcohols in serum, urine, feces, and bile can also contribute to the diagnosis as well as the demonstration of reduced CYP27A1 enzymatic activity in the liver, fibroblasts, or lymphocytes.

5. *Molecular genetic testing:* Sequence analysis of *CYP27A1* detects mutations in 90–100% of the affected individuals. Deletions and duplication mutations require special methods for detection.

Differential Diagnosis

The combination of a progressive neurological syndrome and typical systemic manifestations generates a unique phenotype with relatively restricted differential diagnosis. CTX shares some clinical manifestations such as xanthomas and accelerated atherosclerosis with other lipid storage disorders, including familial hypercholesterolemia and sitosterolemia. However, progressive neurological symptoms, diarrhea, cataract, and pulmonary insufficiency are not common features of these disorders. See **Table1** for neurogenetic syndromes associated with presenile cataract and **Table 2** for neurogenetic syndromes associated with peridentate region T2 hyperintensity (**Figure 4**).

Treatment and Prognosis

CTX diagnosis may be difficult because of its clinical heterogeneity and because the classic systemic symptoms, juvenile cataract, and tendon xanthomas, may be absent on presentation. However, early diagnosis of CTX is crucial as CTX is one of a few neurometabolic disorders with potential medical treatment. Long-term treatment with CDCA (250 mg t.i.d) was reported to arrest and possibly reverse the progression of the disease. Supplementing the bile acid pool with exogenous CDCA is thought to inhibit the abnormal endogenous bile acid synthesis. Under treatment, serum cholestanol levels are markedly reduced, urine excretion of bile acid metabolites is normalized, and neurophysiologic findings are improved. A few studies reported the prevention of neurological deterioration and even some improvement of existing deficits. Yet, the clinical efficiency of CDCA awaits further validation. The use of HMG–CoA

Table 1 Neurogenetic syndromes associated with presenile cataract

Cerebrotendinous xanthomatosis
Cockayne syndrome
Congenital cataracts, deafness, Down syndrome-like facies, short stature, and mental retardation
Congenital cataracts, facial dysmorphism, and neuropathy (CCFDN)
Congenital cataracts, mental impairment, and dentate gyrus atrophy
Congenital disorder of glycosylation type I
Down syndrome
Fabry disease
Galactosemia
Hypomyelination and congenital cataract (HCC)
Mannosidosis
Martsolf syndrome (microcephaly, mental retardation, cataract, hypogonadism, and short stature)
Marinesco-Sjogren syndrome
Micro syndrome (congenital cataract, microphthalmia, hypoplasia of corpus callosum, hypogenitalism)
Mitochondrial encephalomyopathy with diabetes mellitus, cataract, and corpus callosum atrophy
Myotonic dystrophy
Oculocerebrorenal sydrome of Lowe
Optic atrophy 3 (optic atrophy and cataract)
Refsum disease
Sengers disease (congenital cataract, mitochondrial myopathy, and lactic acidosis)
Spastic paraplegia 9
Spastic paraplegia 21
Spastic paraplegia 25
Zellweger syndrome

Table 2 Neurogenetic syndromes associated with peridentate region T2 hyperintensity

Adrenoleukodystrophy
Cerebrotendinous xanthomatosis
Fragile-X associated tremor ataxia syndrome (FXTAS)
L-2-hydroxy-glutaric aciduria
Pyruvate dehydrogenase deficiency
Refsum disease
Spinocerebellar ataxia type 3 (SCA3, MJD)
Succinic semialdehyde dehydrogenase deficiency
Wilson disease

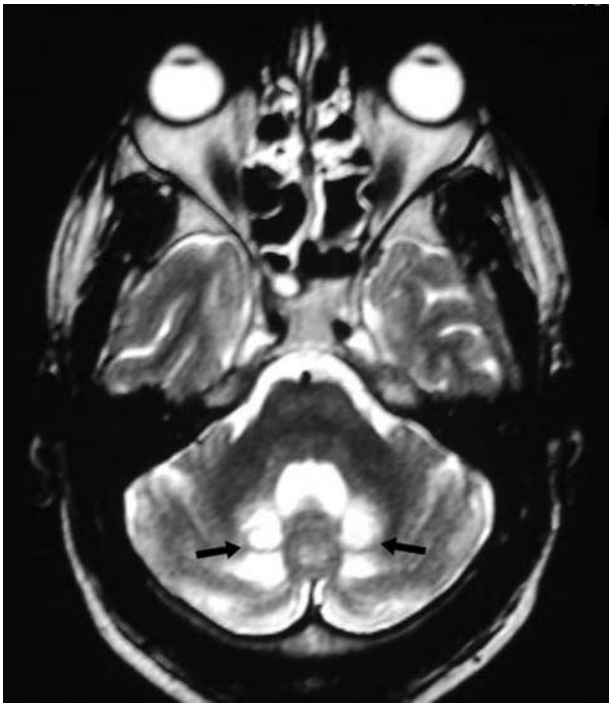

Figure 4 Peridentate region T2 hyperintensity. Brain MRI of a CTX patient showing increased T2 signal within the dentate nuclei and the surrounding white matter bilaterally (arrows).

reductase inhibitors and low-density lipoprotein apheresis was also reported, but their effectiveness is still controversial.

If untreated, CTX is a debilitating and lethal disease. Early diagnosis and treatment with CDCA or the combination of CDCA and a HMG–CoA reductase inhibitor might prevent further deterioration.

See also: Ataxia; Choreiform Disorders; Dysarthria; Eye Movement Abnormalities in Movement Disorders; Spastic Paraparesis.

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Cervical Dystonia

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Glossary

Basal ganglia – Deep region of the brain involved in initiating and maintaining movement.
Botulinum toxin – Toxin produced by clostridium botulinum, which can cause muscle weakness and botulism.
Cervical dystonia – The most common form of idiopathic focal dystonia involving muscles of the neck.
Dystonia – Simultaneous cocontraction of agonist and antagonist muscles which usually causes an abnormal twisting posture.
Idiopathy – A condition for which no known cause can be determined.
Torticollis – A subclass of the cervical dystonia that causes head rotation.

Definition and History

Cervical dystonia (CD) is a simultaneous cocontraction of both agonist and antagonist muscles of the neck, resulting in abnormal postures and/or movements. Based on head posture, CD can be described as torticollis (neck rotation), anterocollis (head-forward flexion or pulled forward), retrocollis (head-posterior extension or pulled backward), or laterocollis (head tilt or lateral flexion). Most of the time, patients present with a combinations of these postures. In the sixteenth century, Rabelais applied the term 'torty colly' meaning wry-neck. Almost 200 years later in 1911, Oppenheim, used the term dystonia to describe the abnormalities in tone seen in patients with generalized dystonia.

Pathogenesis/Pathophysiology

The pathophysiology of idiopathic CD is not well understood. Recent studies have explained the pathogenesis of CD at the peripheral and central nervous system level.

Although any muscle in the neck may be involved, some muscles such as the splenius capitis are more commonly associated with abnormal head posture.

There are several physiologic variables that may contribute to the development of cervical dystonia. The first potential cause is loss of central inhibition as indicated by several studies. One hypothesis suggests that with a directed movement, a certain area of the motor cortex

activates for the desired movement and unwanted movements are inhibited by surround inhibition which has a concept similar to what has been described in the visual system. A few studies have shown that the basal ganglia affect cortical inhibition. SPECT studies have demonstrated that striatal D2 receptor binding decreases in focal dystonia. Assessing by SPECT, Naumann concluded that disturbances of the indirect pathway cause disinhibition of thalamocortical circuitry in cervical dystonia.

Another potential cause of dystonia is sensory deficit and sensorimotor mismatch. Trauma and other abnormal inputs could lead to focal dystonia. 'Geste antagonistique/sensory trick' is a sensory phenomenon used to improve abnormal postures in focal dystonia. These examples suggest that dystonia is, at least in part, a sensory-related disorder. Bara-Jimenez showed abnormal spatial discrimination in patients with writer's cramp, supporting the theory of sensory dysfunction in focal dystonia. Several studies suggest that improper sensory assistance in a motor activity may be the cause of the cocontraction of agonist and antagonist muscles seen in focal dystonia.

Aberrant neuroplasticity is another potential cause of dystonia. The nervous system is capable of neural adaptation and network reorganization, and brain injury or external stimuli can cause maladaptive reorganization. Recently, Bara-Jimenez showed an abnormal cortical somatosensory homunculus in patients with focal dystonia of the hand. Using TMS, the reversible reorganization of the motor cortex was shown for non-task-specific focal dystonias, such as torticollis. It suggested that aberrant neuroplasticity is correlated with both motor cortex and affected cervical muscles.

Abnormal basal ganglia discharges have also been suggested as another potential cause of dystonia. Sanghera compared the discharge rates and neuronal patterns in parkinsonian patients with those in patients with dystonia. He found that in both dystonia and Parkinson's disease (PD), the discharge rates in the putamen are very low, but discharge rates are much lower in the globus pallidus neurons in dystonia compared with PD. Recently, Zhuang analyzed neuronal discharges in the GPi, ventral thalamic nuclear group, ventral oral posterior/ventral intermediate (Vop/Vim), and subthalamic nucleus (STN) in patients with dystonia. Results were similar to Sanghera's, suggesting an association of dystonia with alteration in neuronal discharge in the basal ganglia and thalamus.

Epidemiology/Risk Factors

Cervical dystonia (CD) is the most common form of focal dystonia. Multiple studies have shown the prevalence of CD to be 9–30 per 100 000 in the United States. Currently, the number of cases of cervical dystonia in the United States is estimated to be greater than 90 000. Other studies show that prevalence differs among various ethnic groups. Claypool in 1995 reported an incidence of 1.2 per 100 000, while an incidence of 5.4 per 100 000 was published in a practice-based survey of dystonia in Munich.

Women are affected 1.3–2-fold more often than men. CD can occur at any time of life but most individuals experience their first symptoms in middle age. Chen reviewed the clinical details of cervical dystonia in 266 patients. In this study, the median age of onset was 41 years. A familial history of dystonia was found in 12% of cases and spontaneous remission occurred in 9.8% of patients.

Clinical Features and Diagnostic Criteria

Dystonia is usually classified according to the age of onset, etiology, or anatomic distribution. The age of onset is usually either in childhood or in adulthood (age >25 years). Primary dystonia may be hereditary or idiopathic. Anatomic classification includes focal (confined to one body part), segmental (affecting more than one contiguous region), multifocal (two or more nonadjacent areas), hemidystonia (one side of the body), or generalized. Cervical dystonia typically begins in adulthood and is idiopathic. It may remain focal but there is a risk of spread to nearby regions. Cervical dystonia may be part of more widespread involvement, especially in younger onset cases.

Idiopathic dystonia usually begins in adulthood, whereas childhood onset is often associated with the DYT-1 genetic mutation. Idiopathic, adult onset, focal dystonia usually involves the head and neck regions. Cervical dystonia is the most common form of focal dystonia. The onset is usually insidious with gradual worsening. Patients may notice only vague neck pain or discomfort or they may complain of neck tightness or a pulling sensation. Abnormal head postures may first be noticed by family or friends, especially if pain is not significant. The head can be pulled in any direction of movement. Although CD is often referred to as 'spasmodic torticollis,' this term is not always appropriate. The term torticollis refers to head rotation, laterocollis to head tilting, retrocollis to neck extension, and anterocollis to neck flexion. Patients commonly exhibit a combination of movements rather than movement in only one plane. The movements may be sustained or spasmodic. Dystonic head tremor may also occur and should be differentiated from other causes of head tremor by the presence of abnormal neck posturing. Neck pain may be present in up to 75% of patients, but the severity of pain does not necessarily correlate with the severity of neck movements. Shoulder elevation and anterior displacement are also common.

Symptoms of CD are usually progressive early in the course. It is thought that most of the progression occurs within the first 5 years after onset but this course has not

been well studied in large cohorts. Approximately 10–20% of patients will experience spread of dystonic symptoms to adjacent regions, including the jaw, eyes, lower face, vocal cords, trunk, and upper limbs.

Hand tremor is also more common in CD than in the general population. This tremor is usually present with action or posture holding and may or may not be associated with dystonic postures of the limb. The precise etiology of this tremor is unclear and debate exists as to whether it is of dystonic origin or whether there is a higher risk of developing essential tremor in patients with dystonia.

Some patients with torticollis find a sensory trick to alleviate their symptoms partially or completely. Sensory trick or 'geste antagoniste' is a unique feature of dystonia and is reported in more than 50% of patients with cervical dystonia. Typically, placing the hand on the chin, side of the face, or the back of the neck reduces muscle contraction. Interestingly, in some patients just thinking about a 'geste antagoniste' diminishes their symptoms. The exact mechanism of action of 'geste antagoniste' is still unknown. The presence of a sensory trick is very supportive of the diagnosis of idiopathic rather than secondary dystonia.

Patients with torticollis also show a high incidence of psychiatric comorbidities such as depression and anxiety. Psychiatric comorbidity is not just secondary to chronic disease or disfigurement and may have its own pathogenesis primarily related to dystonia. In some patients with cervical dystonia stress, emotion, self-consciousness, walking, carrying objects, writing, running, social situations, fatigue, and lack of sleep have been reported as detrimental factors. On the other hand, some patients reported sleep, lying on their back or side, relaxation and a 'geste antagoniste' as ameliorating factors.

Differential Diagnosis

Cervical dystonia can be the initial manifestation or presenting sign of diseases such as multiple sclerosis, spinocerebellar ataxia 17, and systemic onset juvenile rheumatoid arthritis. Rarely, cervical dystonia can be secondary and due to a variety of identifiable pathologies, including Wilson's disease, progressive supranuclear palsy, corticalbasal ganglionic degeneration, tardive dystonia, spinal cord ependymoma, posterior fossa tumor, pseudotumor cerebri, systemic lupus erythematosus, Huntington's disease, Langerhans cell histiocytosis, hemorrhagic and ischemic stroke, cerebello-pontine angle tumors, intramedullary glioma, cerebellar cavernous angioma, syrinx, retropharyngeal abscess, ocular pathology, electrical injury, arteriovenous malformation, multiple sclerosis, pantothenate kinase-associated neurodegeneration (PKAN), and ataxia-telangiectasia. As with all movement disorders, cervical dystonia may be psychogenic in origin. The diagnosis of psychogenic dystonia is difficult to make and should be done by someone with expertise in movement disorders.

Other diseases of the neck may be confused with dystonia. Cervical radiculopathy may cause neck pain with abnormal posturing or limited range of motion. Neurologic findings other than dystonia on examination (i.e. muscle weakness, reflex asymmetry) suggest a diagnosis other than idiopathic dystonia and require more diagnostic testing.

Diagnostic Workup/Tests

Cervical dystonia is a clinical diagnosis and there is no laboratory test or imaging study to confirm the diagnosis. Imaging studies of the brain and/or cervical spine may be indicated if secondary dystonia is suspected. Basic screening laboratory studies are also usually obtained during the initial workup to rule out metabolic disorders and Wilson's disease. However, in typical, long-standing cervical dystonia, imaging and laboratory studies are not diagnostic and usually not necessary. Patients may desire testing and this may be appropriate in some cases to relieve patient anxiety.

Management

Oral Medical Therapy

Many medications have been used to treat symptoms of cervical dystonia. However, medication trials have showed only a limited success rate in control of the symptoms. The medical treatment of CD is often limited by side effects and the benefit is usually modest. Medications that can be tried as medical therapy include anticholinergics, benzodiazepines, mexiletine, Baclofen, riluzole, tetrabenazine, valproate, olanzapine, and clozapine

Botulinum toxin

The treatment of cervical dystonia was revolutionized with the introduction of botulinum toxin type A in 1989. Botulinum toxin therapy is now considered as the treatment of choice for all forms of focal dystonia, including CD. Seven different serotypes of botulinum toxin have been identified. Their specific site of action is at the neuromuscular junction to block the presynaptic release of acetylcholine. This causes muscle weakness, resulting in a decrease in inappropriate cocontraction of agonist and antagonist muscles in dystonia. Over the last 15 years, intramuscular injection of botulinum toxin has become the treatment of choice for mild, moderate, and severe cervical dystonia. Botulinum toxin type A and B are used clinically for the treatment of cervical dystonia.

The mechanism of action of both serotypes is similar, although each has a specific site of action. All botulinum toxins initially bind to receptors on presynaptic

cholinergic nerve terminals, and then are incorporated into a vesicle and internalized. The active part of the toxin molecule is then released into the cytoplasm, where it then acts as an enzyme on its specific target protein. Type B toxin specifically cleaves synaptic vesicle associated membrane protein (VAMP), also known as synaptobrevin. Type A toxin cleaves another target protein, synaptosome-associated protein of 25 kDa (SNAP 25). Cleavage of these proteins blocks the docking and fusion of the synaptic vesicles with the nerve terminal membrane: a necessary step for neurotransmitter release.

A variety of injection techniques has been employed with success. Multiple controlled trials have shown between 60 and 90% improvement in abnormal head movements following intramuscular toxin injection. Pain is also significantly improved with treatment with botulinum toxin. Both type A and type B toxins have a similar clinical effect and duration of effect when used in comparable doses. Patients usually notice improvement of their symptoms in 5–10 days after injection with lasting benefit for 3–4 months.

Botulinum toxin type A

Botulinum toxin type A is effective and safe and has been shown to be more effective than medical therapy in controlling symptoms of cervical dystonia with a better side effect profile.

The efficacy and safety of botulinum toxin type A have been established in several clinical trials, with 70–90% of patients with cervical dystonia benefiting from this formulation. Botulinum toxin type A had been the most widely used and longest studied serotype. There is a risk of developing neutralizing antibodies with repeated therapy. The presence of neutralizing antibodies is associated with a loss of clinical efficacy, which is believed to be life-long. In general, avoidance of using high doses and extending the interdose interval to a minimum of 3 months duration is believed to lower this risk. In some early reports, neutralizing antibodies have been shown in up to 17% of patients but Jankovic, using the current formulation of botulinum toxin type A, did not detect the presence of blocking antibodies in a 3-year open-label observation. A large-scale, prospective study recently showed the risk of antibody production to be about 1% per year.

The effect of botulinum toxin may be potentiated by other drugs that interfere with neuromuscular transmission such as aminoglycoside antibiotics and other neuromuscular blockers. One study showed an antagonistic action of chloroquine with botulinium toxin by preventing internalization of the toxin. Adverse effects such as dysphagia, neck weakness, local pain, lethargy, dysphonia, and xerostomia are temporary but can last for weeks or months prior to waning. The most common side effects are local and related to excessive muscle weakness.

Botulinum toxin type B

Botulinum toxin type B was the first toxin approved by the FDA in December 2000 for the treatment of cervical dystonia. This serotype has also been shown to be effective in reducing the pain, severity, and disability associated with cervical dystonia in both botulinum toxin type A responsive and type A resistant. Dry mouth, dysphagia, and injection site pain are the most common reported side effects with botulinum toxin type B, and dry mouth is more common with this serotype than with type A.

Surgery

Surgical procedures for the treatment of cervical dystonia are considered in the uncommon case of botulinum toxin inefficacy or the development of resistance to both serotypes A and B, as well as failure of medical therapy. Both central and peripheral nervous system procedures have been used to treat cervical dystonia recalcitrant to medical intervention. To date, surgical therapy remains strictly an option when other treatments fail or become ineffective. Deep brain stimulation, usually of the globus pallidus, has been approved by the FDA for compassionate use in the treatment of dystonia.

Brain lesioning

Since the early 1940s, brain lesioning as a treatment for CD has been undertaken with variable results. Several targets have been explored in the basal ganglia and thalamus to treat movement disorders. Meyers reported a surgical procedure for postencephalitic tremor in 1941. Afterward, he reported his 10 years of surgical experience to treat movement disorders, including dystonia, by creating lesions in selected regions of the basal ganglia and thalamus. These results have been replicated by placing lesions in various regions of basal ganglia. Thalamotomy as a traditional stereotactic therapy for cervical dystonia shows controversial results. Bilateral thalamatomy can be modestly effective in treating symptoms of cervical dystonia but can cause serious side effects, including weakness and dysphagia. In contrast, unilateral thalamatomy shows less beneficial response but a more favorable safety profile. The lesioning of the globus pallidus was later reported as a treatment for cervical dystonia. The posteroventral medial pallidotomy targets the pallidothalamic pathway and is hypothesized to interrupt abnormal neurocircuitry involved in dystonia. Interestingly, most reports show gradual improvements over several months in dystonic patients following pallidotomy. Yoshor compared pallidotomy and thalamotomy to treat patients with different forms of intractable dystonia. The long-term outcome with pallidotomy was significantly better than thalamotomy for all patients with dystonia, including

cervical dystonia. Several reports show thalamotomy as a more effective procedure for secondary dystonia than primary dystonia.

Deep brain stimulation

Deep brain stimulation (DBS) is being used to treat several types of movement disorders. It has advantages over brain lesioning, because it is reversible and adjustable. DBS was used initially in the 1960s to control chronic pain, and decades later, it was used for various movement disorders such as Parkinson's disease, tremor, and dystonia. Several studies have shown DBS as a relatively safe procedure and a very useful therapeutic option for disabling cervical dystonia in patients who do not respond to medical therapy and botulinum toxin injection. The mechanism of action of DBS in dystonia is poorly understood. The target used for DBS in dystonia is located in the posteroventral lateral GPi, a target also used in Parkinson's disease. Several investigators are in favor of bilateral DBS over unilateral DBS because of the evidence showing bilateral basal ganglia dysfunction in patients with cervical dystonia. Postoperative improvement has been reported to be gradual, sometimes several weeks or months after surgery, but progressive and sustained in nature. Compared with DBS for other movement disorders like Parkinson's disease, initial settings require higher voltages and pulse widths, followed by gradual increment of intensity. Prospective studies have shown ongoing benefit in a gradual and exponential manner for up to 2 years.

Peripheral surgical intervention

Peripheral denervation is another surgical alternative to the treatment of patients with botulinum toxin resistant cervical dystonia. There are various types of peripheral surgical techniques, but selective peripheral denervation is the most commonly performed procedure. In 1987 and 1988, Bertrand et al. reported their observations and analysis with significant success rate in patients with cervical dystonia who underwent selective denervation. There are several well-established procedures for selective peripheral denervation such as denervation of the accessory nerve and the posterior rami of the cervical spinal nerves and more recently the levator scapulae muscle with a wide range of response rates. In an open-label study Ford et al. concluded that the best candidates for selective ramisectomy were those patients with secondary botulinum toxin failure. In contrast, Cohen et al. in a retrospective analysis concluded that outcome was not predicted by preoperative head position, severity and duration of symptoms, or response to botulinum toxin. The effects of surgical treatment are permanent and irreversible, and therefore, surgery should not be performed unless other noninvasive treatments have failed. A conservative approach with repeated procedures, if necessary, is considered to be safer and leads to fewer long-term complications.

Prognosis

Cervical dystonia can be sustained, may spread to other muscles, or may go into remission. Developing segmental or rarely generalized dystonia has been reported in some cases. Chen et al reported remission in 9.8% of their cases, but spontaneous remissions in up to 20% of patients also were observed in some reviews. In general, this is not a progressive disorder and most patients experience stabilization of symptoms within the first five years of toxin therapy.

Summary

Cervical dystonia is the most common form of focal dystonia. It is usually idiopathic and causes abnormal head movements and postures. Pain is also a common feature of CD. Once established, CD is a lifelong condition, which may occasionally spread to adjacent regions. Many symptomatic treatments are available but the safest and most effective treatment consists of local injections of botulinum toxin. Although not life-threatening, CD can have a significant impact on the quality of life.

See also: Basal Ganglia; Basal Ganglia, Functional Organization; Botulinum Toxin; Deep Brain stimulation; Dystonia; Rhizotomy.

Further Reading

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Relevant Websites

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http://www.mdvu.org – Movement Disorders Virtual University.
http://www.spasmodictorticollis.org – ST/Dystonia Group.
http://www.torticollis.org – National Spasmodic Torticollis Association.
http://www.ninds.nih.gov/disorders/dystonias – National Institute of Neurological Disorders and Stroke.

Cholinesterase Inhibitors in Parkinson's Disease

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Glossary

ADAS-cog (Alzheimer's Disease Assessment Scale-cognitive subscale) – A cognitive screening test commonly used for patients with Alzheimer's disease.
Amyloid plaques – Protein fragments including β-amyloid, accumulated to form hard, insoluble plaques typically found in Alzheimer's disease.
Butyrylcholinesterase – Enzyme involved in the hydrolysis of brain acetylcholine. Among multiple variants of the gene for BuChE, the most common variant is *BCHE*-K, which is associated with a 30% reduction in serum BuChE activity.
Cholinesterase inhibitor – Class of drugs which inhibit the hydrolysis of brain acetylcholine.
Executive functions – Loosely defined collection of cognitive processes including planning, cognitive flexibility, and abstract thinking and information processing.
Homocysteine – Amino-acid, risk factor for vascular diseases and associated with deficiency of vitamin B12 or folate, and may be toxic for dopaminergic neurons. Elevation reported in PD.
Neurofibrillary tangles – Insoluble twisted fibers found inside the brain's cells typically found in Alzheimer's disease, consisting primarily of tau protein, which is abnormal in Alzheimer's disease.
Neuropsychiatric inventory – Standardized clinical interview which rates frequency and intensity of 12 psychiatric symptoms commonly found in people with brain disease.
Pedunculopontine nucleus – Located in the brainstem, caudal to the substantia nigra, including cholinergic, glutamatergic, and GABAergic cells, commonly affected in Parkinson's disease.

The Cholinergic System in Parkinson's Disease

The cholinergic system is one of the most important modulatory neurotransmitter systems in the brain and controls the activities that depend on selective attention and cognitive processing speed as well as other cognitive functions. In addition to the defining loss of dopaminergic neurons in substantia nigra, Parkinson's disease (PD) is associated with a profound disturbance of the cholinergic system, with involvement of the basal forebrain from stage III of the Braak staging for PD. The cholinergic deficits are particularly marked in patients with dementia (PDD), where the changes are even more pronounced than in Alzheimer's disease (AD). In addition to neuronal loss in cholinergic forebrain nuclei projecting to the hippocampus and neocortex, there is loss of cholinergic neurons in the striatum and the pedunculopontine pathways that project to the thalamus. As a consequence, there are extensive reductions of cholinergic markers in neocortical regions as well as in the thalamus. Furthermore, there are important changes in cholinergic receptor systems in PD, including upregulation of muscarinic receptors and reduced nicotinic binding both in the striatum and neocortex.

These cholinergic changes are related to clinical symptoms, highlighting the clinical relevance of cholinergic changes in PD. The most important clinical correlates of cholinergic deficits in PD probably include attention and executive function, hallucinations, and depression. Whether postural instability and gait symptoms are influenced by cholinergic changes in the pedunculopontine nucleus is not yet clear.

Cholinesterase Inhibitors in PD

Given the marked cholinergic deficit and their clinical correlates, drugs that stimulate the cholinergic system are attractive candidates to improve cognition and other symptoms in PD. However, since a cholinergic–dopaminergic balance in the striatum has been proposed as critical for normal motor symptoms, cholinergic agents may worsen motor symptoms.

The first report of cholinesterase inhibitors in PD was published as early as in 1996. Seven patients with PDD received open-label treatment with tacrine 40 mg day^{-1}. Remarkable and pronounced improvements of cognition, hallucinations, and even parkinsonism were reported. Although these findings have not been replicated by independent groups, this article spurred the interest in cholinesterase inhibitors and was followed by a number of studies. The available evidence was reviewed in 2004, including 12 studies, which included one parallel group and one cross-over, placebo-controlled randomized

trial (RCT) and 10 open-label case series, the majority including patients with PDD. The majority of studies used donepezil or rivastigmine, and one used galantamine, and treatment duration was usually <12 weeks. Overall, the results were positive, with a median improvement on the Mini-Mental State Examation (MMSE) score of 2.3 points over the treatment period, and improvement of hallucinations was reported in several studies. Most studies reported no or only mild worsening of parkinsonism. The two small RCTs were conducted with donepezil, and both studies reported statistically significant effects on cognition. Due to peripheral cholinergic side effects such as nausea, vomiting, and diarrhea, 57% withdrew due to adverse events in the donepezil group in one study, and 25% during donepezil compared with none during placebo treatment in the cross-over trial.

Rivastigmine

Subsequent to this review, several other studies have been published, including the first large RCT of a cholinesterase inhibitor in PDD. In this study, more than 500 patients with PDD were included, and two-thirds were treated with rivastigmine and one-third received placebo for 24 weeks. The primary outcome measures were a cognitive rating scale, the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog), and clinical global impression of change, and both measures were significantly different between the two groups in favor of rivastigmine. A favorable response, defined a priori as any improvement on a global change scale, was noted in 41% of the rivastigmine group compared with 30% in the placebo group. Similarly, on all the secondary analyses, including neuropsychiatric symptoms, activities of daily living, and tests of executive function, rivastigmine compared significantly superior to placebo. Peripheral cholinergic side effects occurred in 29% of the rivastigmine group compared with 11% of the placebo group, but most events were mild or moderate. The proportion reporting serious adverse events were similar in both groups. Discontinuation due to adverse events occurred in 17% of the rivastigmine group compared with 8% in the placebo group. Although there were no differences in the motor subscale of the Unified Parkinson's Disease Rating Scale, suggesting no worsening of parkinsonism on rivastigmine, tremor was noted as an adverse event in 10% of the rivastigmine group compared with 4% in the placebo group (p=0.01), although tremor was severe enough to cause withdrawal of only 1.7% of patients in the rivastigmine group.

Donepezil

In addition to the two small RCT reported above, a third small placebo-controlled cross-over RCT with donepezil was reported in 2005. Donepezil was well tolerated and adverse events were usually mild. There was a nonsignificant trend towards improvement on the primary outcome measure (ADAS-cog), and significant differences in favor of donepezil were reported on global improvement and MMSE, a cognitive screening test, but not on daily functioning or psychosis.

A large, multicenter, parallel group RCT including 550 patients with PDD has been conducted, with three arms receiving placebo, donepezil 5 mg, and donepezil 10 mg, but the results have not yet been reported in full. Preliminary results were, however, reported as an abstract and poster presentation. One of the two primary outcome measures, a global impression of change scale, showed significant differences between the groups in favor of donepezil. However, the cognitive primary measure, ADAS-cog, showed only a nonsignificant, dose-dependent difference in favor of donepezil. Of the secondary analyses, MMSE, but not activities of daily living or neuropsychiatric symptoms, showed significant differences between the groups.

Which Symptoms Improve?

Improved cognition has been reported in most studies, including most of the RCTs, but little is known regarding the effect of the different cognitive domains. Executive functioning and attention improved on rivastigmine administration in the large RCT, and attention improved in an open-label study with donepezil. Improvement of activities of daily living was also reported in the large rivastigmine study. Similarly, improvement of neuropsychiatric symptoms has been reported in several studies. In the rivastigmine RCT, improvement was reported on the total Neuropsychiatric Inventory Score, but no information on specific symptoms was provided. Several of the open studies have reported improvement on visual hallucinations, including patients unresponsive to atypical antipsychotics. Psychotic symptoms are common in PD, and have important clinical implications such as caregiver burden, mortality, more rapid cognitive decline, and institutionalization. Currently, there is evidence of antipsychotic effect in PD only for clozapine. Given the potential of antipsychotic agents to worsen motor symptoms and cognition in PD, and in particular, PDD, the risk of severe neuroleptic sensitivity reactions, as well as increased risk for cerebrovcascular incidents and mortality, there is therefore a clear need for controlled studies to explore whether cholinesterase inhibitors, which have a better safety profile, can improve visual hallucinations and other psychotic symptoms in PD.

It is not known how long the treatment effect of cholinesterase inhibitors will continue in PD. The duration of the RCTs have been up to 24 weeks, and an extension study showed that the effect and safety profile of rivastigmine could be sustained for a further 24 weeks.

Sudden withdrawal seems to be detrimental, at least of donepezil, producing acute cognitive and behavioral decline. Although recommencement on donepezil appears to reverse this deterioration, abrupt discontinuation of cholinesterase inhibitors should probably not be made in this population.

Which Patients Improve?

The response to cholinesterase inhibitor treatment varies. Some patients have a marked response whereas others have no or only marginal response. However, since cognitive decline is progressive in PD, even stabilization of cognitive functioning should be considered an effect, although it is difficult to ascertain in individual patients due to the variation in rate of cognitive decline. Post hoc analyses of the large rivastigmine RCT have attempted to identify which patients would respond better to rivastigmine. In one study, exploring the response to rivastigmine and placebo in PDD patients with and without hallucinations, the effect was most pronounced in the group with hallucinations, and this group also had a more rapid cognitive decline on placebo. In another report, patients with hyperhomocysteinemia had a better response than those with normal or low homocysteine. In dementia with Lewy bodies (DLB), a syndrome with clinical and pathological similarities with PDD. There is preliminary evidence to suggest that patients with the butyrylcholinesterase wild-type genotype may have a preferable treatment response to rivastigmine than those with the K-variant, which is associated with reduced activity of the enzyme, but this has not yet been reported in PDD.

Mechanisms of Effect

Cholinesterase inhibitors, probably, exert their effect by amplifying the natural spatial and temporal pattern of acetylcholine release, leading to transient, symptomatic improvement but not affecting the underlying disease process. The physiologically relevant effect of cholinesterase inhibitors has been convincingly demonstrated in terms of increased perfusion in bilateral cingulate and frontal regions in both PD and AD. There are marked pharmacodynamic and pharmacokinetic differences between the three available cholinesterase inhibitors. Both the nicitonic agonist effect of galantamine and the additional inhibition of butyrylcholinesterase may have clinical implications in treating cognitive impairment in PD, although convincing comparative studies have not yet been reported.

However, there is evidence that cholinergic drugs may also influence the underlying disease mechanisms and improve neuronal survival. Patients with PD who had received chronic treatment with antimuscarinic drugs during life had more severe amyloid plaques and neurofibrillary tangles than those who had not been treated with such drugs, despite being comparable for age and disease duration. The resulting hypothesis that cholinesterase inhibitors might, therefore, reduce the severity of Alzheimer-type pathology was recently supported in a study of patients with DLB. In patients with DLB, treatment with cholinesterase inhibitors was associated with less severe amyloid deposition. Similarly, in AD, donepezil treatment has been found to be associated with slower progression of hippocampal atrophy. A potential neuroprotective effect of cholinesterase inhibitors is the stimulation of muscarinic receptors, which have been shown to influence the processing of amlyoid. In one study, this hypothesis was supported since (123)I-QNB uptake, a measure of postsynaptic M1-density, which has been linked with neuroprotection in AD is better preserved in AD patients on cholinergic treatment than on placebo. Finally, another potential mechanism for a disease modifying effect is the preliminary finding that cholinergic loss is associated with the loss of endogeneous stem cells, the brain's own capacity for neuroprotection and repair, and thus, it is possible that treatment with cholinesterase inhibitors may increase the number and activity of endogeneous stem cells.

Safety

Overall, the safety profile of cholinesterase inhibitors in PD seems to be acceptable. There is a relatively high proportion with troublesome peripheral cholinergic side effects, as in other patient groups receiving cholinergic drugs. In addition, there is a risk for disease-related adverse events. Although, overall, most studies report no worsening on rating scales of parkinsonism, there is a slightly increased risk for worsening of tremor during treatment with cholinesterase inhibitors. However, in a detailed analysis, it was found that the worsening is mild and transient in the titration period. In a 24-week extension observation study of the rivastigmine RCT, there was no evidence of adverse long-term motor outcomes. Similar findings of mildly increased tremor on rivastigmine in PD were also observed in a detailed assessment where tremor amplitude was also measured using accelerometers. No clinically significant drug–drug interactions between donepezil and levodopa/carbidopa were observed at steady state. Autonomic failure is common in PDD, and may be particularly sensitive to the cardiovascular effects of donepezil, such as reduction in heart-rate variability. An increase in falls and autonomic dysfunction amongst DLB patients treated with donepezil has been reported.

Summary and Discussion

There is convincing evidence that treatment with cholinesterase inhibitors can benefit some patients with PDD to a clinically meaningful degree. This is particularly true for rivastigmine, where a large RCT over 24 weeks showed significant effect on all primary and secondary outcome

measures, and which has been approved for the treatment of PDD in Europe and the United States. The novel patch treatment has been shown to have similar therapeutic effect but with improved tolerability compared with tablets in AD, but has not yet been tested in PD.

Several guidelines/recommendations on the use of cholinesterase inhibitors in PDD have been reported. A joint task force of the European Federation of Neurological Societies (EFNS) and the European section of the Movement Disorder Society (MDS) classified clinical evidence with rivastigmine as class I and donepezil as class II, although they acknowledged that improvement was modest. Similarly, a Cochrane review identified the rivastigmine trial as the sole study that met inclusion criteria, and concluded that rivastigmine appears to improve cognition and activities of daily living in patients with PDD, and that clinically meaningful benefit can be achieved in about 15% of cases. However, the need for more studies utilizing pragmatic measures such as time to residential care facility and both patient and carer quality of life assessments was underlined.

See also: Acetylcholine; Alzheimer's Disease and Parkinsonism; Cognitive Assessments and Parkinson's Disease; Dementia with Lewy Bodies; Dementia, Movement Disorders; Executive Dysfunction.

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Chorea

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Glossary

Acanthocytes – Contracted erythrocytes with thorny protrusions.
Chorea – A hyperkinetic movement disorder characterized by rapid, irregular movements of different body parts.
Neuroacanthocytosis – Neurological conditions in which there are abnormalities of red blood cell membranes, resulting in thorny protrusions.

Definition

Chorea, although technically derived from the Greek word for 'dance,' is used to describe an involuntary movement disorder characterized by irregular movements, which rapidly flit from region to region in an irregular pattern. The use of videography to document movement disorders has enabled a standardization of the use of such descriptive terms.

Pathogenesis

Chorea appears the same whether it is the result of a metabolic disturbance which disrupts neurotransmission in the putamen, neurodegeneration affecting the same structure, or a stroke affecting the subthalamic nucleus.

Despite its limitations, the model developed by Albin, Penny, and Young in 1989 can still be used to understand many of the pathophysiological aspects of movement disorders, and may be applied to chorea. In general, the direct pathway is responsible for the activation of a motor program following an input from the motor cortex, while the indirect pathway focuses and selects the

movements. This process most likely happens at several levels of the basal ganglia, including the caudate/putamen, subthalamic nucleus (STN), and the globus pallidus internal segment (GPi), and signal selection probably involves temporal coding in addition to anatomical interactions. Disruption of the pathway at several sites, for example, putamen and STN, may result in similar movements. According to the model, chorea arises when there is a decrease in the activity of the indirect pathway from the caudate/putamen to the external segment of the globus pallidus (GPe), resulting in overactivity of this nucleus. This inhibits its projection targets, the STN, the GPi, and the substantia nigra pars reticulata (SNr), which decrease their activity. This correlates with the fact that lesions of the STN are also well known to cause chorea (hemiballismus). According to this model, the excess involuntary movements are due to a decrease in the inputs from the STN to the GPi (the indirect pathway), causing the loss of specificity of motor signals which have arrived from the striatum via the direct pathway. Chorea may also be due to an increase in the activity of the direct pathway as may happen with L-DOPA-induced dyskinesias in Parkinson's disease, which are a form of chorea. Consequently, the inhibited GPi/SNr has decreased inhibition of the motor thalamus, and an increased signal is conveyed to the motor cortex. The model fits well with some disorders, for example, Huntington's disease (HD), in which the enkephalinergic neurons of the indirect pathway typically degenerate first, causing a decrease in the activity of this pathway, and with hemiballismus due to STN lesions. For other conditions, the model fits less well.

Clinical Features and Diagnostic Criteria

Chorea may be due to a very large number of neurological disorders, and it may often be part of a mixed movement disorder syndrome, coexisting in particular with dystonia. The term 'choreoathetosis' is not used as much at present as in previous years, but refers to a writhing movement with dystonia and choreiform components.

Etiologies of chorea include structural, metabolic, pharmacological, infectious, and inherited neurodegenerative causes. The phenomenology of chorea does not often give clues to the underlying diagnosis, as much as the features of the family and clinical history, and medical and neurological examination. Despite an extensive work-up, some patients may remain undiagnosed.

Differential Diagnosis

A number of features may provide diagnostic clues in the patient with chorea.

Family History

If positive, a family history may be extremely helpful, and should be taken carefully and in great detail, documenting all family members for whom the patient can provide any information. Any possible neurological or psychiatric disorder may be of significance. Autosomal dominant inheritance may be obscured by the unavailability of parental medical history due to various factors such as nonpaternity, or by parental death before disease onset. This is especially true for trinucleotide repeat diseases in which anticipation is found, characterized by younger age of onset for successive generations. Small family sizes may mean that an autosomal recessive pattern is not apparent. X-linked recessive disorders are suggested by the absence of male–male transmission, and when the unaffected mother of a male proband has affected male relatives. Mitochondrial disorders may be maternally inherited, but are often due to de novo mutations.

The absence of a family history does not rule out a genetic disorder. In addition to the points listed above, adoption may be an issue.

The ethnic background may be informative. Huntington's disease-like 2 (HDL2) has been reported to date almost exclusively in patients of African ancestry, although in some cases, the ancestry can be quite obscure and only revealed by haplotype analysis. One patient of Middle Eastern ancestry has been reported.

A couple of disorders appear to be more common in Japanese populations, likely due to a founder effect. Chorea-acanthocytosis (ChAc) appears to be of increased frequency in Japan, although it has been reported in most ethnic groups to date. Dentatorubropallidoluysian atrophy (DRPLA) has been found in only a very small number of families outside Japan.

Almost any movement disorder developing in a person of Filipino heritage raises the question of Lubag – X-linked parkinsonism-dystonia (DYT3) – which can present with a range of phenotypes, and can manifest in female carriers.

Time Course

The time course of the illness can be interpreted by an approach similar to the one used for other neurological conditions. A sudden onset indicates a vascular event, either ischemic stroke, or hemorrhage. A subacute onset, over weeks or months, may suggest a slowly growing mass lesion, particularly in the presence of localizing signs and asymmetry, a relationship to an underlying medical condition resulting in a metabolic condition such as hyperthyroidism or paraneoplastic syndrome, or prion disease.

A chronic and slowly progressive time course over years raises the likelihood of a neurodegenerative process. A chronic, nonprogressive course, following an acute or subacute onset, may suggest that the chorea is due to a medication, or alternatively, that it is benign hereditary chorea.

Episodic involuntary movements, especially starting in childhood, are characteristic of the paroxysmal dyskinesias, and the diagnosis is suggested by precipitating factors such as caffeine, alcohol, fatigue, movement, or stress.

Phenomenology

As mentioned earlier, the phenomenology of the chorea alone is rarely informative. One exception to this is when the chorea is purely unilateral, indicating either a structural lesion or that it is due to nonketotic hyperglycemia in noninsulin-dependent diabetes. The other situation is when the movements are more severe of the mouth, tongue, and lower face. These are often seen in tardive dyskinesia, due to neuroleptic use: in children with pantothenate kinase-associated neurodegeneration (PKAN); in boys with Lesch–Nyhan syndrome; and in the presence of self-mutilating tongue- and lip-biting, and specifically eating-induced dystonic tongue protrusion, in autosomal recessive ChAc.

Exacerbating/Relieving Factors

Episodic chorea following specific precipitants suggests one of the forms of paroxysmal dyskinesias. The precipitating factors, which may include movement, alcohol, caffeine, prolonged exertion, or fatigue, are informative in classification, as are the characteristics of the movements and any interictal features, such as spasticity or ataxia. As genetic linkage is performed in affected families and gene mutations are identified, it is becoming possible to distinguish these disorders on molecular grounds, and many appear to be due to mutations of ion channels.

Other Medical Conditions

It is important to note the presence of any other medical conditions, by history and by clinical examination, and medications which are taken for them.

The most common cause of chorea in childhood is Sydenham's chorea, which may follow pharyngitis due to a streptococcal infection. This diagnosis can be confirmed by the presence of antistreptolysin O antibodies, which may also interact with neuronal components of the putamen. This disorder is self-limiting, but the movements can be quite violent and bizarre and disabling, and require aggressive management.

Several endocrine disorders may be associated with chorea. One of the most common situations, in which typically unilateral chorea of relatively sudden onset is seen, is diabetic nonketotic hyperglycemia. It is not known why the chorea is asymmetric, but T2-weighted MRI shows oedema in the contralateral putamen, suggestive of inflammation and breakdown of the blood–brain barrier.

Hyperthyroidism may occasionally cause chorea. Hyperparathyroidism and other causes of disrupted calcium metabolism may result in the radiological finding of intracerebral calcium deposition (known by the nonspecific term of Fahr's disease). This is usually prominent in the basal ganglia and dentate nucleus of the cerebellum, and causes a variety of movement disorders.

Antibasal ganglia antibodies (whose target is not yet well defined) are likely to be the cause of chorea in several autoimmune disorders. These include antiphospholipid antibody syndrome, systemic lupus erythematosus, and systemic sclerosis.

A subacute time course, with onset over weeks, correlates with the diagnosis of a paraneoplastic syndrome. Chorea has been associated with renal, small-cell lung, and breast cancer, and with Hodgkin's and non-Hodgkin's lymphoma.

A history of gastrointestinal disturbance may indicate coeliac disease. The relationship of this disorder to several neurological findings has been postulated and debated, but there is evidence for chorea, ataxia, and peripheral neuropathy, which may in some cases respond to a gluten-free diet.

Chorea gravidarum should be considered in women in whom pregnancy is a possibility. The etiology may be related to the sensitization of basal ganglia dopamine receptors by estrogens, but antibasal ganglia antibodies have also been reported in this condition. The use of estrogens, either in the form of the contraceptive pill, or a hormone replacement therapy, has also been reported to cause chorea.

Medications

One of the commonest medication-related causes of chorea is L-DOPA in Parkinson's disease. Although the phenomenon is known as 'L-DOPA-induced dyskinesias,' the movements are typically choreiform. Dystonia can also occur, or a mixture of the two types of movements. These may be seen either at peak effect of the medication dose, or when the medication is taking effect or wearing off ('on-off' dyskinesias). These more often involve the legs rather than the arms or trunk. Orofacial chorea as an effect of L-DOPA is seen more often with the atypical parkinsonisms, such as multiple system atrophy or progressive supranuclear palsy.

Stimulant drugs of abuse which release dopamine or block its reuptake, specifically cocaine, especially 'crack' cocaine, and amphetamine, can cause chorea.

Chorea has also been reported with the use of various anticonvulsant medications, lithium, and other stimulants.

Estrogens, either in the form of oral contraceptives or hormone replacement therapy, have been reported to cause chorea, probably by a similar mechanism to that of *chorea gravidarum*, possibly involving an increased sensitivity of dopamine receptors.

Another very common form of chorea is tardive dyskinesia (TD). Again, the terminology is imprecise, but it is typically used to refer to choreiform movements. Tardive dystonia is not uncommon, and the fixed postures and action-induced overflow of movements seen in this condition are often more disabling than the fluid movements of tardive chorea. While a minimum total period of exposure to the causative agent of 3 months is usually accepted, occasionally cases may be seen where a briefer exposure appears responsible. The classically responsible agents are the typical neuroleptics, but there have been case reports of TD following the use of most of the newer atypical antipsychotics. As the temporal relationship is more poorly defined than one of a direct medication side-effect, causality can be harder to prove. Involuntary movements may appear or worsen on withdrawal of the offending medication, or following the use of a cocktail of possible agents. TD is reported to have developed following the use of anticonvulsants, lithium, selective serotonin reuptake inhibitors, and others.

The movements of TD typically involve the lower face and tongue, and are usually not distressing to patients. Similar movements have been reported in never-treated elderly schizophrenics and edentulous patients. If the upper face is involved, the movements are typically dystonic – blepharospasm; a variety of jaw, lingual, pharyngeal, and laryngeal tardive dystonias, including spasmodic dysphonia can also be seen.

The use of neuroleptics for the psychiatric symptoms seen in many of the basal ganglia neurodegenerative disorders may mask appreciation of movement disorder due to these etiologies (e.g., HD, HDL2, ChAc, McLeod syndrome); thus the development of new neurological features in a psychiatric patient should be carefully evaluated.

Other Neurological Features

Any asymmetry or localizing signs on neurological examination indicate a structural intracerebral lesion, or nonketotic hyperglycemia.

Psychiatric disease or personality change may be the first sign of a basal ganglia neurodegenerative disorder such as HD. Slowly progressive cognitive impairment, especially subcortical dementia, often with frontal signs, such as abulia or disinhibition, may also be due to the involvement of the basal ganglia.

Chorea may be seen as either a presenting or secondary feature in the inherited ataxias, both autosomal dominant and recessive. The presence of ataxia, hyper- or hyporeflexia, eye movement abnormalities, or sensory changes may be informative, particularly in the presence of a family history. Chorea has been reported in spinocerebellar ataxias 1, 2, 3, and 17; dentatorubropallidoluysian atrophy; Friedreich's ataxia, and the ataxias with oculomotor apraxia.

Decreased reflexes also suggest the neuroacanthocytosis (NA) syndromes of autosomal recessive ChAc, or X-linked McLeod syndrome.

The presence of seizures along with chorea may be seen in young-onset HD (although this is usually parkinsonian in phenotype), in paroxysmal kinesogenic dyskinesia, and in approximately 50% of patients with McLeod syndrome or ChAc.

Diagnostic Work-Up

Laboratory Work-Up

The diagnostic work-up (**Table 1**) will be guided by the clinical presentation, age of onset, time course, family history, etc., of the symptoms.

Routine blood chemistry may demonstrate electrolyte abnormalities, including calcium, which may cause chorea. Hyperglycemia in noninsulin-dependent diabetics with nonketotic hyperglycemia is a well-recognized cause, as mentioned earlier.

It is important to assay levels of liver enzymes, including γ-glutaryl transferase in addition to transaminases, total and direct bilirubin, and lactate dehydrogenase. The presence of liver disease may indicate Wilson's disease (WD), one of the few treatable neurodegenerative conditions, which should be considered and excluded in any unusual presentation of a movement disorder. Presentation of WD with chorea has not been reported, although it may be part of a mixed movement disorder phenotype, characterized by facial dystonia (risus sardonicus) and a flapping arm tremor.

If WD has been excluded as the cause of elevated liver enzymes, this finding strongly suggests one of the NA syndromes, ChAc or McLeod syndrome.

McLeod syndrome can be diagnosed by determining antigenicity of red blood cells to a panel of 23 antibodies to the Kell system, and to the XK antigen site known as Kx. This testing is usually performed in regional blood centers; most smaller blood centers will not have the full panel of antibodies. A request should be made to 'exclude McLeod phenotype' (which refers to the erythrocyte antigen profile) and not just to test for Kell, as this is nonspecific. Testing for mutations of the causative XK gene can be performed on a research basis, but is not required for diagnosis.

ChAc can at present be diagnosed only on a research basis by assaying levels of the affected protein, chorein,

Table 1 Laboratory evaluation of the patient with chorea

Test	*Possible diagnosis*
Blood chemistry	Hyper/hypoglycemia; hyper/hyponatremia; hypomagnesemia hyper/hypocalcemia; Lesch-Nyhan syndrome
CBC with smear	Neuroacanthocytosis syndrome (ChAc, MLS, HDL2, PKAN)
Liver function tests	Wilson's disease; ChAc; MLS
Thyroid function tests	Hypo-/hyper-thyroidism
Parathyroid levels	Hypo-/hyper-parathyroidism
Pregnancy test	Chorea gravidarum
Creatine phosphokinase	ChAc; MLS
Ceruloplasmin	Wilson's disease; aceruloplasminemia
Ferritin	Neuroferritinopathy
Sedimentation rate, antinuclear antibodies	Autoimmune disease
Lupus anticoagulant	Systemic lupus erythematosus
Antiphospholipid antibodies	Antiphospholipid syndrome
ASO titres	Sydenham's chorea
HIV test	HIV/AIDS-related infection
Anti-gliadin antibodies	Coeliac disease
Antineuronal antibodies (anti-CRMP-5, anti-Hu, anti-Yo)	Paraneoplastic syndromes
Erythrocyte Kx and Kell antigens	MLS
Genetic testing	As per test
MRI/CT + contrast	Structural lesions; iron deposition, calcification
EEG	Seizure-related syndrome; Creutzfeldt-Jakob disease
Lumbar puncture	Creutzfeldt-Jakob disease; chronic infection
Urinary and serum organic and amino acids	Organic/amino acidopathies

Abbreviations; ChAc = chorea-acanthocytosis; HDL2 = Huntington's disease-like 2; MLS = McLeod syndrome; PKAN = pantothenate kinase-associated neurodegeneration.

in peripheral blood. The responsible gene, *VPS13A,* consists of 73 exons with no particular hot-spot for mutations, thus screening for mutations is not practical, and is only performed on a research basis.

A peripheral blood smear should be examined for acanthocytes; however, their absence does not exclude the diagnosis of an NA syndrome, as their presence appears variable. If the clinical phenotype is suggestive of this diagnosis, and especially if there are elevated liver enzymes or creatine kinase, the appropriate protein-directed diagnostic tests should be pursued. CK elevation is very strongly suggestive of an NA syndrome, and is not attributable to chorea, as it is not seen in HD.

The sensitivity of the peripheral blood smear to acanthocytosis can be increased by incubating the fresh blood for 30–120 min on a shaker with normal saline containing 10 IU ml^{-1} heparin. At least five fields should be examined using phase-contrast microscopy, and over 6.3% acanthocytes is pathological. Care should be taken to distinguish acanthocytes, which should be contracted and irregular, with echinocytes, which have smaller and more regular protrusions. Electron microscopy of glutaraldehyde-fixed blood is confirmative. Acanthocytes are found in approximately 10% of patients with PKAN and with HDL2, which may confound the diagnosis.

Ceruloplasmin levels are reduced in WD, and often absent in aceruloplasminemia.

Low ferritin is suggestive of neuroferritinopathy, but can be elevated into the normal range in premenopausal women.

If the time course of the presentation is relatively acute or subacute, a paraneoplastic syndrome should be considered. Serum and cerebrospinal fluid (CSF) should be tested for anti-Hu, anti-Yo, and anti-CRMP-5 antibodies which have, to date, been associated with chorea. As paraneoplastic syndromes are often associated with occult malignancies, full-body imaging should be performed.

Lumbar puncture should be performed if there is a suspicion of an infectious encephalitis, or if the time course of progression over weeks or months suggests Creutzfeldt–Jakob disease (CJD). A positive test for 14-3-3 protein is highly suggestive of this diagnosis in the appropriate clinical context (although it may also be seen in more chronic neurodegenerative disorders).

Children with acute onset of chorea or a mixed hyperkinetic movement disorder should be tested for Sydenham's chorea by checking for antistreptolysin O antibodies.

Apart from this diagnosis, chorea in children and infants is most likely due to inherited metabolic disorders. Glutaric aciduria is a disorder which may present in infants with an acute deterioration and encephalopathy, along with hyperkinetic movements. The specific presentation and age will guide the testing, which should include serum and urinary organic and amino acid testing, assay of lysosomal enzymes and lactate and pyruvate levels, which if elevated, should lead to screening for mitochondrial mutations.

Genetic Testing

Genetic testing should always be preceded by thorough discussion of the possible ramifications of both positive and negative test results, ideally by a qualified genetic counselor. A positive result for an autosomal dominantly-inherited disease such as HD has potentially life-changing implications for the patient's parents, siblings, and children.

Genetic testing for HD is readily available, and is usually the first genetic test to be done once the other etiologies have been excluded. As mentioned earlier, a negative family history should not preclude such testing, although in young patients whose parents' medical

histories are fully known, the question of nonpaternity may be raised by a positive result.

Depending upon the clinical phenotype and other factors such as ethnic background, genetic testing may be considered for autosomal dominant and recessive ataxias, HDL2, and DRPLA. Information on the current availability of the tests for clinical and research purposes is available at http://www.geneclinics.org/.

Neuroimaging

All patients with chorea, with the exception of those whose symptoms are clearly medication-related, merit neuroimaging. The procedure of choice is an MRI scan with gadolinium contrast, to clearly identify any vascular or other lesions and whether there may be breakdown of the blood–brain barrier. If possible, a gradient echo sequence should be requested to increase sensitivity to iron deposition.

Atrophy of the caudate nuclei may be interpreted as being consistent with HD, but is nonspecific and can be seen in a number of neurodegenerative conditions such as the NA syndromes.

Iron deposition in the basal ganglia indicates one of the conditions grouped under the term 'neurodegeneration with brain iron accumulation' (NBIA). Probably the commonest and the best-known of these is PKAN, in which the classic 'eye-of-the-tiger' sign was first reported. The particular vulnerability of the basal ganglia to metabolic disruptions may be due to high metabolic demands of these regions. In PKAN, this is due to the deficiency of acetylcoenzyme A synthesis. Other conditions in which iron deposition is seen are aceruloplasminemia (due to homozygous mutations of the ceruloplasmin gene) and neuroferritinopathy (due to heterozygous mutations of the gene for ferritin light chain). The rare Karak syndrome has been reported in a single family and is due to the same mutation of *PLA2G6* which causes neuroaxonal dystrophy.

Symmetric necrotic lesions of the basal ganglia in infancy and childhood suggest a mitochondrial disorder such as Leigh's syndrome. These can also be seen following an infectious illness, specifically *mycoplasma pneumoniae* infection, or parvovirus.

Functional imaging of cerebral blood flow using radionuclide tracers is not currently used on a diagnostic basis in chorea. Both hyper- and hypometabolic states have been found with various diagnoses.

Neurophysiological Testing

Electroencephalography can be informative, both in indicating whether there is global cerebral dysfunction, and whether there are focal abnormalities, either contributing to the movement disorder or as a secondary symptom, for example in young-onset HD, or one of the NA syndromes. In CJD, periodic lateralizing epileptic discharges (PLEDs) support the diagnosis.

Electromyography and nerve conduction studies can define whether there is a peripheral neuropathy, as can be seen in some of the inherited ataxias and the NA syndromes.

Management

If possible, treatment of chorea should be directed first at the underlying cause. If this is not possible, as for many of the neurodegenerative conditions, it should be determined whether chorea is disabling, or whether other aspects of the condition are more functionally limiting. It is vital to treat psychiatric symptoms, particularly depression in HD, in which suicide is common. When the involuntary movements of chorea are mild or moderate, they may not interfere with functioning.

Symptomatic medical treatment is usually aimed at reducing dopaminergic neurotransmission with dopamine-blocking or -depleting agents. Atypical neuroleptics are used in preference to typical neuroleptics, in light of the potential for tardive dyskinesia; however, the higher dopamine D2 receptor blocking activity of the classic neuroleptics may still be important. Tetrabenazine depletes dopamine from presynaptic terminals and may have some weaker blocking activity (although TD has never been reported with this agent). Patients taking this medication should be carefully monitored for parkinsonism and depression.

Patients may benefit from anticonvulsants such as valproic acid, carbamazepine, and levetiracetam, presumably through a membrane-stabilizing effect or an effect upon neurotransmitter release. Occasionally these medications may worsen involuntary movements. Therefore treatment requires individualization.

The glutamate NMDA-receptor antagonists, amantadine and riluzole, may be tried. These drugs presumably work by blocking glutamate overactivity of corticostriatal projections.

A small number of patients with chorea of various etiologies has been reported to respond to deep brain stimulation. However, the choice of targets has varied and includes the internal segment of the globus pallidus, the motor nuclei of the thalamus, and the subthalamic nucleus. In addition, the optimal frequency remains a subject of debate, as specific benefits have been shown at moderate (60 Hz) and high (130 Hz) frequencies.

There are reports of promising early results following transplantation therapies in HD; however, these will not halt disease progression.

Of most practical help to many patients and families are paramedical therapies. A team approach can be invaluable in identifying problems and developing

strategies to address them while empowering the patient. Early involvement of physical and occupational therapists is vital to maintain mobility and independence in activities of daily living. Speech and swallowing are often involved in the neurodegenerative disorders. Maintenance of communication is essential, as is nutritional evaluation to prevent weight loss.

Advances in molecular medicine have made it possible to diagnose many patients whose diseases were previously obscure. Correct diagnosis is of course essential for genetic counseling.

See also: Chorea–acanthocytosis; Chorea Gravidarum; Choreiform Disorders; Huntington's Disease-like 2; Huntington's Disease; Neuroacanthocytosis Syndromes.

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Chorea–acanthocytosis

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Glossary

Acanthocytes – Contracted erythrocytes with thorny protrusions.
Chorea–acanthocytosis – An autosomal recessive neurodegenerative disease characterized by involuntary movements (chorea) and acanthocytosis.
Neuroacanthocytosis – A term for the group of neurological conditions in which there are abnormalities of red blood cell membranes resulting in thorny protrusions.

Definition

Chorea–acanthocytosis (ChAc) is one of the core neuroacanthocytosis syndromes (along with the X-linked McLeod syndrome). ChAc is inherited in an autosomal recessive manner, and is due to mutations of the gene *VPS13A* located on 9q21 which encodes for the protein chorein.

Acanthocytosis, the appearance of contracted red blood cells (RBCs) with thorny protrusions, is typically, but not invariably, present and is not required to make the diagnosis. The basis for this abnormality of RBC membrane structure is not well understood. The presence of elevated creatine kinase (CK) or liver enzymes supports the diagnosis and is more informative than the acanthocytosis in suggesting the diagnosis.

The neurologic features developed in young adulthood, but may be predated by the appearance of a variable spectrum of cognitive and psychiatric symptoms in late adolescence.

Pathogenesis

The relationship of decreased or absent chorein to neurodegeneration of the central and peripheral nervous systems is not known. Chorein is widely expressed throughout the brain and various internal organs. Its function is not known, but it may be involved in protein sorting and membrane structure. All mutations to date appear to result in total absence or markedly decreased levels of chorein; thus there do not appear to be any partial manifestations of the disease.

Neurodegeneration affects predominantly the caudate nucleus, putamen, and globus pallidus, in addition to the thalamus and substantia nigra. Neuropathological findings consist of gliosis of these regions, but no inclusion bodies of any nature have been detected. Striking atrophy of the head of the caudate nucleus, found on volumetric neuroimaging studies, may correspond with the development of obsessive–compulsive symptoms.

Epidemiology

ChAc is very rare; however, there are likely to be a number of undiagnosed cases. As of 2008, about 1000 cases have been identified worldwide. Cases have been reported from many countries, from many ethnic backgrounds; however, the incidence is remarkably high in Japan, suggesting a founder effect. There may also be increased incidence in Brazil. Clusters of cases may be found in isolated areas with a high degree of consanguinity, as has been reported in a French-Canadian community.

Clinical Features and Diagnostic Criteria

The neurological features of ChAc typically develop in the 20s–30s with slow progression over the next 2–3 decades. It is increasingly recognized that symptoms of the obsessive–compulsive spectrum, including tic disorders, may be the initial presentation, particularly in those developing the disease in adolescence. Severe self-mutilating lip and tongue biting is typical of ChAc. Other features of self-mutilation, such as finger biting and head scratching suggest a behavioral compulsion as the etiology of these features, rather than the movement disorder.

The progression of the cognitive impairment and the development of the movement disorder, which is often initially attributed to neuroleptics, may suggest the diagnosis in patients with psychiatric disease. Orofaciolingual dystonia can be quite severe. Dystonic protrusion of the tongue induced by eating is often prominent and extremely disabling. In addition to this, a variety of movement disorders may be seen, including chorea and parkinsonism. The gait can appear quite bizarre due to truncal dystonia and leg buckling.

Seizures are found in approximately 50% of patients and are often of temporal lobe origin. These may predate the appearance of other features by as much as a decade.

The development of peripheral sensorimotor neuropathy and areflexia supports the diagnosis of ChAc. The neuropathy, which along with the myopathy causes hypotonia and peripheral weakness, is often more debilitating than the involuntary movements. Nerve conduction studies may show either axonal loss with electromyographic findings of myopathy or may be normal.

Hepatosplenomegaly may be seen, although less frequently than in McLeod syndrome. Unlike McLeod syndrome, cardiac involvement is extremely unusual; however, autonomic dysfunction has occasionally been reported and may be a cause of cardiac arrhythmias and sudden death.

Differential Diagnosis

The differential diagnosis of ChAc depends upon the presentation. The syndrome of a movement disorder, peripheral neuropathy, seizures, and cognitive changes is similar only to X-linked McLeod syndrome; however, the presence of the self-mutilating lip and tongue biting is very strongly suggestive of ChAc. Self-mutilation of this nature may be seen in boys with Lesch–Nyhan syndrome; however, in these cases, the age of onset is very much younger. Patients with pantothenate kinase-associated neurodegeneration may develop lingual dystonia, but this diagnosis will be indicated by the finding of iron deposition in the basal ganglia ('eye-of-the-tiger') and confirmed by genetic testing.

The initial work-up may be that of a peripheral neuropathy or myopathy, especially if CK is elevated. Recognition of the syndrome may avoid the need for invasive and nondiagnostic tests such as muscle or bone marrow biopsy. Similarly, abnormalities of liver enzymes may prompt the performance of an unnecessary liver biopsy. If liver enzymes are elevated, Wilson's disease should be excluded as this is currently the only treatable neurodegenerative condition.

The involvement of siblings of both genders may indicate an autosomal recessive disorder, particularly in consanguineous families. Huntington's disease should be excluded, especially if there is a possibility of nonpaternity. In highly consanguineous populations, inheritance may appear pseudodominant. Autosomal dominant ChAc has been reported in Japan, but remains to be fully confirmed.

Diagnostic Work-up

ChAc may be suggested if acanthocytosis is found on peripheral blood smear (**Figure 1**). Sensitivity can be increased by incubating the RBCs with an equal volume of normal saline containing 10 μl ml^{-1} heparin for 30–120 min on a shaker. Electron microscopy of glutaraldehyde-fixed RBCs is confirmatory. However, the presence of acanthocytes in the neuroacanthocytosis syndromes is

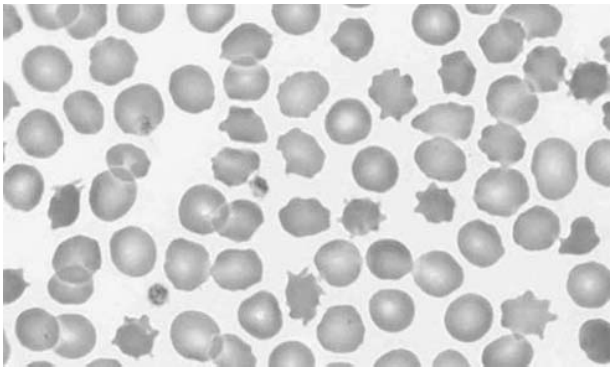

Figure 1 Acanthocytosis on peripheral blood smear. Courtesy of Dr. Hans H. Jung. Reprinted from Danek A and Walker RH (2005) Neuroacanthocytosis. *Current opinion in Neurology* 18(4): 386–392. Philadelphia, PA: Lippincott, Williams and Wilkins, with permission from Lippincott, Williams and Wilkins.

not constant, for reasons which are not well understood, and their absence does not preclude the diagnosis.

Elevated CK, often into the thousands, is very suggestive of either ChAc or McLeod syndromes.

Neuroimaging is often reported as being consistent with the diagnosis of Huntington's disease, with bilateral atrophy of the caudate nuclei.

The diagnosis of ChAc is made by performance of Western blot for chorein on a sample of peripheral blood. If no band for chorein is detected on the gel, the diagnosis is confirmed. This test is at present available on a research basis (see below for website). The diagnosis can be confirmed by sequencing of *VPS13A*; however, this gene is very large, with 73 exons and a variety of mutations have been found, making genetic screening challenging.

Electroencephalography may be helpful if seizures are a feature.

Management

Management is at present purely symptomatic. Self-mutilating lip and tongue biting can sometimes be managed by mouth guards. Feeding-induced tongue protrusion dystonia may respond to injections of botulinum toxin into the genioglossus. Chorea does not typically impair function as much as focal dystonia and peripheral neuromuscular abnormalities. Psychiatric and cognitive symptoms should be treated appropriately.

Results of deep brain stimulation have been variable, and the optimal site and stimulation parameters remain to be determined; however, low frequency stimulation of the globus pallidus pars interna may be beneficial.

Seizures usually respond to standard anticonvulsants, although lamotrigine and carbamazepine have been reported to worsen the involuntary movements.

Evaluation by a speech therapist is essential to minimize problems due to dysphagia and weight loss. Physical and occupational therapists can assist with difficulties with gait, balance, and activities of daily living.

Prognosis

ChAc is slowly progressive and ultimately fatal. Sudden death may be due to seizure, or possibly autonomic dysfunction, but there may be gradually progressive, generalized debility, as seen in Huntington's or Parkinson's disease, with patients succumbing to aspiration pneumonia or other systemic infections.

See also: Chorea; Choreiform Disorders; McLeod Syndrome; Neuroacanthocytosis Syndromes.

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Chorea Gravidarum

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Glossary

Chorea – Abnormal involuntary movements that are brief, random, usually distal, and without purpose.

Epitopes – Antigens.

β-Hemolytic *Streptococcus* – Strains of *Streptococcus* that have the ability to induce autoimmune reaction and that cross-react with antigens of the brain, heart, joints, and skin.

Jones criteria – Set of clinical and laboratory criteria used to diagnose rheumatic fever.
Neuroleptics – Agents that block dopamine receptors.
Sydenham's chorea – Chorea resulting from autoimmune process triggered by β-hemolytic *Streptococcus*.

Definition and History

'Chorea' (derived from the Latin word choreus meaning 'dance') refers to abnormal involuntary movements that are brief, random, usually distal, and without purpose. Chorea gravidarum (CG) is the expression used to designate chorea occurring during pregnancy. This definition implies that CG is a syndrome with potentially numerous causes. The first description of CG was presumably made by Horstius in 1661. However, studies performed in the late nineteenth and early twentieth centuries, particularly by McCann in England and Wilson and Preece in the United States, were instrumental to forge the contemporary concept of CG.

Etiology and Pathogenesis

Gowers was the first to draw attention to the relationship between CG and rheumatic fever (RF). Currently, the hypothesis to account for the mechanism responsible for CG states that patients with a previous history of RF, not necessarily expressed by Sydenham's chorea (SC), are left with a subclinical dysfunction of the basal ganglia. Hormonal changes occurring during pregnancy lead then to the emergence of chorea. A similar phenomenon may occur with exposure to oral contraceptives. Although the precise mechanism leading to chorea in CG remains to be determined, it is speculated that hormones can change dopaminergic systems in the basal ganglia. For further details of the pathogenesis of SC, please refer to the entry on this subject.

In the remaining minority of patients where chorea during pregnancy is unrelated to RF, CG is merely a coincidence of other processes. Stroke, the most common cause of acute chorea in adults, can cause chorea as a result of lesions in the subthalamus and also in other areas. Vascular lesions associate with chorea are almost invariably consequence of hyperglycemia. This is particularly true of diabetes mellitus type II among Asian patients. The mechanism is not clear, but it seems to be related to microhemorrhages of the pallidum, which are visible on MRI scans. Systemic lupus erythemahosus (SLE), as well as primary antiphospholipid antibody syndrome, is believed to induce chorea and other neurological abnormalities by means of vasculitis. Infections (particularly AIDS, syphilis, and viral encephalitis) cause chorea either by direct lesion by the etiologic agent or by autoimmune mechanism. The latter seems to be the case in ADEM, where the process is often triggered by an infectious agent. Finally, prescription (antiepileptic drugs, dopaminergic agents and dopamine receptor blockers) or illicit drugs (cocaine and amphetamine) have also been described as causing chorea in pregnancy.

Epidemiology

Even up to the middle of the twentieth century, when RF and SC were an important public health problem throughout the world, CG was a rare condition. Even in the busy infirmary of Olser, he was able to find only five patients of whom just one had been personally examined by him. In 1932, it was estimated that there was an incidence of 1 CG for 2275 pregnancies. With the development of antibiotics and the sharp decline of frequency of RF and SC, the incidence of CG was down to 1:139000 pregnancies in 1968. In our unit, located in a part of the world where RF still remains a significant public health problem and where there is a special interest in chorea, CG accounts for less than 3% of all choreas.

Clinical Features and Diagnostic Criteria

Most patients develop chorea at pregnancy at ages less than 22 years. In fact, in our series of patients the median age of onset was 18 years with a range of 14–26. Gowers had already described that the onset of CG after age 24 is usually a recurrence of a previous episode. The movement disorder starts in the first two trimesters of the pregnancy in the majority of patients, being rare in the first and the last 3 months. The mean gestational age of our patients at the onset of CG was 10 weeks with a range of 4–24 weeks. As for the intensity of the movement disorders, earlier descriptions emphasize the occurrence of severe cases, which in fact meet criteria of ballism. In the large series of patients at the Federal University of Minas Gerais, however, the intensity of their chorea is comparable to that of the usual forms on SC unrelated to pregnancy. There are no descriptions of nonmotor neurological abnormalities, such as behavioral and cognitive changes in CG. The clinical experience indicates, nevertheless, that emotional labiality is common in pregnant women with chorea.

Nonneurological findings, however, have been recognized in CG since the early descriptions of chorea in pregnancy. Indeed, the occurrence of carditis, and less commonly, arthritis, led the first investigators of this condition to suspect the relationship between CG and SC.

The current diagnostic criteria of SC, which also apply to CG, are a modification of the Jones criteria: chorea with acute or subacute onset and lack of clinical and laboratory evidence of alternative cause. The diagnosis is further supported by the presence of additional major or minor manifestations of RF.

Differential Diagnosis

As long as chorea occurs during pregnancy, it is called CG, which implies that there is no differential diagnosis. One should bear in mind, however, that other hyperkinesias can occur during pregnancy. Recently, there are reports of dystonia and myoclonus with onset at pregnancy. The latter can be one of the first signs of adult-onset subacute sclerosing panencephalitis.

Diagnostic Work-Up

Pregnant women with chorea should undergo complete neurologic examination and diagnostic testing to investigate the myriad causes of chorea. Those are the tests helpful in the diagnostic workup of patients suspected to have rheumatic chorea: Tests of acute phase reactants such as erythrocyte sedimentation rate, C-reactive protein, leukocytosis; other blood tests like rheumatoid factor, mucoproteins, and protein electrophoresis; and supporting evidence of preceding streptococcal infection (increased antistreptolysin-O, antiDNAse-B, or other antistreptococcal antibodies; positive throat culture for group A *Streptococcus*; recent scarlet fever). These tests, however, are much less helpful in SC than in other forms of RF due to the usual long latency between the infection and the onset of the movement disorder. Anti-DNase-B titers, however, may remain elevated up to 1 year after strep pharyngitis. Heart evaluation (i.e., doppler echocardiography) is mandatory, because the association of SC with carditis is found in up to 80% of patients. The test of antineuronal antibodies for SC is not commercially available, being just performed for research purposes. Preliminary evidence, moreover, suggests that these antibodies are not specific to SC. Serologic studies for systemic lupus erythematosus and primary antiphospholipid antibody syndrome must be ordered to rule out these conditions. Neuroimaging helps to define the vascular nature of chorea, but, obviously, its use is limited in pregnancy.

Management

In some patients chorea is so mild, not associated with meaningful disability, that no treatment is necessary. Such a conservative approach is further supported by the finding that spontaneous remission in the last trimester of pregnancy occurs in up to one-third of patients. Treatment is mandatory in cases where chorea is more severe because of the high-risk of abortion. Despite the lack of evidence-based recommendations, the first-choice agents are dopamine receptor blockers. Most physicians caring for CG patients choose haloperidol.

Prognosis

Data of the early literature unanimously described an ominous prognosis of CG with up to 18% of the mothers dying during pregnancy or puerperium. With progress in gynecological and neurological care and a significant decline of the incidence of RF, the current mortality rate of CG is zero. In 30% of patients, there is spontaneous disappearance of chorea in the last trimester of the pregnancy. In the remaining patients, chorea disappears hours or few days after delivery. Patients who experienced CG not uncommonly have recurrence of chorea in future pregnancies.

See also: Chorea; Choreiform Disorders; Sydenham's Chorea.

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Choreiform Disorders

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Glossary

Basal ganglia – a group of nuclei (putamen, caudate, globus pallidus, subthalamic nucleus, and substantia nigra) that control the rate and pattern of movement.
Chorea – hyperkinetic movement disorder resulting in rapid unpredictable contractions of the limbs, face, and trunk. Slower writhing movements are called athetosis, and proximal flinging movements are called ballism.
Huntington's disease – hereditary adult onset neurodegenerative disorder associated with chorea, as well as cognitive and psychiatric changes.
Secondary chorea – chorea due to a toxic, metabolic, or structural problem, usually affecting the basal ganglia.
Tardive dyskinesia – stereotypic choreiform buccolingual movements due to exposure to neuroleptics, or other dopamine-blocking medications.

Definition and History

Chorea is a hyperkinetic movement disorder characterized by rapid, random contractions which may be continuous or intermittent, and are typically seen in the distal limbs, face, and trunk. The term is derived from the Greek word χορει´α, a circle dance. When the movements are more distal and sinuous, the term athetosis is used. Proximal flinging movements are referred to as ballism. All the three are likely part of the same movement continuum.

Current evidence suggests that chorea results from an imbalance between the indirect and direct basal ganglia circuitry. Due to the disruption of the indirect pathway, there is underactivity in the GABA-ergic pallidothalamic pathway, releasing thalamocortical activity and allowing hyperkinetic movements to occur. Enhanced activity of dopaminergic receptors may be responsible for the development of chorea at the level of the striatum. Distinctions based on the phenomenology between chorea, athetosis, and ballism are less important, as choreic syndromes are increasingly being classified based on the etiology.

Classification of Chorea According to Onset

Acute/Subacute Onset Chorea

Causes of acute/subacute onset of chorea are listed in **Table 1**. When chorea is sudden in onset, diagnostic considerations include metabolic factors such as hyperglycemia, hyponatremia, hypomagnesemia, hypocalcemia, hepatic failure, and renal failure. Acute chorea is also associated with exposure to toxins and substances of abuse including amphetamines, heroin glue sniffing, thallium, and mercury. A careful history eliciting drug use is important in any acute onset presentation of chorea (**Table 2**).

The most common cause of immune-mediated chorea is Sydenham chorea, a delayed complication of a group of beta hemolytic streptococcal infections occurring in 10% of cases of rheumatic fever. Chorea occurring during pregnancy is increasingly rare. Affected patients have usually had previous episodes of chorea associated with the use of oral contraceptives and/or a history of rheumatic fever. Central nervous system involvement in SLE occurs in 50–70% of cases, but chorea has been reported in less than 2% of these patients. Chorea is seen in about 1.3% of patients with antiphospholipid syndrome (APLS); generalized or hemichorea develops at an average age of 21 years with female predominance. In childhood, chorea can appear long before the other manifestation of SLE or APLS.

Chorea can be associated with other autoimmune diseases including Behcet disease, polyarteritis nodosa, isolated angiitis of the central nervous system, and primary Sjogren's syndrome. Hashimoto's encephalopathy with high antithyroid antibody titers can present with chorea. It has rarely been reported in paraneoplastic syndromes associated with Anti-Hu and anti-CRMP5 antibodies in patients with small lung carcinoma.

Other important causes of acute chorea are infections such as bacterial meningitis, encephalitis, tuberculous meningitis, tuberculoma, and aseptic meningitis. Hemichorea and hemiballismus are relatively common in AIDS because of toxoplasmosis abscesses in the basal ganglia, or direct HIV invasion. Lyme's disease has been reported to cause chorea. CNS infections may also present with gradual onset of chorea.

Chorea due to vascular causes is uncommon, affecting only 2% of stroke patients, with hemichorea as the usual manifestation. The subthalamic nucleus is the most

Table 1 Causes of acute/subacute onset chorea

1. Drugs (**Table 2**)
2. Vascular Chorea
   a. Stroke
   b. Moyamoya disease
   c. Post pump chorea
   d. Arteriovenous malformations with bleeding
3. Trauma
   a. Bilateral subdural hematoma
4. Immune-mediated chorea
   a. Sydenham's chorea
   b. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)
   c. Systemic lupus erythematosus (SLE)
   d. Antiphospholipid antibody syndrome (APLAS)
   e. Vasculitis
   f. Hashimoto's encephalopathy
   g. Paraneoplastic syndrome
5. Pregnancy
   a. Oestrogen
   b. OCP
   c. Hormone replacement therapy
6. Infectious chorea
   a. Bacterial meningitis/encephalitis
   b. Viral encephalitis
   c. Tubercular meningitis
   d. Aseptic meningitis
7. Metabolic disorders causing chorea
   a. Hyperglycaemia/hypoglycaemia
   b. Hypernatraemia/hyponatraemia
   c. Hypocalcaemia
   d. Hypomagnesaemia
   e. Hepatic failure
   f. Renal failure
8. Toxins/substance abuse
   a. Alcohol
   b. Amphetamines
   c. Heroin
   d. Glue sniffing
   e. Thallium
   f. Mercury

Table 2 Drugs causing acute/subacute onset chorea

1. Dopaminergic medications
2. Antipsychotic medications
3. Lithium
4. Anticonvulsants:
   a. Carbamazepine
   b. Phenytoin
   c. Valproate
   d. Gabapentin
5. Central nervous system stimulants:
   a. Amphetamines
   b. Cocaine
   c. Methylphenidate
6. Benzodiazepines
7. Oestrogens and oral contraceptives
8. Antihistamines: HI and H2
9. Baclofen
10. Cimetidine
11. Aminophylline

Modified from Jain K and Bradley W (2001) *Drug-Induced Movement Disorders. Drug-Induced Neurological Disorders*, pp. 171–209. Seattle: Hogrefe & Huber.

commonly involved site because of either hemorrhage or ischemia. Lesions may occur in the subthalamus, striatum, and even cortex. Other uncommon causes include moyamoya disease, postpump chorea, and cerebral arteriovenous malformations. Acute onset generalized chorea has been reported with bilateral chronic subdural hematoma as a rare complication.

Chorea of Gradual Onset

Hereditary causes of chorea should be considered when it is gradual in onset. Of these, Huntington's disease (HD) is the most common in European populations, with a reported prevalence of up to10 cases per 100 000. It is inherited as an autosomal dominant trait and caused by mutation in a gene located on the short arm of chromosome 4. The mutation results in expansion of an unstable CAG repeat in the first exon, causing an expanded polyglutamine tract in the protein huntingtin. The disease is characterized by adult onset, and psychiatric, cognitive and behavioral problems, in addition to chorea. Other abnormalities include dystonia and slowness of voluntary gaze. With a very large expansion, onset can occur in childhood, the clinical features being seizures, Parkinsonism, and behavioral problems.

Dentatorubropallidoluysian atrophy is an autosomal dominant disorder due to an unstable CAG triplet repeat expansion in the open reading frame of a gene encoding for atrophin-1, located on chromosome 12p. The presentation is variable, depending on the age of onset and includes ataxia, choreoathetosis, dystonia, seizures, myoclonus, psychiatric disturbances and dementia. It is most common in Japanese populations. Other trinucleotide repeat disorders such as the spinocerebellar ataxias may be associated with adult onset chorea, as can other hereditary disorders such as HDL 1, 2, and 3, and neuroferritinopathy.

Benign hereditary chorea is an autosomal dominant condition with onset in infancy. It is nonprogressive and may improve with age. This disease is due to mutation in the TITF-1 gene on chromosome 14q.

Choreoacanthocytosis is a rare autosomal recessive disorder characterized by progressive orofaciolingual dyskinesia, tics, limb chorea, hypotonia, muscle atrophy, and absent or diminished reflexes. Onset is typically in adolescence or early adulthood. Laboratory testing reveals increased serum creatine phosphokinase and normolipoproteinemic acanthocytosis. Neuroimaging demonstrates progressive degeneration of the caudate and putamen. It results from mutations in VPS13A on chromosome 9q21, which encodes a large protein called chorein.

Wilson's disease (WD), an autosomal recessive condition, is caused by mutations to the gene coding for the copper transporting beta polypeptide (ATP7B), located on chromososme 13. It is biochemically characterized by low ceruloplasmin and total serum copper levels, increased 24 h urinary copper excretion, and abnormally high hepatic copper content. The mean age of onset of WD is the second to third decade of life, although it has sometimes been reported to be as late as 72 years of age. Patients present with extrapyramidal, cerebellar, and/or cerebral-related symptoms. Early diagnosis is critical because of the treatable nature of this disorder.

Table 3 Causes of gradual onset chorea

1. Genetic chorea
   a. Autosomal Dominant
      i. Huntington's disease
      ii. Benign hereditary chorea
      iii. Dentatorubropallidoluysian atrophy
      iv. Spinocerebellar ataxia (type 2, 3, 17)
      v. Neuroferritinopathy
      vi. HDL 1 and 2
   b. Autosomal Recessive
      i. Chorea-acanthocytosis
      ii. Wilson's disease
      iii. Ataxia telangectasia
      iv. HDL-3
   c. X-linked Recessive
      i. Lesch–Nyhan disease
   d. Mitochondrial disorders (maternally inherited)
2. Dopaminergic blocking agents (Tardive dyskinesia)
   a. Neuroleptic medications
      i. Typical neuroleptics (thioridazine, chlorpromazine, haloperidol, etc.)
      ii. Atypical neuroleptics (quetiapine, risperidol, olanzapine)
   b. Gastrointestinal Agents
      i. Metoclopramide
      ii. Prochlorperazine
3. Infectious causes
   a. Direct HIV infection of brain
   b. Creutzfeldt–Jakob disease
4. Miscellaneous causes
   a. Hyperthyroidism
   b. Polycythemia rubra vera
   c. Nutritional: Vitamin B12 deficiency

Ataxia-telangiectasia is an autosomal recessive disease that results from mutations in the ataxia-telangiectasia mutated gene (ATM) (11q22–23), which is involved in the repair of double-stranded DNA breaks. AT patients typically present with progressive cerebellar ataxia early in childhood. Associated features include neuropathy, oculomotor apraxia, chorea, dystonia, and myoclonus. Affected individuals later develop conjuctival telangiectasias and sinopulmonary infections as well as increased susceptibility to malignancy.

Lesch–Nyhan disease, an X-linked recessive disorder of purine metabolism, is due to deficiency of the enzyme hypoxanthine phosphoribosyltransferase. The disease is characterized by a childhood onset of self mutilation, choreoathetosis, hyperuricemia, and gout.

Chorea is a common feature of Leigh's disease in children, but few cases of chorea have been reported in mitochondrial cytopathies with adult onset.

A common cause of choreiform movements in adults is the use of dopamine-blocking agents and referred to as tardive dyskinesia. These are characterized by involuntary stereotypic repetitive movements affecting the mouth and tongue. The head, trunk, and extremities may be affected in more severe cases. It is more common in elderly females, and has an incidence of 24–56% of patients chronically treated with neuroleptics.

Rarely, chorea can be associated with hyperthryroidism, polycythemia rubra vera, and nutritional deficiency (Vitamin B12). See **Table 4** for a detailed list of causes of chorea of gradual onset.

Paroxysmal Chorea

There are four main types of paroxysmal chorea: (1) Paroxysmal nonkinesigenic dyskinesia; (2) Paroxysmal

Table 4 Paroxysmal choreoathetotic disorders affecting children

	Gene	*Provoking events*	*Duration of attack*	*Frequency*	*Treatment*	*Associated condition*
Paroxysmal nonkinesigenic dyskinesia	2q	Alcohol, caffeine, hunger, stress, fatigue	>5 min to hours	< Several times/day	Benzodiazepine gabapentin	Migraine; dystonia, dysarthria, dysphagia
Paroxysmal kinesigenic choreoathetosis	16q	Sudden movement, startle, hyperventilation	<5 min	May be 100/day	Carbamazepine or phenytoin	
Infantile convulsions and paroxysmal choreoathetosis	16q	Sudden movement, stress, excitement	<5 min	Variable, may be 100/day	Carbamazepine or phenytoin	Benign neonatal seizure
Choreoathetosis and spasticity	IP	Exercise, stress, fatigue, and alcohol	20 min	<5 times/day		Spasticity during and between attacks

Adapted from Mathews KD (2003) Hereditary causes of chorea in childhood. *Seminars in Pediatric Neurology* 10: 20–25.

kinesigenic choreoathetosis; (3) Infantile convulsions and paroxysmal choreoathetosis; (4) choreathetosis and spasticity. Most have onset before the age of 20 years and all are inherited as autosomal dominant conditions (**Table 4**).

Diagnosis of Chorea

Diagnosis involves a careful history, with assessment of whether the chorea is of acute or chronic onset, or paroxysmal, and examination for associated neurologic and systemic symptoms. It is important to note exposure to drugs, toxins, and presence of a positive family history. These features will help guide the investigations (see **Table 5**).

Table 5 Recommended investigations in patients with chorea

1. Basic workup: Complete blood count, electrolytes, calcium, magnesium, liver and renal function, thyroid function
2. Autoimmune causes: Antinuclear antibody, antiphospholipid antibody, ESR, antistreptolysin O titre
3. Infectious causes: Venereal Disease Research Laboratory test, HIV antibodies, Lyme antibodies, toxoplasmosis titers, CSF examination
4. Serum ceruloplasmin, serum copper and 24-hour urine copper: if onset is under the age of 40, especially with a family history of neuropsychiatric symptoms or a medical history of liver disease
5. CT scan of brain in suspected intracranial haemorrhage, cerebral calcifications
6. MRI: in rule to intracranial structural lesion, especially in the setting of acute choreiform movements
7. Electroencephalography: when need to differentiate between paroxysmal movement disorders and seizures
8. Genetic testing: DNA testing, HD, DRPLA, SCAs, blood smear for neuroacanthocytosis

Table 6 Medications for the management of chorea

A. Neuroleptics
  1. atypical-clozapine, olaanzapine, risperidone, quetiapine (high dose only)
  2. typical – chlorpromazine, thioridazine, etc.
B. Dopamine-depleting agents
  1. tetrabenazine
  2. reserpine
C. NMDA-antagonists
  1. amantadine
D. Anticonvulsants
  1. carbamazepine, oxcarbazepine
  2. topiramate
  3. levetiracetam
  4. sodium valproate
  5. gabapentin

Treatment of Chorea

The treatment of chorea depends on the underlying cause. Correction of metabolic or hormonal abnormalities, withdrawal of offensive drugs and toxins, and control of infections alleviate acute chorea in many cases. As Wilson's disease is a potentially treatable disease, early diagnosis and institution of treatment with a copper chelating agent are imperative. In Sydenham's chorea, prophylaxis for rheumatic fever needs to be considered. In autoimmune chorea, steroids may be of help. In hereditary choreas, genetic counseling is very important.

In cases of chronic and/or more severe choreiform movements, treatment with medications that suppress chorea may be needed (see **Table 6**). Most commonly, the dopamine-depleting and-blocking agents are recommended. In resistant cases, anticonvulsants or amantadine may be considered. Treatment should always be started at a low dose and increased very gradually to determine the minimum amount required for symptom control.

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Climbing Behavior

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Glossary

Apomorphine – A wide-spectrum dopamine receptor agonist (i.e., an agonist of both D1- and D2-type dopamine receptors). Apomorphine is widely used in neuroscience research to achieve a pharmacological activation of brain dopamine receptors. As a medication, apomorphine is used in the treatment of Parkinson's disease. Apomorphine is a potent emetic (i.e., it induces vomiting) and should not be administered without an antiemetic such as domperidone.

Dopamine – Dopamine is a neurotransmitter occurring in a wide variety of animals, including both vertebrates and invertebrates. In the brain, it can activate five types of dopamine receptors – D1, D2, D3, D4, and D5, and their variants. Dopamine is produced in several areas of the brain, but the largest aggregates of dopamine-producing neurons are found in two midbrain nuclei named 'substantia nigra' and 'ventral tegmental area.' Dopamine is also a neurohormone released by the hypothalamus. Its main function as a hormone is to inhibit the release of prolactin from the anterior lobe of the pituitary. Severe dopamine deficiency in the striatum is the prime cause of parkinsonian motor symptoms (in particular, slowness of movement, poverty of movement, difficulty in movement initiation, resting tremor, rigidity).

Neuroleptics (antipsychotics) – Neuroleptics (also referred to as antipsychotics) are a class of drugs used to treat psychosis (which is typified by schizophrenia). Over time, a wide range of neuroleptics/antipsychotics have been developed. A first generation of drugs, known as typical antipsychotics, was discovered in the 1950s. The prototype of this class of drugs is haloperidol, a potent dopamine D2 receptor antagonist, producing significant motor side effects (parkinsonian motor features and tardive dyskinesia). The first atypical anti-psychotic, clozapine, was discovered in the 1950s, and introduced clinically in the 1970s. Atypical neuroleptics also have some antagonistic activity on dopamine receptors, but they encompass a wide range of additional receptor targets. A number of side effects have been observed in relation to specific atypical neuroleptic medications (e.g., weight gain, agranulocytosis). The development of new antipsychotics, and the relative efficacy of different ones, is an important ongoing field of research.

Noradrenaline – Noradrenaline, also called norepinephrine, is a catecholamine with dual roles as a hormone and a neurotransmitter. As a stress hormone, it is released from the adrenal medulla into the blood, and together with adrenaline (epinephrine) it mediates the so-called fight-or-flight response (increased heart rate, release of glucose from energy stores, and increased blood flow to skeletal muscle). As a neurotransmitter in the central nervous system and sympathetic nervous system, noradrenaline is released from the nerve endings of noradrenergic neurons into their target organs. The actions of norepinephrine are carried out via the binding to adrenergic receptors. Noradrenaline is synthesized from dopamine by the enzyme, dopamine β-hydroxylase.

Serotonin – Serotonin (often referred to as 5-hydroxytryptamine, or 5-HT) is a monoamine neurotransmitter in the central nervous system. Serotonin is produced in, and released from, the brainstem raphe nuclei, which send widespread and highly ramified projections to the entire brain and spinal cord. Serotonin is involved in a variety of neurobiological processes, such as the control of appetite, mood and anger, sleep and wakefulness, and cognition. Genetic variation in serotonin receptors and the serotonin transporter (which facilitates reuptake of serotonin into presynapses) have been implicated in neurological and psychiatric diseases. Brain serotonin projections show a variable degree of degeneration in both Alzheimer's and Parkinson's disease. Outside of the brain, serotonin is found extensively in the gastrointestinal tract. About 80–90% of the human body's total serotonin is found in the enterochromaffin cells in the gut where it regulates intestinal movements.

Stereotypies – Inflexible repetition of movement patterns or simple action sequences, which are not abnormal per se but become pathologic because they disturb or replace normal behaviors. In rodents, stereotypies are induced by treatment with apomorphine or psychoactive drugs such as amphetamine, and they include behavioral components such as licking, gnawing, grooming, and head nodding. In humans, stereotypies may be simple movements, such as body rocking, or more

complex actions, such as self-caressing, crossing and uncrossing of legs, and marching in place. Stereotypies occur in patients with mental retardation, autism spectrum disorders, or drug-induced dyskinesias.

Rodents can engage in vertical movements and climb on the enclosing walls of confined environments. This behavior occurs spontaneously as a part of normal exploratory responses, which are dependent on the integrity of ventral and dorsal striatum. Spontaneous climbing behavior increases in intensity and duration when animals are placed in a novel environment. Dopamine receptor agonists can be used to elicit robust climbing responses in a predictable manner, and drug-induced climbing is exploited in neuropharmacological research. In particular, apomorphine-induced climbing is used as a behavioral assay to test the efficacy of neuroleptic agents in mice. In this assay, mice are placed in a transparent cage lined with wire mesh, where they can move around by holding on to the wire mesh with their four paws. The time spent in climbing is monitored during the 40–50 min that follows an injection of apomorphine, which is given at doses below those causing continuous oral stereotypies. Pretreatment with both typical and atypical neuroleptics significantly attenuates apomorphine-induced climbing in this assay. Specific forms of nondrug-induced climbing have been exploited in behavioral tests that are widely used in neuroscience and neuropharmacology research. In the cylinder test of forelimb use asymmetry, rats or mice are placed in a relatively small glass cylinder, where they rear and lean on the walls of the cylinder using the forepaws for support. Forelimb use during this vertical exploration is assessed in short testing sessions by counting the number of supporting wall contacts executed independently with the right and the left paw. Cortical infarcts, traumatic lesions, or dopamine deafferentation in one cerebral hemisphere cause asymmetry in forelimb use during the climbing response, and specific therapeutic interventions ameliorate this deficit. Another form of climbing behavior occurs within the context of the forced swim test, which is widely used in the preclinical screening of antidepressant drugs. In this test, rodents are placed in an inescapable cylinder full of water, where they engage in three main forms of behavior, that is, immobility (passive floating), swimming (horizontal movement), or climbing (upward-directed movements of the forepaws along the walls of the swim chamber). Swimming behavior is increased by antidepressants that potentiate serotonergic neurotransmission, while climbing is increased by treatments that act primarily on the noradrenergic system. Also invertebrate model organisms exhibit forms of climbing behavior that are exploited for research purposes. The fly *Drosophila* climbs up the wall of a cylinder after being tapped to its bottom. This vertical escape response is called 'negative geotaxis,' and it is utilized to measure locomotor ability and to track age-related locomotor impairment in this organism.

See also: 6-OH Dopamine Rat Model; Antidepressants and Movement Disorders; Basal Ganglia; Cylinder Test (Paw Reach Test); Dopamine Receptors; Dopaminergic Agonists in Parkinson's Disease; *Drosophila* Models of Parkinson's Disease; Locus Coeruleus and Norepinephrine; Neuroleptics and Movement Disorders; Serotonin and Tryptophan; Substantia Nigra.

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Cock-walk

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Glossary

Cock-walk – A type of dystonic gait characterized by toe-walking, flexed elbows, and erect spine.
Manganese – A brittle metallic element that is essential for normal human function and is commonly used in steel production.
Manganism – A clinical syndrome caused by chronic exposure to manganese characterized by dystonia, parkinsonism, and neuropsychiatric disturbances.
Propulsion – A disorder of locomotion marked by a tendency to walk forwards.
Retropulsion – A disorder of locomotion marked by a tendency to walk backwards.
Talipes equinus – A congenital deformity of the foot in which the sole is permanently flexed so that walking is done on the toes without touching the heel to the ground.

Definition and History

Cock-walk refers to a type of dystonic gait characterized by toe-walking, flexed elbows, and erect spine; classically seen in manganism. The use of manganese (Mn) has been recorded as far back as the Stone Age when manganese dioxide was used as black pigment for cave paintings and in the Greco-Roman times, as a way to remove color from glass. Mn was not widely used in the production of goods until the late eighteenth century at which time it was discovered that Mn could be used as a metallic catalyst. It was with the use of manganese dioxide in the production of chloride for bleaching powder that James Couper described a peculiar neurologic condition in five patients exposed to manganese dust in 1837:

> During the height of the disease, the weakness of the contractile muscles was much greater in the legs than in the arms. It was of such nature that the patient reeled in walking and leaned forward when he wished to walk.

Despite being the first to describe what eventually will be known as manganism, Couper's observations fell into obscurity. It was not until the nineteenth century that the use of Mn exploded after the discovery that the addition of Mn to steel produced a steel alloy of superior strength and brittleness. Almost three-quarters of a century after Couper's descriptions, Rudolph von Jaksch renewed the interest in manganism in 1901 with his description of three individuals exposed to manganese dioxide dust:

> He felt stiffness in the knees which made pronounced bending of the legs impossible. At the same time, he found he could not walk backward without falling and speech became noticeably slow.

While von Jaksch was the first to coin the peculiar gait seen in manganism as cock-walk, he initially attributed the cases to an atypical form of multiple sclerosis. Later, von Jaksch correctly concluded that the cases were due to chronic Mn toxicity. In the ensuing 12 years, at least another 15 cases of manganism were described by Embden, Friedel, Seelert, and Casamajor, further outlining the details of this unique disorder. Today, Mn exposure continues to be a potential occupational hazard as Mn ranks as the fourth most used metal behind iron, aluminum, and copper.

Clinical Features and Pathophysiology

Manganism is a condition characterized by dystonia, parkinsonism, and neuropsychiatric changes due to chronic Mn exposure. Manganism shares many features with Parkinson disease (PD) including presence of bradykinesia, rigidity, and gait changes. However, important clinical features help to differentiate manganism from PD. One of the distinguishing features of manganism that is not typically seen in PD is the presence of early gait and postural dysfunction. Gait changes described in manganism include retropulsion, propulsion, freezing of gait, and a unique type of gait pattern, cock-walk. Other names have been used to describe the same phenomenon including démarche de coq, coq au pied, and von Jaksch's gait.

Seelert's description of this gait abnormality is considered classical for all cases of manganism:

> The feet touch the floor only with the region of the metatarsophalangeal joints. While walking, the knee joints are slightly flexed and the right leg is circumducted. Usually when using quick, lively gait, a curious posture is recognized, with the arms raised and abducted, and with the forearms flexed.

Cock-walk is a type of gait in which individuals have a tendency to walk on the metatarsophalangeal joint associated with an erect spine and flexed elbows. During a

normal gait cycle, the heel strikes the ground during the initial stance phase. As the stance phase progresses, weight is shifted forward towards the toes until the swing phase is reached. In cock-walk, the initial heel strike is lost due to abnormal ankle plantar flexion altering the normal gait cycle.

Cock-walk can occur unilaterally or bilaterally. While cock-walk is regarded as one of the most characteristic feature of manganism, the incidence of cock-walk varies per report. In a well-known series from Taiwan, only one out of six cases manifested with cock-walk. In an earlier and larger series from Egypt, over 50% presented with cock-walk, and in a more recent study in methcathinone users, 10 out of 23 patients had features suggestive of cock-walk. This variation in presentation does not appear to correlate with Mn levels.

Earlier explanations for cock-walk centered on a possible cerebellar role. However, most cases of cock-walk do not have evidence of cerebellar dysfunction on examination. While the exact pathogenesis of cock-walk is not known, dystonia is thought to be a leading explanation. Cock-walk is usually accompanied by increased tone in the legs unequally affecting agonist and antagonist muscles resulting in abnormal posturing around the ankle joint. It is possible that the abnormal posture seen in the spine and arms also reflects an underlying dystonic process. Another feature in cock-walk is task specificity, a characteristic frequently seen in dystonia. Descriptions of cock-walk point out that during normal stance, the feet appear to be flat on the ground, but after a few steps, the heels begin to rise with the center of mass shifted to the metatarsophalangeal joints. The other features of cock-walk such as the erect spine, flexed elbows, and abduction of the arms away from the trunk also appear to manifest with walking and not with normal stance. Finally, in animal models of chronic Mn intoxication, abnormalities of the extrapyramidal system, including dystonic postures were seen in monkeys exposed to manganese dioxide.

Differential Diagnosis

While there are other etiologies that can cause a propensity to walk on the metatarsophalangeal joint or toe-walking, cock-walk is unique in that it also has features of dystonic posturing in the spine and arms. In the pediatric literature, toe-walking can be due to a congenital deformity, talipes equinus or club foot. Cerebral palsy resulting in spastic diplegia is another important cause of toe-walking. Duchenne muscular dystrophy can also present with toe-walking that is thought to be due to muscle fibrosis leading to a fixed plantar flexion contracture. Other neuromuscular conditions, including a rare disorder, rippling muscle disease, have been associated with toe-walking. This autosomal dominant myopathy is characterized by muscle hypertrophy, peculiar rolling or rippling muscles, and muscle rigidity that can result in toe-walking, especially in the morning.

Dystonia is another important cause of toe-walking. This can include focal dystonias of the foot resulting in abnormal plantar-flexion while walking. Dopa-responsive dystonia (DRD) that results in a fluctuating course of dystonia is a unique disorder seen mostly in children. The majority of cases are due to a defect in the guanosine triphosphate (GTP) cyclohydrolase 1 enzyme which is necessary for the production of a cofactor in the conversion of tyrosine to levodopa. One of the most common manifestations of DRD is dystonia of the lower extremity that manifests with rigidity in the legs, dystonic posturing of the foot and a tendency to walk on the toes similar to cock-walk. Wilson disease is an autosomal recessive disorder due to abnormal copper accumulation in the liver and brain. Similar to manganism, Wilson disease also presents with parkinsonism, neuropsychiatric symptoms, and dystonia that can include lower extremity dystonia and toe-walking. The presence of Kayser-Fleischer rings and liver abnormalities help to differentiate Wilson disease from manganism. Certain brain disorders with abnormal iron accumulation can also present with an abnormal gait similar to cock-walk. Formerly known as Hallervorden–Spatz syndrome, neurodegeneration with brain iron accumulation (NBIA) encompasses a heterogeneous group of disorders characterized by dystonia, chorea, and brain iron accumulation. The most common cause of NBIA is Pantothenate kinase-associated neurodegeneration (PKAN) due to a defect in the pantothenate kinase 2 (PANK2) gene.

Conclusion

In summary, cock-walk is a unique type of dystonic gait classically seen in manganism. The major features of cock-walk include walking on the metatarsophalangeal joint associated with an erect spine and flexed elbows. A patient with known Mn exposure and presence of cock-walk should be considered a sine qua non for manganism.

See also: DYT5; Hallervorden–Spatz Syndrome (PKAN); Manganese; Wilson's Disease.

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Co-enzyme Q_{10}

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Coenzyme Q_{10} (coQ_{10}) is a lipid-soluble component of virtually all cell membranes. CoQ_{10} is an isoprenylated benzoquinone and transports electrons from complexes I and II to complex III in the mitochondrial respiratory chain and can enhance oxidative phosphorylation. It is essential for the stability of complex III and also functions as an antioxidant.

CoQ_{10} deficiency has been implicated in several diseases, and CoQ therapy has been proposed as a treatment not only for these deficiency states, but also for other degenerative diseases.

Primary CoQ_{10} Deficiency

The first report of human disease associated with coQ_{10} deficiency was in a patient with encephalomyopathy and recurrent myoglobinuria with ragged red fibers and changes of lipid storage on muscle biopsy. Relatively severe coQ_{10} deficiency was then described in six patients with early-onset (age range birth – 16 years) myopathy and ataxia. Seizures, weakness, and mental retardation were described in some and cerebellar atrophy found in all. Genetic testing for Friedreich ataxia (FRDA) and spinocerebellar ataxia was negative, and inheritance was consistent with an autosomal recessive pattern. Muscle biopsy in these patients showed nonspecific abnormalities only, and in particular, no evidence of mitochondrial pathology. Residual muscle coQ_{10} levels were 26–35% of normal. Administration of coQ_{10} (300–3000 mg day^{-1}) resulted in significant improvement in the ataxia.

Subsequent assay of muscle coQ_{10} levels in 135 patients with genetically undefined childhood onset ataxia identified significantly reduced levels in 10%. All patients had cerebellar atrophy and some had seizures, developmental delay, and pyramidal features. Lactic acidosis in the ataxic patients is rare, and in contrast to the myopathic form, the muscle biopsy may appear normal. The same group subsequently described muscle coQ_{10} deficiency in two brothers with adult onset (age 29 and 39 years) progressive cerebellar ataxia with cerebellar atrophy and hypergonadotrophic hypogonadism. Muscle morphology showed neurogenic changes only. coQ_{10} 750–1200 mg day^{-1} resulted in improved ataxia, neurophysiology, and normal testosterone levels within 2 months. A pure myopathic form of coQ_{10} deficiency, without recurrent myoglobinuria but with mild mitochondrial changes on muscle biopsy has recently been described.

Friedreich Ataxia (FRDA)

FRDA is an autosomal recessive disease caused in 97% of patients by an abnormal expansion of the GAA repeat of intron 1 of the *frataxin* gene. The remainder are due to an expansion on one allele and a point mutation in the *frataxin* gene on the other. The *frataxin* gene product is a mitochondrial protein and the mutations lead to a loss of this protein. Deficiency of frataxin protein is associated with a decrease in mitochondrial respiratory chain complexes I, II, and III and aconitase activities in postmortem heart and skeletal muscle from FRDA patients. Various

markers have indicated increased oxidative stress and damage in FRDA patients including raised urine levels of 8-hydroxyl-2′-deoxyguanosine (8OH2′dG) suggesting elevated oxidative damage to DNA; decreased free glutathione levels in blood, suggesting extensive gluathionylation of proteins in response to oxidative stress; and raised plasma malondiadehyde (MDA) levels indicative of increased lipid peroxidation.

A 4 year open-label trial of CoQ in combination with vitamin E was completed with 10 genetically confirmed FRDA patients given 2100 IU day^{-1} vitamin E and 400 mg day^{-1}) CoQ_{10}. The International Cooperative Ataxia Ratings Scale (ICARS) was used to evaluate clinical progression, in addition to biomarkers of in vivo mitochondrial bioenergetics (cardiac and skeletal muscle ^{31}P MRS) and cardiac hypertrophy (echocardiography) to evaluate the effect of therapy. During the course of the therapy, all patients demonstrated an increase in serum vitamin E (2.2 – 6-fold increase over baseline) and CoQ_{10} levels (2.3 – 7.4-fold increase over baseline), demonstrating good bioavailability. Most remarkable was the improvement in cardiac (phosphocreatine: ATP ratio) and skeletal muscle (postexercise maximum rate of mitochondrial ATP synthesis, V_{max}) bioenergetics after 3 months of therapy, which was maintained throughout the 4 years of the trial. This clearly demonstrated that the combined vitamin E and CoQ_{10} therapy had a significant and prolonged benefit upon the defective mitochondrial function in these peripheral tissues. While the prolonged improvement in cardiac bioenergetics did not have any impact upon cardiac hypertrophy, fractional shortening showed a progressive improvement that reached significance after 3 years.

On the basis of these positive results, 50 FRDA patients were randomly divided into high (600 mg day^{-1} CoQ and 2100 IU vitamin E) or low (30 mg day^{-1} CoQ and 4 IU vitamin E) dose CoQ_{10}/vitamin E groups in a double blind controlled trial. Patients were assessed at baseline and every 6 months over 2 years. The change in ICARS was used as the primary end point. A post hoc analysis was made using cross-sectional data from 77 untreated FRDA patients. The results showed baseline serum CoQ_{10} and vitamin E levels were significantly decreased in the FRDA patients. During the trial, CoQ_{10} and vitamin E levels were significantly increased in the both dosage groups. The primary and secondary end points were not significantly different between the therapy groups.

The results of this study indicate that over 2 years 'high dose' CoQ_{10} and vitamin E have no benefit over the 'low dose' combination in terms of improving ICARS scores. The important and unexpected finding was plasma CoQ_{10} and vitamin E deficiency in FRDA. In a post hoc analysis, 49% (21/43) of the patients responded over the 2 years of the trial with improved ICARS compared to cross-sectional data, with equal numbers of responders in the two treatment groups. Of most significance was the observation that the responder patients had significantly lower baseline CoQ_{10} levels suggesting the clinical efficacy of the low- and high-dose therapies may relate to restoration of normal serum CoQ_{10} levels. The low-dose CoQ_{10} (30 mg day^{-1}) was sufficient to raise significantly the plasma levels in the patients to control levels. The cause of the CoQ_{10} deficiency may be related to an increased turnover because of excess free radical production. If this in turn contributed to the pathogenetic events underlying progressive neurodegeneration, 30 mg day^{-1} CoQ_{10} was sufficient supplement to restore levels and may have been the reason why differences were not seen between the treatment arms. Higher doses produced no additional benefit over the period of the trial.

Parkinson's Disease

The relationship between Parkinson's disease (PD) and mitochondria was first established with the identification of a deficiency in the activity of complex I in PD substantia nigra and subsequently in the peripheral tissues of patients. Complex I is the target of toxins known to produce parkinsonian features in humans, for example, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and anonnacin, and also the target of toxins used to produce animal models of PD, for example, rotenone and tetrahydroisoquinolines. The pathogenesis of PD also includes protein aggregation (Lewy bodies). Mitochondrial dysfunction will contribute to dysfunction of the energy-dependent ubiquitin proteasomal system (UPS) and oxidative stress will add to the substrate load. This combination has been shown to enhance dopaminergic cell damage and death.

Environmental and genetic factors known to be important in PD interact with mitochondrial function. As noted earlier, environmental toxins that induce dopaminergic cell death and parkinsonism in man and animal models inhibit complex I. Genetic causes of familial PD affect mitochondrial function. For instance, α-synuclein overexpression inhibits mitochondrial activity, parkin-knockout mice have a striatal respiratory chain defect, parkin-knockout flies have skeletal muscle mitochondrial abnormalities, and parkin-positive PD patients have complex I deficiency. Overexpression models of parkin have shown localization of the protein to mitochondria. DJ1 localizes to the outer mitochondrial membrane under conditions of oxidative stress and is thought to play a role in antioxidant defenses. Mutations in the PINK1 gene, causing autosomal dominant PD, have been described and the protein product localizes to the mitochondrion. The function of PINK1 is not known, but it is a protein kinase and mutations enhance sensitivity to UPS inhibitors and lower the threshold to apoptotic cell death. Thus, the current pathogenetic model of PD reflects a complex network of

interacting biochemical abnormalities that are in turn a consequence of genetic and environmental factors.

Based upon the evidence that mitochondrial dysfunction plays an important role in PD pathogenesis, it seemed reasonable to test the hypothesis that drugs that improve mitochondrial function might slow the progression of the disease. The first of these studies used a double blind placebo-controlled design and recruited 16–23 patients per arm to asses the efficacy of three doses of CoQ_{10} (300 mg day^{-1}, 600 mg day^{-1}, and 1200 mg day^{-1}) in early PD patients. Over a 16 month period, the highest dose group progressed at a lower rate in terms of the worsening of motor function and activities of daily living (United Parkinson Disease Rating Scale parts II and III) (UPDRS) compared to control, although much of this benefit was related to the activities of daily living component and was established very early in the trial. A futility analysis assessed coQ_{10}, using historic control data and the total score of the UPDRS and failed to show futility, that is, suggested that the compound was worthy of future study. However, the authors called into question the validity of their historic control data in the light of more recent placebo progression rates in the UPDRS, and with these, coQ_{10} did suggest futility. A small study of 28 treated PD patients supplemented with 360 mg day^{-1} of coQ_{10} showed a mild symptomatic motor effect over a period of 4 weeks. However, a larger study of 300 mg day^{-1} (which produced the same plasma levels as 1200 mg day^{-1} in the Shults study) found no symptomatic effect on the UPDRS. A large double blind study of high-dose CoQ_{10} in early PD is underway at the time of writing.

Further Reading

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Cognitive Assessments and Parkinson's Disease

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Glossary

Apathy – Impairment in goal-directed behavior; may have affective, behavioral, and cognitive components.
Bradyphrenia – Slowness of mental processing.
Episodic memory – Memory that involves the ability to learn, store, and retrieve information related to ongoing experiences or events; typically includes memories that have a temporal and spatial context; conceptualized as an ability to transfer information from primary (short term) to secondary (long term) memory.
Executive function – A descriptive term comprising a broad range of cognitive processes including planning, initiating, and monitoring behavior. Executive functions include working memory, abstract reasoning, problem solving, and mental flexibility.
Luria sequence – A measure of motor programming in which the patient is required to repeat a series of hand movements, such as fist-edge-palm.
Punding – Activities of a compulsive, repetitious, and purposeless nature that may involve the assembly and disassembly of mechanics, collecting or sorting of objects; may occur in substance abuse but also with overactive dopaminergic stimulation in Parkinson's disease.
Stroop test – A test in which the patient is presented with a succession of names of colors printed in nonmatching inks and then asked to name the color of the ink as quickly as possible; performance on this test requires directed attention and inhibition of the tendency to read the word.
WAIS-IV – The latest revision of the Wechsler Adult Intelligence Scale; comprised of 10 different subtests that generate index scores for Verbal Comprehension, Perceptual Reasoning, Working Memory, Processing Speed, and Full Scale IQ.
Working memory – A limited-capacity memory storage system for retaining information over a matter of seconds and for performing mental operations on the contents of this store.

The Neuropsychological Assessment

Neuropsychological Issues in PD

Besides the motor dysfunction, Parkinson's disease (PD) is associated with nonmotor features affecting cognition,

behavior, and mood. Cognitive changes range from mild impairment to dementia and commonly affect domains including executive function, attention, visuospatial/perceptive function, and memory. PD patients may exhibit slowed information processing; deficits in planning, switching tasks, or multi-tasking; forgetfulness; and subfluency or word-finding difficulties. Although PD dementia is typically considered as a predominantly dysexecutive syndrome, some studies have reported more severe deficits and greater memory dysfunction with PD patients, thereby exhibiting a phenotype more similar to Alzheimer's disease (AD). The pathology of PD dementia is likely heterogeneous with contributions from Lewy bodies, Lewy neurites, and brainstem degeneration, as well as neurofibrillary plaques and tangles. Mild cognitive changes have been reported in 20–40% of early or de novo PD patients, and dementia may occur in about 40% of patients, although estimates vary depending on study methodologies.

Behavioral issues in PD encompass hallucinations, psychosis, impulse control disorders, mood disorders, and apathy. Hallucinations occur in about a third of PD patients treated with chronic dopaminergic medications and likely are related to both extrinsic (e.g., medications) and intrinsic factors (e.g., cognition, disease duration). Psychosis occurs less frequently and is often coupled with cognitive impairment; common delusions are those of infidelity, paranoia, or misidentification syndromes. Impulse control disorders include pathological gambling, hypersexuality, binge eating, compulsive shopping, punding, and other repetitive and reward-seeking behaviors. This disorder may relate to excessive D3 stimulation, particularly with dopamine agonists. Apathy, defined as an impairment in goal-directed behavior, occurs in 16–40% of PD patients. It may be linked to executive dysfunction and may occur with or without depression.

Mood disorders such as depressed mood, depression, dysthymia, anxiety, and panic disorder are common in PD and occur throughout different stages of the disease. Depression and anxiety may even be some of the very earliest manifestations of PD, reflecting early brainstem degeneration with alteration of noradrenergic and serotonergic systems (i.e., Braak PD pathological staging II). In addition, mood disorders can occur as intrinsic to the disease, reactive disorders related to having PD, and as nonmotor fluctuations or wearing off of dopaminergic medication effects.

Reasons for Neuropsychological Referral

When PD patients are referred for a clinical neuropsychological evaluation, the referral questions often are:

1. Does the patient have cognitive impairment or dementia?
2. Is there an underlying mood disorder?
3. Are these nonmotor features consistent with PD or are there other contributory factors (e.g., AD, cerebrovascular disease, toxic/metabolic syndromes, delirium)?

Neuropsychological referrals may provide information on diagnosis, deficit localization, and quantifiable data on cognitive impairment or neuropsychological function. In PD patients, neuropsychological testing also may be performed as part of a presurgical evaluation for surgical interventions such as deep brain stimulation. Serial clinical neuropsychological evaluations may permit assessment of cognitive change over time, effects of interventions such as medication changes on cognition, and guidance for therapies and decisions about the patient's condition. In addition, neuropsychological testing is an important part of many PD motor and nonmotor research studies.

The Neuropsychological Evaluation

PD patients referred for neuropsychological evaluation receive a clinical interview and neuropsychological testing. In the interview, demographic information (e.g., age, education, gender, handedness, occupation history, current and prior function) is collected to help to establish an estimate of premorbid level of functioning. Information regarding the patient's movement disorder, other health information such as medication use and social history, and motor status (e.g., 'on' or 'off') may be pertinent. A battery of paper-and-pencil neuropsychological tests is typically administered to address the referral question. These neuropsychological tests are chosen for adequate reliability, validity, sensitivity, and specificity, as well as satisfactory normative data. Selection of neuropsychological tests that can be administered orally and that can thus minimize motor demands may be important when testing patients with PD and other movement disorders who have bradykinesia, tremor, or dyskinesias. It is important to consider issues such as medication effects, comfort, fatigue, and sleepiness, particularly in PD patients, as well as impairment in sensory function (vision and hearing). In addition to addressing cognitive issues, patients are interviewed for emotional changes, primarily depression and anxiety, and other behavioral problems. Obtaining collateral history from an informant (e.g., spouse, relative, or caregiver) comprises an important part of the interview, especially in cognitively impaired patients.

The typical neuropsychological battery consists of a measure(s) of global cognitive functioning as well as assessments of a range of cognitive domains. These cognitive domains broadly include memory, executive function, attention, language, and visuospatial function. Examination of memory may include testing episodic, semantic, procedural, and working memory function. Neuropsychological tests may assess verbal learning and memory, visual learning and memory, free and cued recall, and working memory

function. Examination of executive function may include tasks for set elaboration and planning, set shifting, and set maintenance as well as other frontal lobe functions. Other cognitive aspects examined include intellectual functioning, processing speed, sensory-perceptual functions, and motor speed.

Specific Cognitive Assessments in PD

Although there are numerous neuropsychological tests available, this section will highlight selected, specific cognitive assessments that are often used in PD evaluations.

Global Cognitive Function

A variety of neuropsychological instruments has been used to evaluate global cognitive function or screen for dementia or cognitive impairment in PD. Among others, these tests include the Mini-Mental Status Examination (MMSE), Mattis Dementia Rating Scale (DRS), the Cambridge Cognitive Assessment (CAMCOG), Scales for Outcomes in Parkinson's disease-cognition (SCOPA-cog), Parkinson Neuropsychometric Dementia Assessment (PANDA), Parkinson's Disease – Cognitive Rating Scale (PD-CRS), Montreal Cognitive Assessment (MoCA), and the Alzheimer's Disease Assessment Scale-cognitive (ADAS-cog).

The MMSE, a 30-point test, is a quick screening exam for cognitive impairment; questions assess orientation, attention, recent memory, language, and visuoconstruction. Since the MMSE is relatively insensitive to executive dysfunction, a cut off score of <25 has been proposed for PD dementia in a recent article by the Movement Disorders Society (MDS) Task Force. The MMSE is affected by age and education for which normative data are available.

The DRS provides a more comprehensive assessment of global cognitive function, particularly with increased sensitivity to the dysexecutive syndrome of PD, and is comprised of five subscales: Attention, Initiation/Perseveration, Construction, Conceptualization, and Memory. The DRS takes about 20 min; has age and education normative data; and has been used in longitudinal assessments of cognitive function.

The CAMCOG is a 107-point complete cognitive assessment, which tests eight different cognitive domains (orientation, language, memory, attention, praxis, calculation, abstract thinking, and perception). Overall scores less than 80 have been suggested as a cut-off for dementia; it has demonstrated greater sensitivity and specificity for the diagnosis of dementia compared with the MMSE. Administering a revised version of the CAMCOG (the CAMCOG-R) to a community population of PD patients, Athey et al. found that the CAMCOG-R detected a wide range of cognitive ability in those PD patients previously deemed not having significant cognitive impairment by MMSE. In a 2006 follow-up study, Athey and Walker reported a decline of 3.9 CAMCOG-R points over a 13-month period in their PD cohort.

The SCOPA-cog was developed as a short, practical instrument that was sensitive to the cognitive deficits of PD; its main use, as described by Marinus et al., was for research situations or the assessment of cognitive change, rather than as a screening tool or diagnostic instrument. The SCOPA-cog includes 10 items that encompass memory (nonverbal and verbal), attention, executive function (Luria maneuver, dice task, animal fluency), and visuospatial function (figure completion). Administration time is about 10–15 min, and the SCOPA-cog correlates highly with the CAMCOG and MMSE.

The PANDA is a short (8–10 min) screening tool for detecting neuropsychological dysfunctions in PD patients in clinical practice. The instrument includes four cognitive tasks (word pair associate learning with immediate and delayed recall, alternating verbal fluency, visuospatial imagery, and working memory/attention using number sequencing) plus a depression questionnaire. In their 2008 study of 124 PD patients and 108 neurologically normal controls, Kalbe et al. report high specificity and sensitivity of the cognitive tasks for PDD (91% and 90%) and a sensitivity of 77% for cognitively impaired PD (both PDD and PD with mild cognitive impairment).

The PD-CRS was designed to evaluate the full spectrum of cognitive deficits associated with PD. The PD-CRS includes 10 subcortical items (attention, working memory, Stroop test, phonemic, semantic, alternating, and action verbal fluencies, immediate and delayed verbal memory, clock drawing) and 2 cortical items (naming, clock copying) with an administration time ranging from 13 to 31 min. Paragonabarraga et al. report that the PD-CRS showed a strong concurrent validity with the DRS, sensitivity and specificity for diagnosing PDD of 94% and 94%, and a differentiation of a mildly cognitive impaired PD group on tasks of alternating verbal fluency and delayed verbal memory.

The MoCA was developed as a short (10-min) cognitive screening tool to aid clinic physicians in the detection of mild cognitive impairment. Subsequently, the MoCA has been applied to PD patients and compared with the MMSE in PD in several studies. The MoCA, a 30-point test, evaluates orientation, verbal memory, attention (serial 7's, target detection using tapping, and digit span), visuospatial function (clock drawing, cube copying), language (naming, repetition), and frontal functions (modified Trail Making Test Part B, verbal fluency, and abstraction task). In the PD studies, the MoCA appears to have a greater sensitivity than the MMSE to mild cognitive impairment.

Although the ADAS-cog is primarily used in AD settings including trials with cholinesterase inhibitors and other cognitive medications, it is included in this section

as it was used as the primary outcome measure in a large multicenter, double-blind, placebo-controlled trial for 24 weeks of rivastigmine in patients with mild to moderate PD dementia. The ADAS-cog is a 70-point test with 11 parts (7 performance items and 4 clinician-rated items assessing memory, language, praxis, and orientation) and can take 30–45 min to administer. In the PD trial comparing rivastigmine and placebo, patients receiving rivastigmine had a mean improvement of 2.1 points in the ADAS-cog, whereas control subjects had a 0.7-point worsening, thereby reflecting changes similar to those seen in patients with AD.

Memory

The memory deficits of PD have generally been considered to reflect the underlying subcortical-frontal disturbances, in contrast to mesial temporal lobe dysfunction more typically seen in the deficits of episodic memory in AD. Encoding and retrieval deficits, in contrast to storage deficits, characterize the impaired recall in PD. In addition, PD patients perform worse when the material is not semantically organized or requires internally generated retrieval strategies. Thus, PD patients often perform better on cued recall or recognition tasks compared to AD patients, although more severe PD dementia patients may also be impaired on cued recall. When testing memory function in PD, it may be useful to control for the encoding and retrieval of information.

Tests of verbal memory typically include trials of list learning, followed by immediate recall, delayed recall, and recognition tests. Some verbal memory tests such as the California Verbal Learning Test-II (CVLT-II), Hopkins Verbal Learning Test-Revised (HVLT-R), and Free and Cued Recall Test incorporate semantic categories (e.g., kitchen utensils, sports), which may aid in encoding and retrieval. Other commonly used verbal memory tests include the Rey Auditory Verbal Learning Test (RAVLT) and the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) word list. The CERAD word list is a brief 10-word list that the patient reads and that has been shown to differentiate normal control subjects from mild dementia. The HVLT-R is a word list in which 12 words belonging to three categories aid in recall. These word lists differ in the number of words (10–15 words), use of semantic categories, number of trial presentations (3–5), and delayed recall. Time intervals for delayed recall tasks vary from about 15–30 min.

The Free and Cued Recall Test as described by Grober and Buschke may be particularly useful in memory evaluation in PD, because it controls encoding and retrieval with the same semantic cues. It has been proposed to differentiate encoding deficits of AD from the retrieval impairment of frontal/subcortical dysfunction. In this task, encoding of items is controlled by having the subject point to and read aloud each of the items to be learned, in response to its semantic category cue. All the 16 items must be retrieved before proceeding to the memory tests of free and cued recall. For items not produced during free recall, the semantic cue is provided to facilitate retrieval. Free and cued recall scores are then compared.

Most measures of nonverbal memory, typically employing visual memory, unfortunately are not 'pure' measures and involve language to some degree. Many tests of visual memory also involve a visuomotor component, such as drawing. In the Visual Reproduction subtest of the Wechsler Memory Scale-IV (WMS-IV), patients are shown a series of designs on cards, for 10 s each. Patients are asked to draw the designs from memory for an immediate trial, as well as a 30-min delayed trial. The WMS-IV includes a new subtest, Designs, which is an attempt to develop a 'purer' measure of visual memory. In the Designs subtest, the patient views a stimulus card with 2–8 designs placed on a 4×4 grid. After viewing the stimulus card for 10 s, the patient is required to pick out the correct designs from a group of cards which includes foils, and place in the right location as in the stimulus picture. This subtest also has a 30-min delayed trial.

Working memory is often described as a 'mental workspace' that holds information while it is being processed. Working memory theories cite three principal components: a Central Executive System that controls and coordinates the other systems via strategy and integration, an Articulatory Loop System that circulates verbal information during processing, and a Visuospatial Scratchpad that temporarily stores and manipulates visuospatial information. Working memory can be evaluated using the Digit Ordering test or the Digit Span and Letter-Number Sequencing subtests from the WAIS-IV. In the Digit Ordering test, subjects are read a random selection of digits and are asked to reorder them by repeating them in ascending order. In the Digit Span task, the subject recalls increasing lengths of digits first forwards, then backwards, then in ascending order. While repetition of digits forward relates more to attention, reversed order digit span and sequencing of digits assess working memory, as the numbers must be temporarily stored for mental manipulation. The Letter-Number Sequencing subtest involves ordering increasing lengths of random numbers and letters, with the numbers in order first, followed by the letters in alphabetical order.

Executive Functions

Executive function refers to the mental processes that underlie goal-directed behavior. It includes planning, conceptualization, flexibility of thinking, insight, judgment, self-monitoring, and regulation. Frontal/subcortical circuitry, including the basal ganglia and prefrontal cortex, is integral for executive function. PD cognitive impairment and dementia are characterized by a

dysexecutive syndrome. Many of the executive functions are also related to attention and working memory.

Tests of executive function can be categorized as those related to working memory, conceptualization, set activation, set shifting, and set maintenance. Conceptualization abilities, set elaboration and planning can be tested by conceptualization subscales of the DRS, similarities tasks (e.g., Similarities from the WAIS-IV), which involve the presentation of word pairs in increasing difficulty to ascertain verbal concept formation or the Wisconsin Card Sorting Test (WSCT; Heaton, 1981), which often serves as a paradigm for testing executive function. The WSCT requires subjects to sort cards according to one criterion (color, form, number) that they must figure out based on the examiner's feedback on whether their response is correct or not. After 10 consecutive correct responses, the examiner shifts the rule without telling the subject and the subject must deduce the new rule. The WSCT tests not only conceptualization but also set shifting and set maintenance. Performance is impaired in PD dementia and some nondemented PD.

Tests of set activation, set shifting, and set maintenance in PD include verbal fluency, Trail Making Test (TMT; Reitan, 1955), Stroop Test (Golden, 1978), Odd Man Out test (Flowers & Robertson, 1985), Symbol Digit Modalities Test (Smith 1991), among others. Verbal fluency tasks provide insight as to activation strategies, attention, and temporary storage of information. Retrieved words can be semantic/category (e.g., animal naming) or phonological/letter (e.g., words beginning with the letters F, A, and S). Typically, patients are asked to name as many words as possible for the designated category or letter in trials of 60 s. Verbal fluency is impaired in PD dementia, and in some, but not all studies, to a greater degree than in AD. The TMT, originally part of the Army Individual Test Battery, and incorporated into the Halstead-Reitan test battery, has two parts: Part A, which involves linking a series of randomly positioned numbers in consecutive order (i.e., 1–2–3, etc.) and Part B, which involves joining a series of randomly positioned numbers and letters alternately in a respective sequence (i.e., 1-A-2-B-3-C, etc). Both nondemented PD, including de novo PD, and demented PD may exhibit deficits on the TMT. The Stroop Test is considered to reflect cognitive flexibility or set-shifting abilities and is often impaired in PD patients. In the Stroop interference condition, subjects are presented with names of colors printed in a color other than is the word (e.g., the word blue is printed in green ink) and asked to say aloud the color of the word, thereby inhibiting the tendency to read the word.

Attention

Attentional processes may be impaired in PD. Often tests of attention, however, are linked to those associated with vigilance, working memory, and processing speed. Furthermore, attention may be affected by medications, sleep disturbances, and fatigue, as well as intrinsic disease processes. Measures of attention may include simple tests such as Digit Span Forward or more complicated assessments such as the Coding (previously called Digit Symbol) subtest from the WAIS-IV and the Symbol Digit Modalities Test. PD patients are impaired on tests that make greater demands on attention. Fluctuations in attention are a striking feature of dementia with Lewy bodies but also may be evident in some patients with PD dementia. In the Coding subtest, patients copy symbols that are paired with numbers. The Symbol Digit Modalities Test is similar to the Coding subtest, although the patient is copying numbers paired to symbols over 90 s. The SDMT also has an oral version that may be especially well suited for PD subjects with significant motor impairment.

Language

Assessment of language usually includes aphasia-type tests with evaluations of expressive language, receptive language, and repetition. Measures of expressive language are sensitive to cortical functions and the progression of dementia. Visual confrontation naming, a measure of expressive language, is typically preserved in PD. In the Boston Naming Test, patients are asked to name line drawings of items that vary in level of familiarity. As previously discussed, verbal fluency, another measure of expressive language that overlaps with executive function, is often impaired in PD. Receptive language is assessed by tests of verbal comprehension, including following commands. Verbal repetition is assessed by the patient repeating phrases and sentences.

Visuospatial Function

Impairment in visuospatial (or visuoperceptual) abilities refers to the inability to appreciate the relative position of stimuli and objects in space, to integrate those objects into a coherent spatial framework and to perform mental operations involving spatial concepts. Visuospatial impairment is reported to be common in PD. Some tests of visuoperception require a motor component and are called visuoconstructive tasks. Such visuoconstructive tasks require either drawing or manipulation of test materials (e.g., WAIS-IV Block Design). Common drawing tasks include the Clock Drawing Test, and copying complex figures, such as the Rey Complex Figure Test. Tests of visuoconstruction are typically timed, therefore patients with PD are at a disadvantage on these tests, due to both the degree of motor disturbance and bradyphrenia. However, visuoperception may be affected even when motor demands are minimized. The Raven's Progressive Matrices

test, a measure of perceptual problem-solving, has been reported to be impaired in patients with PD. However, this test requires a high degree of conceptualization, which may be affected by the executive dysfunction seen in PD. Visuoperception is more impaired in PDD than nondemented PD or AD, but in several studies, visuoperception is similarly impaired compared with dementia with Lewy bodies.

Other

The Frontal Assessment Battery (FAB) provides a short (10 min), bedside test of 6 tasks of general frontal lobe function. The tasks relate to conceptualization, mental flexibility, motor programming, sensitivity to interference, inhibitory control, and environmental autonomy. Although this battery overlaps with other tests of conceptualization (Similarities of the WAIS-IV) and lexical fluency (FAS test), these tests are brief, including only 3 similarities and one letter, 'S.' Furthermore, the FAB addresses motor components with the Luria sequence, a tapping task presented with conflicting instructions, a 'Go-No-Go' task for inhibitory control, and prehensile behavior. The FAB scores demonstrated sensitivity to frontal lobe function, good psychometric properties, and correlated with the DRS and features of the Wisconsin Card Sort test when administered to 121 patients with frontal lobe dysfunction (including PD, corticobasal degeneration, progressive supranuclear palsy, frontotemporal dementia, and multiple system atrophy) and 42 normal controls.

Proposed Test Batteries and Diagnostic Guidelines

In recent years, there have been several organizations that have proposed batteries of neuropsychological tests (e.g., Parkinson's Disease Data and Organizing Center, Movement Disorders Society Task Forces), published critiques and recommendations for various cognitive and behavior rating scales (e.g., Movement Disorders Society, practice parameters by the American Academy of Neurology, NINDS/NIMH Work Group), and presented revised clinical diagnostic criteria for PD dementia (e.g., Movement Disorders Society Task Force). References are provided under Further Reading, and these proposed test batteries and diagnostic guidelines will be discussed briefly.

Parkinson's Disease Data and Organizing Center's (PD-DOC)

The Parkinson's Disease Data and Organizing Center (PD-DOC) is supported by the National Institute of Neurological Disorders and Stroke (NINDS) and administered by the University of Rochester. PD-DOC aims at facilitating and promoting collaborative clinical research in PD through a shared database of clinical, environmental risk and neuropathological data from PD subjects. The PD-DOC Cognitive/Behavioral battery, one part of the PD-DOC Core Data Set, includes the following: a Cognition/Behavior Questionnaire, the Mini Mental State Exam (MMSE), the Hopkins Verbal Learning Test, the Controlled Oral Word Association Test (COWAT), the Letter-Number Sequencing Test (LNS), the Geriatric Depression Scale (GDS-15), and the Neuropsychiatric Inventory Questionnaire (NPI-Q_). The proposed battery incorporates several widely used tests, but has limited visuospatial measurements.

Movement Disorders Society (MDS) Task Forces

In 2007, Emre et al. published clinical diagnostic criteria for PD dementia on behalf of a Movement Disorders Society (MDS) Task Force on PD dementia. The proposed criteria for the diagnosis of probable or possible PD dementia differ from criteria for dementia due to PD (294.1) in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV). The MDS criteria do not specifically require a memory deficit and state that impairment in at least two of the four core cognitive domains (impaired attention that may fluctuate, executive functions, visuospatial functions, and free recall memory that usually improves with cueing) should be present. In addition, there is a greater emphasis on behavioral symptoms such as apathy, depressed or anxious mood, hallucinations, delusions, and excessive daytime sleepiness.

In a follow-up article to the MDS criteria for PD dementia, the MDS Task Force for PD dementia addressed recommended diagnostic procedures for PD dementia. Dubois et al. propose practical guidelines based on a two-level process depending on the clinical scenario and expertise of the evaluator. Level I diagnostic recommendations, suited for the clinician who requires a simple, practical, and relatively quick set of tests, included a diagnosis of PD based on the Queen's Square Brain Bank criteria, development of PD prior to dementia onset, MMSE below 26, cognitive deficits severe enough to impact on daily living, and impairment in at least two tests (months reversed or seven backward, lexical fluency or clock drawing, MMSE pentagons, or 3-word recall), in the absence of major depression, delirium, or other abnormality. Additional testing that would provide greater neuropsychological detail, called Level II testing, is proposed for neuropsychological evaluation, clinical monitoring, research studies or pharmacological trials. Level II testing proposed several test options that could be used to assess cognitive and neuropsychiatric domains including global efficiency (Mattis DRS); executive function: working memory (Digit Span, Spatial Span [CANTAB], Digit Ordering test), conceptualization (Similarities, Wisconsin CST), set activation (verbal fluency), set shifting (Trail Making Test), set maintenance (Stroop Test, Odd Man Out), and behavioral control

(prehension behavior); memory (Rey Auditory Verbal Learning Test, Free and Cued Recall Test), Instrumental function: language (Boston Naming Test), visuoconstructive (Clock Drawing), visuospatial (Benton Line Orientation Test, Fragmented Letters from the Visual Object and Space Perception (VOSP) battery; and neuropsychiatric functions: apathy (Apathy Scale), depression (MADRS, Hamilton, Beck Depression Inventory, GDS-15), and visual hallucinations (Parkinson Psychosis Questionnaire), psychosis (NPI).

Other working groups

Critiques of rating scales for anxiety, depression, apathy, and psychosis and guidelines for diagnostic criteria have been published by several MDS Task Forces as well as NINDS/NIMH Work groups, among others. Clinimetric properties of the rating scales for these neuropsychiatric aspects in PD were systematically reviewed by MDS Task Forces. Proposed diagnostic criteria for depression and psychosis in PD are delineated in 2 papers by the NINDS/NIMH Work groups.

American Academy of Neurology (AAN) Practice parameters

In 2006, the AAN published an evidence-based review on the evaluation and treatment of depression, psychosis, and dementia in PD. Regarding screening for PD dementia, the authors reported one Class I and one Class III study. In the Class I study, the Cambridge Cognitive Examination and MMSE were administered to 126 PD subjects, 44% of whom had PD dementia. The CAMCOG and MMSE had similar sensitivities (95% and 98%, respectively); however, the CAMCOG was more specific (94% vs. 77%) but also took longer to administer. In conclusion, the MMSE and CAMCOG were recommended to be considered as screening tools for dementia in PD patients (Level B).

Other Considerations for Neuropsychological Assessment

It is important to consider other factors that may influence the neuropsychological, particularly the cognitive, assessment. Medications such as anticholinergics, sedatives, pain medications, among many others, may affect cognitive performance on tests. The effects of dopaminergic medications on cognitive function are highly variable with reports of no effect, worsening, and of improvement. Depression and anxiety may also influence test performance and cognitive function. Furthermore, sleep disturbances (nocturnal disruption and excessive daytime sleepiness) are found to have increasingly important effects on cognition.

Besides cognitive tests, the neuropsychological evaluation includes a brief psychiatric assessment. Although specific psychological rating scales are beyond the scope of this article, information from the patient and informant is usually obtained on depression, apathy, anxiety, hallucinations, and compulsive behavior.

Conclusions

In summary, the neuropsychological evaluation in PD comprises various tests aimed at assessing a number of cognitive domains. The evaluation documents whether cognitive impairment or dementia is present. Neuropsychological assessment is helpful in differential diagnosis, monitoring the course of disease progression, determining the possible benefits of cognitive interventions, and identifying psychological issues that may become the focus of treatment.

See also: Alzheimer's Disease and Parkinsonism; Bradyphrenia; Dementia with Lewy Bodies; Dementia, Movement Disorders; Executive Dysfunction; MMSE - Mini-Mental State Examination.

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Complex I Deficiency

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Glossary

Complex I – One of five multisubunit complexes of the mitochondrial electron transport chain involved in oxidative phosphorylation to generate ATP.
Cybrid – Cytoplasmic hybrid ('cybrid') cell lines that express mtDNA from an exogenous source.
Free radical – A highly reactive atom or molecule with an unpaired electron that tends to react with and damage other molecules.
Haplogroup – A set of DNA sequence variants that are found together in individual members of a population.
Heteroplasmy – A mix of wild-type and mutant mitochondrial DNA within the same cell or tissue.
MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) – A toxin that inhibits the activity of complex I of the mitochondrial electron transport chain.
Oxidative stress – A condition of excess reactive oxygen species (free radicals) resulting in cellular damage.
Somatic mtDNA mutation – A mitochondrial DNA mutation that was acquired rather than inherited.

Definition and History

Parkinson's disease (PD) is a complex disorder that results from the combined and interactive effects of multiple genetic and environmental factors (**Figure 1**). As our understanding of these diverse genetic and environmental influences increases, a convergence of data points towards an important role for mitochondrial complex I (CI) dysfunction in PD. CI, known also as NADH:ubiquinone oxidoreductase, is a multisubunit enzyme located in the inner mitochondrial membrane that is a component of the mitochondrial electron transport chain and catalyzes the transfer of electrons from NADH to coenzyme Q10 (ubiquinone). This process is coupled to the generation of a proton gradient that is used for the generation of ATP. There is a decrease in CI proteins in the substantia nigra (SN) of PD patients, and CI activity in this brain region is impaired. This CI dysfunction is an early feature of PD and is not a consequence of PD medications as it is present in early untreated patients. Within the brain, there appears to be specificity of the CI defect for the SN. On the other hand, reports of a CI defect in platelets indicate that there may be a systemic defect in CI activity in PD. CI activity in the SN is reported to be normal in multiple system atrophy, suggesting that it is not a non-specific consequence of neurodegeneration.

The presence of a CI defect in PD does not necessarily imply a causal relationship. CI dysfunction could be secondary to the degenerative process that occurs in PD, or could be an incidental feature. Data from CI inhibitors help to address this issue. The first data indicating that experimental inhibition of CI can lead to parkinsonism came from the identification of 1-methyl-4-(2′-methylphenyl)-1,2,3,6-tetrahydropyridine (MPTP). MPTP is a toxin that inhibits CI activity and induces dopaminergic neuronal death and parkinsonism in multiple animals, including in humans following accidental self-injection by human IV drug abusers. However, MPTP also has other actions, leaving uncertainty as to its mechanism of toxicity. Subsequent studies revealed that another specific inhibitor of CI, rotenone, induces progressive and preferential degeneration of dopaminergic neurons following systemic administration over 4 weeks in rats. This confirms that induction of a CI defect can reproduce a key feature of the pathology of PD, and that even systemic inhibition of CI activity can preferentially affect dopaminergic SN neurons.

These data raised the possibility that CI dysfunction in the SN in PD may play an important role in the pathogenesis of PD, thus leading to a search for the origin of the CI defect in PD. Mitochondrial CI dysfunction could result from environmental toxins, genetic factors, or both. Genetic factors might include mutations in nuclear-encoded mitochondrial genes or in genes encoded on the mitochondrial genome. The mitochondrial genome is maternally inherited, and some studies have suggested a maternal bias in PD inheritance, with a greater likelihood of having an affected mother when a parent of a PD patient is also affected. However, results have been inconsistent, and this remains a controversial issue. In an experimental approach to testing the hypothesis that mitochondrial genetic abnormalities might account for the CI defect in PD, cytoplasmic hybrid ('cybrid') cell lines expressing mtDNA have been prepared from PD patients. These cybrid cell lines also manifest CI deficiency, a finding now confirmed by at least three research groups, indicating that the defect can be transmitted via mtDNA, thus suggesting that mtDNA mutations account for the defect.

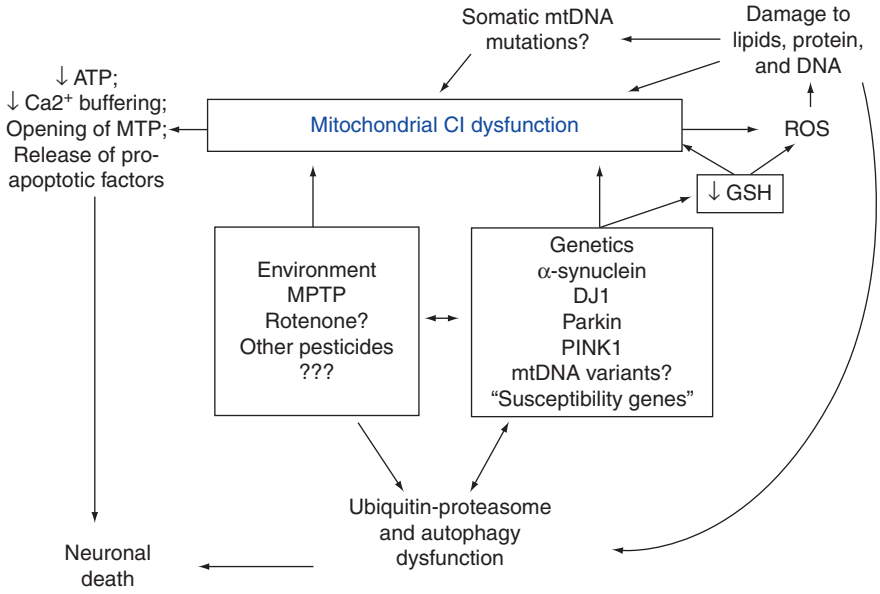

Figure 1 Factors contributing to neuronal death is Parkinson's disease.

Based in part on these results from studies of cybrid cell lines, a set of studies examined the possibility of *inherited* mtDNA mutations in PD patients. A common A to G variant at nucleotide position 10398 in the mtDNA gene encoding the ND3 subunit of CI has been reported to be present at a lower frequency in PD patients, suggesting that this variant may influence PD risk. On the other hand, results have been inconsistent across studies, and the role of this variant in PD remains uncertain. Similarly, variable results have been reported for the association of specific mitochondrial haplogroups with PD. Familial parkinsonism with SN neuronal loss has been reported in association with an inherited G11778A complex I mutation, a mutation more commonly associated with Leber's hereditary optic neuropathy. Familial parkinsonism is also seen in association with multiple somatic mtDNA deletions caused by a mutation in the mitochondrial DNA polymerase gene, Polγ. However, other studies looking at inherited mtDNA mutations in typical idiopathic PD patients have failed to identify pathogenic mtDNA mutations in the vast majority of patients, leaving an apparent discrepancy between results from studies of mtDNA versus the cybrid studies. As a result of this discrepancy, the specific role of inherited mtDNA mutations in the CI defect in PD remains uncertain.

More recently, research has focused on the possibility that acquired (somatic) mtDNA mutations might accumulate with age, eventually reaching levels sufficient to cause mitochondrial dysfunction and neuronal death. Such point mutations may be individually rare, and thus not detectible by standard sequencing methods, yet might accumulate to reach high aggregate levels. Levels of large mtDNA deletions indeed accumulate with age in SN neurons and are reported to reach relatively high levels, with ~43% of mtDNA molecules harboring a mutation in controls compared to 52% in PD, though this difference was of borderline significance ($p = 0.06$). mtDNA deletion levels were higher in cytochrome *c* oxidase deficient neurons, suggesting that the deletions may contribute to mitochondrial dysfunction in these neurons. Low-level (generally 1% or less) heteroplasmy for mtDNA point mutations in the mitochondrial gene encoding the ND5 subunit of CI has been reported to be common in frontal cortex tissue from PD patients but rare in controls. However, this finding requires verification, and the significance of such low-level mutations remains uncertain. Thus, additional data are needed to clarify the role of somatic mtDNA point mutations and/or mtDNA deletions in PD.

An alternative (or additional) cause of the CI defect in PD may be a deficiency of L-γ-glutamyl-L-cysteinylglycine (glutathione). Glutathione is the predominant intracellular thiol antioxidant. Glutathione is deficient at very early stages of PD, even prior to a detectible defect in CI activity. Induction of glutathione deficiency in cell lines and in mice leads to a specific defect in CI activity, raising the possibility that the glutathione deficiency in PD may contribute to CI dysfunction. Pesticide exposure represents another potential cause of CI dysfunction. Some pesticides such as rotenone are CI inhibitors, raising the possibility that environmental factors may also contribute to the CI defect in PD. However, neither glutathione deficiency nor pesticide exposure as a cause of the CI defect in PD would account for the ability to transfer the CI defect to cybrid cell lines expressing mtDNA from PD patients. It is likely that multiple factors contribute to mitochondrial impairment in PD, and our

understanding of the cause of the CI defect in PD remains incomplete.

CI dysfunction may contribute to the pathogenesis of PD by several mechanisms. CI dysfunction leads to an increase in the production of damaging oxygen free radicals. Consistent with this, levels of oxidative damage to protein, lipids, and DNA are increased in the SN in PD. mtDNA, owing to its close proximity to the site of free radical generation and due to its lack of protective histone proteins, is particularly susceptible to oxidative damage, and thus levels of oxidative damage to mtDNA in the SN rise sharply with age and even more so in PD. Impaired CI activity could also lead to reduced generation of ATP, and indeed cybrid cell lines expressing mtDNA from PD patients generate less ATP. Mitochondria also serve roles in buffering transient rises in intracellular calcium, and can mediate apoptosis, providing additional potential mechanisms by which complex I impairment may influence neuronal viability.

Oxidative stress may link CI dysfunction to other mechanisms associated with PD, for example by contributing to proteasome dysfunction and by enhancing the toxicity of alpha-synuclein. Conversely, some genetic causes of PD are linked to mitochondrial dysfunction and oxidative stress. Autosomal recessive PD due to mutations in DJ-1 may result from loss of DJ-1's normal function to stimulate glutathione synthesis. Loss of function of either parkin or PINK1 (a mitochondrial protein kinase), both causes of autosomal recessive PD, leads to mitochondrial structural abnormalities in experimental animals. Thus, a diverse set of data converge on mitochondrial dysfunction, and in particular on dysfunction of mitochondrial CI, in the pathogenesis of PD.

See also: 3-Nitropropionic Acid; Mitochondrial Dysfunction; Mitochondrial Encephalopathies; MPTP; Parkinson's Disease: Definition, Diagnosis, and Management; Parkinson's Disease: Genetics; Pesticides.

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Complex Regional Pain Syndrome

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Glossary

Allodynia – An innocuous mechanical or thermal stimulus is perceived as painful.

Central sensitization – A process similar to long-term potentiation (LTP) in which enhanced synaptic transmission, not dependent on a continued afferent input, occurs.

Cytokines – Cytokines are a category of signaling proteins and glycoproteins produced by hematopoietic and nonhematopoietic cell types.

They have pro- and antiinflammatory effects both on the adjoining cells and throughout the organism.
Hyperalgesia – An increased perception of pain to a painful stimulus.
Hyperpathia – An increased threshold to a painful stimulus that once exceeded, causes pain that reaches maximum intensity very rapidly, is overwhelming, and is not stimulus bound.
Long-term depression (LTD) – Weakening of a neuronal synapse (often from low frequency stimulation of A-delta fibers) that lasts from hours to days.
Long-term potentiation (LTP) – The persistent increase in synaptic efficacy following high-frequency stimulation of A-delta or C-fiber afferents.
Microglia – Central nervous system (CNS) cells that are the main form of acute immune defense in the CNS.
Wind-up – The progressive amplification of a synaptic response after repeated stimulation of afferent fibers.

Definition and History

Complex regional pain syndrome (CRPS), formerly known as reflex sympathetic dystrophy (RSD), was first described by Silas Weir Mitchell in Union soldiers during the American Civil War. It is a term that describes a severely painful condition that follows soft tissue, bone, or nerve injury. The pain does not respect a nerve or root distribution (regional), exceeds the expected magnitude and duration of the inciting event, and is often burning in quality. It is associated with autonomic dysregulation, neurogenic edema, a movement disorder and trophic changes of affected areas. The process spreads over time and may become generalized. Early in its course, it is primarily inflammatory with autonomic dysregulation and neurogenic edema predominant. As it progresses, pain, the movement disorder, atrophy, and dystrophy become more prominent manifestations. Early it is a peripheral process but over time there is centralization with CNS dysregulation of the somatosensory, autonomic, and motor systems.

In CRPS I, terminal nociceptive afferent and C and A-delta fibers are involved in soft tissue and bone whereas in CRPS II, major peripheral nerves are injured.

Epidemiology/Risk Factors

CRPS I occurs in 1–2% of fractures and 1–5% of patients following peripheral nerve injury. An early population-based study from Olmstead County Minnesota demonstrated an incidence of approximately 5.5 per 100 000 person years at risk. A more recent population-based study from the Netherlands reported an incidence of 40.4 for females and 11.9 for males per 100 000 person years at risk. CRPS I is much more prevalent than CRPS II (SII), and injury to the central somatosensory system is the inciting cause in approximately 10% of patients. All studies report a female preponderance of 4:1, the average age of onset occurs between 37 and 50 years of age, and the upper extremity is slightly more involved than the lower. Fractures, sprains, nerve traction injuries, and surgical trauma comprise the majority of initiating events. A great number of patients had been casted prior to the onset of CRPS.

Clinical Features

The statistical technique of factor analysis, which combines statistically relevant combinations of signs and symptoms in a syndrome, has demonstrated four derived factors for CRPS: (1) spontaneous and evoked pain (allodynia, hyperalgesia, and hyperpathia); (2) temperature asymmetry and color change; (3) edema and sweating asymmetry; and (4) motor dysfunction and trophic changes. In a patient with two of four signs and three of four symptoms, a diagnosis of CRPS can be made with 0.85 sensitivity and 0.69 specificity.

Cluster analysis, in which the patterns of CRPS signs and symptoms in groups of patients are analyzed, revealed three statistically distinct subgroups: (1) a mild predominant vasomotor syndrome; (2) a limited neuropathic pain and sensory syndrome; and (3) a severe spreading syndrome containing all factors. If one symptom for each factor and one or more signs in two or more factors are present, the sensitivity is 0.70 and the specificity is 0.96.

In the initial stages of the illness, the extremity is most often warm and associated with neurogenic edema and sympathetic paralysis. As the process centralizes and spreads, patients demonstrate increasing dynamic and static mechano-allodynia, and a spontaneous burning pain often accompanied by a deep aching pain in the muscles and joints, which is frequently interposed with lancinating pain. Cold thermo-allodynia is more common than that due to heat. All patients have difficulty in maintaining smooth precise movements and are weak. An exacerbation of the normal physiologic tremor, spasms, myoclonic jerks, increased reflexes, and dystonia are commonly seen. Edema may persist along with color change, as the extremity becomes cold, cyanotic, hyperhidrotic, and discolored from livedo reticularis and mottling. Severe muscle, bone, skin, and cartilage atrophy destroy the extremity. Nails become thickened and ridged, and there is loss of hair in the affected area. Late-stage patients suffer hyperpathia

in which pain thresholds are higher, but once exceeded, reach maximum intensity too quickly and are not stimulus bound.

Other common signs and symptoms that are not well characterized are (1) sensitization of plexi and nerve roots; (2) fatigue; (3) cognitive dysfunction; (4) syncope and persistent tachycardia; (5) migraine headache; (6) sensitization of the intercosticobrachial nerve (anterior chest wall pain); (7) dysphagia (cricopharyngeus dysfunction); (8) blurred vision; (9) body perception disturbance; (10) dizziness; (11) neglect-like and distorted body perceptions; (12) skin lesions; (13) difficulty in initiating and controlling micturition (when both legs are involved); (14) irritable bowel symptoms and gastroparesis; (15) dysynchiria (pain evoked in the affected area by watching the unaffected area being manipulated); and (16) decreased perceptual learning.

Diagnostic Procedures

CRPS I and II are clinical diagnoses arrived at by factor analysis as noted above. Confirmatory tests are (1) bone X-ray; (2) bone scintigraphy; (3) skin temperature; and (4) magnetic resonance imaging. It should be emphasized that negative results do not disprove the diagnosis of CRPS. Other tests that are also helpful in diagnosis are (1) quantitative and autonomic sensory testing; (2) autonomic function tests (infrared thermometry and thermography; quantitative sudomotor axon reflex tests (QSART), thermoregulatory sweat tests); and (3) laser Doppler flowmetry under controlled body thermoregulation.

Plain X-rays and bone densitometry studies reveal (1) patchy demineralization of periarticular bone and diffuse osteoporosis; (2) bone cysts and subperiosteal bone resorption; and (3) increased endosteal resorption of cortical bone. These changes are most frequently seen in late stages.

Patients suffering from CRPS for less than one year demonstrate (1) early accelerated blood flow into the affected extremity; (2) increased diffuse activity during the blood pool phase; and (3) increased periarticular uptake in the delayed static phase. The study is positive in less than 50% of patients and becomes less effective with disease duration.

MRI demonstrates joint effusions, edema along tissue planes, and in soft tissue. Bone marrow edema is inconsistently present in acute phases and absent in long-standing disease. Sympathetic blocks should be performed early both to establish if the process is sympathetically maintained and for therapy. Underlying maintaining features, such as a poorly healed fracture, neuroma, nerve entrapment, and recurrent disc, are the source of a persistent nociceptive barrage and must be addressed for successful treatment.

Pathophysiology of CRPS

CRPS most often follows injury to peripheral nerves or to their terminal twigs in tissue. The injury induces an afferent barrage of 50–100 Hz which is maintained by an inflammatory soup of cytokines, prostaglandins, protons, bradykinin, serotonin, and neurotrophic factors released from inflammatory and immune cells as well as from the blood. The peripheral C-fiber and A-delta fibers that are injured are sensitized by the activation of intracellular kinases A(PKA) and C(PKC) as well as by the phosphorylation of tetrodotoxin (TTX)-resistant sensory neuron-specific sodium ion channels (SNS). This decreases their activation threshold and the rate of deactivation, and increases their inward sodium current. There is a dynamic interplay from the injured area to the dorsal root ganglia by means of antegrade and retrograde transport. There is concomitant induction of microglia at the injured segmental spinal levels which then secrete inflammatory cytokines and activate astrocytes. These processes may perpetuate and amplify the initial response to injury. New information suggests that immune cells from the site of injury may invade the spinal cord, become fully active, and contribute to this immune response. Free radicals (nitric oxide, aldehydes, and hydroxyl radicals) generated from tissue injury and Wallerian degeneration may also contribute to further injury at the site of injury and in the dorsal horn (DH).

The injury barrage itself or the activation of a specific set of mechano-insensitive C-fibers releases the magnesium block of the glutamatergic *N*-methyl-D-aspartate (NMDA) receptor allowing Ca^{2+} influx into the nociceptive neuron. The concentration of Ca^{2+} achieved and its spatiotemporal sequence of entry determine if the pain transmission neurons (PTN) will demonstrate long-term potentiation (LTP) with increased sodium inward currents, or long-term depression (LTD) in which synaptic activity is depressed. These cascades are extremely complicated and depend on aspects of glutamate clearance, post synaptic density signaling, lateral or synaptic placement of AMPA receptors, and upregulation of NMDA receptor subtypes. The intracellular enzymatic cascades initiated by the Ca^{2+} influx, prominently featuring phosphokinases and phosphatases, determine the novel gene expression that produces abnormal sodium channels and proteins that are axonally transported and inserted into the affected axons of pain transmission neurons. These molecular events that induce peripheral and central sensitization of nociceptive afferents and pain transmission neurons, then lead to spontaneous pain, an increase in the size of their receptive fields, a lowered firing threshold of contiguous PTNs, and abnormal pain processing. A substantial experimental literature has demonstrated structural changes in dendritic spines that correlate with late-stage LTP (enlarged spines) and LTD (shrunken

spines). These structural changes, in addition to the death of inhibitory DH neurons, may contribute to the intractability of late-stage illness. The only human spinal cord material of a CRPS patient demonstrates loss of neurons at the appropriate level (L5 of the original injury with generalized CRPS of 20 years duration), as well as bilateral activation of microglia and astrocytes throughout the cord, but most prominently at L5.

The sympathetic nervous system has a prominent role in maintaining pain in a significant proportion of patients with early CRPS. Anatomic connections between efferent sympathetic fibers and the somatic and pain systems are made in the dorsal root ganglia and in the periphery. Sympathetic fibers derived from blood vessels in the DRG sprout and form baskets around large mechanoreceptive neurons and innervate small, thinly myelinated nociceptive afferents. At the site of injury, there is adrenoreceptor activation of nociceptive afferents sensitized from the adrenal release of epinephrine, as well as indirect effects on these fibers from mediators such as bradykinin, neurotrophic factors, and prostanoids. In addition to sympathetic peripheral nociceptive coupling, adrenergic neurons are pivotal in pain processing at several cortical and brainstem levels. The recent ischemia-reperfusion model of CRPS is compatible with the role of autonomic dysfunction in the pain of CRPS. Most importantly, sympatholysis, early in the course of illness when the pain is sympathetically maintained, has cured a subset of patients.

Early in the process, there is evidence of peripheral inflammatory neurogenic edema related to nociceptive axonal release of vasoactive neuropeptides, increased axon reflex vasodilatation, and disordered endothelial cell function. Sympathetic paralysis and neurogenic edema appear to be the major cause for the warm-affected extremity seen in acute CRPS. In chronic phases of the illness, the extremity is cold and cyanotic due to vascular changes that include increased sensitivity of affected blood vessels to circulating catecholamines, from upregulation of adrenoreceptors, a decrease of neurotransmitter uptake, changes in second messenger systems, and endothelial cell dysfunction.

The use of Doppler fluxmetry has demonstrated loss of control of skin blood flow when sympathetic activation is induced by the cold pressor test or the Valsalva maneuver in CRPS patients. These patients also lose normal sympathetically mediated wave-like fluctuations in venous tone (vasomotion). Recovery of sympathetic vasoconstrictor activity has been shown in one study to coincide with recovery from acute CRPS I.

Under strictly controlled environmental conditions (22–24 °C room temperature, 30° supine position for 30 min), temperature side asymmetry of >2.2 °C is 76% sensitive and 100% specific for the diagnosis of CRPS. Laser Doppler assessment of skin blood flow during whole body warming or cooling has demonstrated (1) an acute phase (mean disease duration of 4 months) with higher skin perfusion and temperature; (2) an intermediate phase (mean duration of 15 months) in which the affected limb was either warmer or colder than the contralateral extremity; and (3) a 'chronic' phase (>28 months) in which the extremity is cold and demonstrates less sympathetically controlled thermoregulatory blood flow.

The quantitative sudomotor axon reflex test (QSART) and the thermoregulatory sweat test (TST) have been shown to be abnormal in CRPS. In acute CRPS (5 weeks), both demonstrated greater sweating, but at >7 years, only the TST demonstrated asymmetry. Sweat glands under normal conditions respond to cholinergic stimulation. Iontophoresis of an α-adrenergic agonist induced significantly increased sudomotor output in CRPS-affected limbs but not in unaffected or control limbs. This is evidence that adrenoreceptor activation may occur in systems not normally under adrenergic control. Alternatively, calcitonin gene-related peptide (CGRP), released during the course of neurogenic inflammation, may also directly stimulate the sweat glands.

The movement disorder of CRPS I and II is seen to some degree in virtually all patients. At the spinal level, experimental studies demonstrate SP and CGRP in the dorsal, ventral, and intermediolateral columns of the spinal cord. They induce (in vitro) prolonged depolarization of anterior horn cells (blocked by $GABA_b$ agonists) and may modulate the gain of the nocifensor withdrawal reflex. The sympathetic system has profound effects on the strength of skeletal muscle contraction (Orbeli effect), neuromuscular transmission, anterior horn function, and spinal cord reflexes. The intrafusal fibers of the muscle spindle and ventral horn motor efferents are sympathetically innervated. A dramatic improvement of motor function has been demonstrated in a subset of CRPS patients following sympathetic blockade.

Electrophysiological studies in CRPS patients with dystonia demonstrate impaired reciprocal inhibition, a decreased threshold of the tonic and phasic components of the stretch reflex, and diminished vibratory inhibition of the H reflex. These patients also have impairment of DH interneuronal circuits that mediate presynaptic inhibition. There is evidence that the (HLA)-DR13 genotype may predispose to multifocal or generalized dystonia in these patients.

The tremor of CRPS is often seen with other components of the movement disorder and (1) has a frequency of 3–7 Hz, (2) is most often intentional but may be postural kinetic, and (3) is an enhancement of the normal physiologic tremor.

Central plastic changes occur in the sensorimotor system during the course of CRPS, as demonstrated by fMRI, SPECT, PET, and magnetoencephalographic studies. The impairment of sensorimotor integration is demonstrated by (1) motor cortical disinhibition; (2) kinematic deficits in target reach and grip; and (3) a mismatch

between sensory input and motor efference. The other aspects of the movement disorder of CRPS that are not well characterized are the difficulty of initiating and maintaining precise movements, myoclonus and spasm as well as increased reflexes.

The dystrophic changes noted in long-standing CRPS patients have been ascribed to the activation of osteoclastic mechanisms and elastases by SP, CGRP (bone inflammatory changes), the destructive effects of free radical generation, and a decrease of nutritive blood supply to the affected areas.

See also: Dystonia; Dystonia, Secondary.

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COMT Inhibitors in the Treatment of Parkinson's Disease

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Glossary

Area under the curve (AUC) – The overall amount of drug in the blood after a dose.
Basal ganglia – Collection of nuclei deep to the white matter of cerebral cortex, including the putamen, caudate, nucleus accumbens, globus pallidus, substantia nigra, subthlamic nucleus.
Bioavailability – The extent or rate of the administered drug that reaches the systemic circulation that becomes available at the physiological site of action.
Bioequivalence – The property wherein two drugs are expected to be essentially the same in bioavailability and effects.
Blood–brain barrier (BBB) – A physiological mechanism between the brain parenchyma and blood that alters the permeability of capillaries that restricts the passage of various substances while allowing the passage of essential substances.
Chorea – Involuntary, random, jerky, irregular, writhing movements.
Choreiform – Characteristic of chorea.
C_{max} (maximum concentration) – The highest concentration of drug in the blood that is measured after a dose.
Dystonia – Sustained muscle contractions that cause twisting and repetitive movements or abnormal postures.
Dystonic – Characteristic of dystonia.
Glucuronidation – The detoxification pathway in the liver in which glucuronic acid is conjugated with toxins.
$t½$ (half-life) – The time required for the concentration of the drug in the body to be reduced by one-half.
T_{max} (time to maximum concentration) – The time C_{max} occurs.

Background/History

Replacing striatal dopamine is the principal pharmacologic strategy in the management of the motor features of Parkinson's disease (PD). Dopamine does not cross the blood–brain barrier (BBB) so its precursor, levodopa, was investigated as a potential dopamine replacement therapy. The introduction of oral levodopa by Cotzias in 1967 constituted a major breakthrough that paved the way for additional pharmacological agents. Levodopa is the most efficacious agent for the treatment of the motor features of PD and is effective in early as well as advanced disease. Every patient eventually requires it to maintain adequate function. However, as the disease advances, many patients on long term levodopa therapy experience motor complications which consist of wearing 'off' motor fluctuations, when the patient's motor response does not last to the next levodopa dose, and choreiform or dystonic involuntary movements known as dyskinesias. The development and expression of motor complications are closely related to the combination of disease severity and the peripheral pharmacokinetics of levodopa, with its relatively short plasma elimination half-life of about 60 min. Postsynaptic striatal dopamine receptors are normally exposed to relatively constant dopamine stimulation. Achieving a prolonged levodopa response requires the uptake of levodopa into remaining nigro-striatal neurons, conversion of levodopa to dopamine, and subsequent storage and controlled release. As dopamine neurons are lost, this storage and slow release capacity is diminished, resulting in a shortening of the duration of the clinical response which more directly reflects the levodopa half-life. When this occurs, postsynaptic dopamine receptors become exposed to nonphysiologic pulsatile dopamine stimulation from levodopa administration, resulting in a cascade of intracellular changes that alter basal ganglia output and cause the clinical expression of dyskinesia. Therefore, attempts have been made to deliver levodopa in a more continuous fashion to reduce wearing off episodes and avoid the development of dyskinesia.

COMT inhibitors modify levodopa's bioavailability by extending its plasma elimination half-life and allowing more levodopa to be delivered to the brain over time, thereby providing more continuous, sustained stimulation of striatal dopamine receptors. In patients with wearing off motor fluctuations on levodopa, the addition of a COMT inhibitor reduces 'off' time, increases 'on' time, and allows a reduction in the levodopa dose. The first generation COMT inhibitors were disappointing, but the second generation compounds tolcapone (Tasmar) and entacapone (Comtan), were found to be more potent

and selective and are currently used in clinical practice. Tolcapone was introduced in 1997 and entacapone in 1998. Because of rare but potentially fatal hepatoxicity associated with tolcapone but not entacapone, tolcapone's use has been restricted, while entacapone is more widely used. This chapter will discuss the development of these COMT inhibitors, the clinical studies that established their place in the management of PD, and current and future status.

Mechanism

COMT is a widely distributed enzyme found in the brain, liver, kidney, erythrocytes, and gastrointestinal tract. In the brain, it is found in glial cells but not in nigrostriatal dopamine neurons. Its function is not specific to the dopamine system and it is also involved in the peripheral metabolism of other catecholamines (adrenaline and noradrenaline).

Levodopa is actively transported through the mucosa of the proximal small bowel where it competes with other large amino acids for systemic absorption. Once absorbed into the bloodstream, it is transported across the BBB with less than 1% of the ingested amount entering the brain. Levodopa is metabolized mainly by two enzymes: (1) by aromatic acid decarboxylase (AADC) to dopamine and (2) by COMT to 3-*O*-methyldopa (3-OMD). To reduce gastrointestinal side effects, including nausea, that are due to the peripheral metabolism of levodopa to dopamine, dopa decarboxylase inhibitors (DCI), such as carbidopa and benserazide, were introduced. Since then, levodopa has been routinely combined with a DCI to reduce nausea and increase central bioavailability. Still, only 10% of administered levodopa enters the brain. When administered with a DCI, the main route of peripheral levodopa metabolism is via COMT to form 3-OMD which is devoid of dopaminergic activity. The addition of a COMT inhibitor to levodopa/DCI increases the elimination half-life of levodopa and increases its central bioavailability.

Tolcapone

Tolcapone (3,4dihydroxy-4′-methyl-5-nitrobenzophone) is a nitrocatechol-type compound and a selective and reversible inhibitor of COMT. It is lipophilic and crosses the BBB to a limited degree. It is rapidly absorbed and highly protein bound with a half-life of 2–3 h and a time to reach peak concentration (Tmax) of 1.5–2 h. When given together with levodopa/DCI, tolcapone increases the bioavailability and plasma elimination half-life of levodopa and the area under the curve (AUC). It does not affect peak plasma concentration (Cmax) or Tmax. Tolcapone is almost completely metabolized, glucuronidation being the most important route of metabolism. It is excreted in urine and feces. Large, multicenter studies in PD patients experiencing motor fluctuations on levodopa/DCI showed that the addition of tolcapone to levodopa/DCI significantly reduces 'off' time, increases total 'on' time, improves motor function, and allows a reduction in levodopa/carbidopa dosage and frequency, compared to placebo. Benefits of tolcapone were also observed in patients with a stable response on levodopa/carbidopa (i.e., without motor fluctuations), with significant reductions in United Parkinson's Disease Rating Scale (UPDRS) scores for activities of daily living and motor function.

Tolcapone is indicated as an adjunct to levodopa/carbidopa for the treatment of parkinsonian signs and symptoms. Because of the risk of fatal hepatotoxicity, it should ordinarily be used in patients experiencing fluctuations who are not responding to other adjunctive therapies.

Entacapone

Entacapone is also a nitrocatechol-type compound and a selective and reversible inhibitor of COMT. Unlike tolcapone, entacapone does not cross the BBB. It is readily absorbed across the intestinal mucosa and is highly protein bound, with a plasma elimination half-life of 0.4–0.7 h. Entacapone 200 mg given 4–6 times daily with levodopa produced a 33% reduction in COMT activity. The administration of entacapone with levodopa/carbidopa immediate release (IR) increases levodopa AUC by 35–40%, and prolongs the levodopa half-life by 1.3–2.4 h. Entacapone does not significantly influence levodopa/DCI Tmax and Cmax. A similar pharmacokinetic effect is seen when entacapone is used with levodopa/carbidopa controlled release.

A double-blind, placebo controlled trial of PD patients with motor fluctuations on levodopa/carbidopa revealed that the addition of entacapone compared to placebo provided a significant increase in 'on' time per day of approximately 1 h, while another study using a similar protocol demonstrated an increase in the mean daily 'on' time by 1.4 h. Both studies allowed a 12% reduction in levodopa dose. Other studies in patients with motor fluctuations demonstrated that the addition of entacapone to levodopa/DCI increased 'on' time and improved motor function as measured by the UPDRS and increased quality of life. In patients with motor fluctuations on levodopa/DCI, the addition of either entacapone or cabergoline (a long acting dopamine agonist) similarly improved UPDRS scores, quality of life as measured by the Parkinson Disease Questionnaire (PDQ)-39, and reduced daily 'off' time. However, the reduction in 'off' time occurred faster in the entacapone group than the cabergoline group. Entacapone has also been demonstrated to provide some benefit for patients who have a

stable response to levodopa (i.e., not experiencing motor fluctuations), including motor improvement and improvement in several quality of life measures. Entacapone is indicated as an adjunct to levodopa/DCI to treat patients experiencing end-of-dose wearing-off. It has no antiparkinsonian effect on its own. It can be combined with immediate or sustained release levodopa/carbidopa.

Levodopa/Carbidopa/Entacapone (Stalevo)

Stalevo combines levodopa, carbidopa, and entacapone in one tablet. It was approved based on demonstration of bioequivalence with levodopa/carbidopa plus entacapone and would therefore be expected to provide the benefits of adding entacapone to levodopa/carbidopa and also offer increased convenience because less pills are required. The majority of fluctuating patients given Stalevo or levodopa/DCI given in combination with entacapone experienced clinical improvement and over 80% experienced a reduction in fluctuations compared to levodopa/DCI treatment alone, but patients preferred one tablet, Stalevo, rather than taking two tablets, levodopa/carbidopa plus entacapone. Patients suboptimally controlled with levodopa/carbidopa controlled release (CR) can also be switched to Stalevo with improvements in motor function and quality of life.

Stalevo is currently indicated for patients with wearing off motor fluctuations on levodopa/DCI. However, two studies have examined its effects as first line therapy in early PD. The first-step studydemonstrated that Stalevo 100 three times a day (TID) provided greater symptomatic benefit than levodopa/carbidopa 25/100 TID without increasing motor complications. However, the recently completed Stalevo Reduction in Dyskinesia Evaluation (STRIDE–PD) trial showed that treatment with Stalevo compared to levodopa/carbidopa in early PD was not associated with a delay in the appearance of dyskinesia.

Current and Future Clinical Implications

Tolcapone should only be used in patients with motor fluctuations refractory to treatment with other medications including entacapone. The initial tolcapone dose is 100 mg TID and this can be increased to 200 mg TID, if necessary. When using tolcapone, liver function tests must be monitored during the first 6 months and periodically thereafter. Entacapone comes in 200 mg tablets and is routinely administered with each dose of levodopa/DCI to a usual maximum of 8 tablets (1600 mg) per day.

Stalevo is available in dose combinations of levodopa/carbidopa/entacapone 50/12.5/200 mg (Stalevo 50), 100/25/200 mg (Stalevo 100), 150/37.5/200 mg (Stalevo 150), and 200/50/200 (Stalevo 200). It provides increased convenience and reduced pill burden compared to levodopa/carbidopa plus entacapone administered separately. Replacing levodopa/carbidopa with Stalevo in patients with mild-to-moderate wearing-off is simple and can be done safely with or without decreasing the levodopa dose. Since COMT inhibition increases levodopa bioavailability, side effects from increased dopaminergic stimulation may occur. These include an increase in dyskinesias or nausea. The levodopa dose may be reduced in an effort to ameliorate these side effects. Diarrhea is the most frequent non-dopaminergic adverse event. Dark yellow to reddish-brown discoloration of urine can also be seen. Overall, COMT inhibitors may be better tolerated than dopamine agonists.

Stalevo was found to be more efficacious in controlling parkinsonian symptoms than levodopa/carbidopa in early PD when administered at the same levodopa dose, without increasing motor complications. The STRIDE-PD, however, did not determine that Stalevo causes less dyskinesia than levodopa/carbidopa when given in early disease. There is great interest in further smoothing levodopa delivery to the brain in an effort to further reduce the occurrence of motor fluctuations and dyskinesias. This might be brought about by the development of longer duration, high efficacy COMT inhibitors, or novel levodopa medication formulations.

See also: Anticholinergics and Movement Disorders; Dopaminergic Agonists in Parkinson's Disease; Levodopa; Monoamine Oxidase Type B Inhibitors; Motor Fluctuations; Parkinson's Disease: Definition, Diagnosis, and Management.

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Concentric Needle EMG

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Glossary

Concentric needle EMG (CNEMG) – One of the types of commonly used EMG needles for standard EMG studies.
Monopolar needle EMG – Another type of commonly used EMG needle for standard EMG studies.
Motor unit action potential (MUAP) – An electrical potential generated by contracting muscle fibers innervated by the same motor unit.
Stiff-person syndrome – A movement disorder characterized by increasing muscle-induced rigidity resulting from continuous muscle contraction, which can be recorded by either a monopolar or concentric needle EMG.

Definition

Electromyograms (EMGs) have been used in the diagnosis of neuromuscular disorders for over 30 years. The test includes two parts: one part is called the Nerve Conduction Study (NCS). An analogous name is the Nerve Conduction Velocity (NCV). In this part of the test, an electrical stimulator is placed on the skin and current is applied to a sensory or motor nerve (via percutaneous stimulation), creating an action potential in order to assess various nerve functions, such as measuring the velocity of nerve conduction and amplitude of an evoked response.

The second part is the EMG. This part of the test is conducted by inserting a needle into a muscle to record muscle potentials. Thus, the needle EMG is essentially a recording electrode. While both portions of the test are commonly performed, the test is often called by the second part of the test: the EMG.

The two most common EMG needles used for performing the study are the concentric needles (CNEMG) and monopolar needles. The difference between them is that the CNEMG contains the active and reference electrodes, while the monopolar needle contains only the active electrode, and thus requires a reference electrode – typically placed on the surface of the skin near the monopolar needle – to complete the recording circuit. Depending on the examiner, either needle can be used, as each records fairly similar potentials from the muscle.

How EMGs 'work' is based on the fact that skeletal muscles generate electricity, and it is this electrical activity that the EMG records much the way electrocardiogram (EKG) electrodes are used to record the electrical activity of cardiac muscle, except that EKG electrodes are placed on the surface of the skin, while the needle EMG is placed directly into the muscle.

In normal muscle physiology, an electrical discharge is produced while the muscle cells contract (depolarizes), generating a motor unit action potential (MUAP). The electrical discharge is picked up by the needle EMG and is transmitted to a digitalized screen where the interpreter can view this electrical potential and determine whether it is a 'healthy' discharge or an unhealthy one. In addition to the visual assessment of the MUAP, the electrical discharge is converted to sound, which assists the interpreter in characterizing the health of the discharging muscle potential.

In addition to assessing the muscle's electrical potential during active contraction, it is also evaluated in the relaxed state. Normally, healthy muscles at rest do not produce electrical discharges, except for a few physiologically important exceptions. On the other hand, when muscles have lost their innervation or have been directly damaged, a spontaneous depolarization of the muscle cells, called fibrillation potentials, occurs.

Aside from its traditional uses, EMGs have also been increasingly used to assist in the evaluation of patients with movement disorders by expanding the accuracy of the physical examination by allowing the examiner to evaluate conditions that are not easily discernable to the naked eye.

Examples of needle EMG in the evaluation in movement disorders include involuntary movements such as myoclonus, dyskinesias, or dystonias. Other examples include assessment of tremors such as essential tremors, cerebellar tremor, or exaggerated physiological tremor. Evaluations further include assessment of tone, including the stiff-person syndrome.

It should be noted that either the monopolar or concentric needle can be used to assess movement disorders, although, in the author's opinion, the compact nature of the concentric needle is better suited to assess these conditions. Some movement disorders are better evaluated with a surface EMG recording electrode. It is the type of condition assessed that dictates which recording method is best used for evaluating a particular movement disorder.

In the example of stiff-person syndrome, the stiffness results from continuous muscle contraction, making it difficult for individuals to move quickly or fluidly. Sensory stimulation induces an increase in spasms. With time, patients may even become bed bound, imprisoned by their spasms, which are often painful. The needle EMG findings reveal normal motor unit potential; however, the motor units discharge incessantly in both agonist and antagonist muscle groups, which is a not a feature normally seen in healthy individuals.

In summary, traditional intramuscular needle EMG recording electrodes or surface recording electrodes have been used to improve the diagnostic accuracy of certain movement disorders.

See also: Electromyography (EMG).

Further Reading

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Confocal Microscopy

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Glossary

Aperture – An opening placed into the optical path to allow only part of the light to pass. The aperture can be of varying sizes or shapes. The construction of the aperture and the position it is placed within the optical path can specifically narrow down the light that passes to exclude out of focus light.

Fluorescence – The property of some molecules to absorb light at a certain wavelength (the excitation illumination wavelength) and to subsequently release that energy at a longer wavelength (the emission wavelength). The difference between these wavelengths allows the specific signal to be discriminated from the background.

Fluorescent probes – A general term to indicate any of a number of molecules that have specific properties of fluorescence. By designing these probes to bind to antibodies or be expressed by genes, one can surmise that the protein or gene expression of interest is located where the fluorescent signal is located.

Optical path – The pathway that the light travels from the source to the specimen and then on to the detector. The lenses, apertures, and filters placed in this light path will determine what wavelengths of light are seen and what spatial resolution of tissue imaging can be achieved.

Definition and History

Confocal microscopy is a specialized form of standard fluorescence microscopy (also called widefield fluorescence microscopy) that uses particular optical components to generate high-resolution images of material stained with fluorescent probes. There were many attempts in the later half of the twentieth century to achieve improved image resolution for fluorescence microscopy by use of various apertures, however the availability of high intensity lasers and sensitive electronic detectors resulted in the production of commercial confocal microscopes in the early 1990s. The enormous advantage in image resolution and detection made possible by commercially produced laser scanning confocal microscopes led to widespread adoption of their use. Confocal microscopy differs from conventional widefield fluorescence microscopy in that the optical path is designed to place in front of the image detector (photomultiplier tube or camera) an aperture (opening) at a point where the image is focused in conjunction with the focal plane of the image. By correctly placing this aperture in the same focal position as the collected image and adjusting the size of the aperture to match the numerical aperture of the objective lens that is collecting the image, it is possible to screen out light from outside the true focal plane of the objective lens. The term confocal derives from the coincidence of these two focal planes (objective lens focus point and the focus point where the aperture is placed). The result is the removal of out-of-focus light, providing a crisp image with the maximal resolution possible for the objective lens being used. With oil-immersion lenses having a numerical aperture of 1.3 or 1.4, it is possible to obtain axial resolution (optical depth of field) below 0.5 μm thickness. Based upon the thinness of the optical depth and the ability to generate successive registered focal planes by fine advancement of the focus position between subsequent images, one can build what is called a z-series. This is simply a series of focal planes (movement in the z axis) at a known interval of focus through a specimen that is in a fixed position (no movement in the x–y axis). Because these images are in spatial registration, they provide a three-dimensional sample of the tissue or cells being examined. As a result, an optical sectioning is performed, making it more attractive to employ tissue sections cut thicker (greater than 30 μm) and to use the optical ability of the confocal microscope as an optical 'microtome' to reveal structural details in three-dimensions.

For investigators of movement disorders, the confocal microscope provides a powerful way to extend the analytical abilities of cellular and histological studies. The use of fluorescent probes permits the localization of substrates without interference with each other as long as certain conditions are met (see below). Thus, it is possible to examine a field of cells in vitro or in vivo and detect unambiguously which cells contain which signal or if a cell coexpresses two or more signals. This is an advantage over using chromatic stains as one darker or denser colored substrate may obscure the presence of a lighter substrate. Furthermore, darker substrates above or below the focal plane may mask detection of signal using brightfield microscopy. Therefore, staining with fluorescence provides for the detection of more information about the spatial distribution of signal within cells or tissue, while confocal microscopy permits very high spatial resolution of those signals without ambiguity. Confocal microscopy is the tool of choice when it is necessary to identify the phenotype of a cell in conjunction with its coexpression of other markers or proteins. For example, it can be used to determine expression of TH-positive cells or the identity of fibers innervating target regions. With the range of tract tracing substrates and fluorescent reporter genes now available, the analytical possibilities are even further enhanced.

In addition to the insertion of an aperture at the correct point in the light path, there are some other aspects to the design of confocal microscopes that differ from conventional brightfield or fluorescence microscopes. The light source must be of high intensity and provide for specific wavelengths of illumination. This is most often achieved by using a combination of lasers to provide a distribution of excitation illumination across the visible spectrum. These types of confocal microscopes are referred to as laser scanning confocal microscopes and the choice of lasers with which they are outfitted will define which fluorophores can be used for staining tissue. This type of confocal microscope scans the laser across the specimen, as the name indicates, and the specimen is thus sampled one point at a time. The emitted light from activation of the fluorophore is then collected by the objective lens, where it passes through an emission filter to narrow the signal to the desired spectral width before being focused through the aperture onto a photomultiplier tube. This type of light detector reads out the intensity of the light and the value of that signal is mapped to its position in the scan so that the computer software controlling the process builds up an image of the focal plane on a pixel-by-pixel basis.

Another increasingly popular type of confocal microscope, the spinning disk type, illuminates the specimen with widefield illumination from a high intensity arc lamp or filament. Specific excitation filters limit the spectra used to excite the stained cells or tissue, however, the

user can easily change these providing more flexibility to the investigator for the choice of fluorophores. Both the excitation light and the returning emission light are focused to a point where they pass through an aperture to achieve confocality (i.e., removal of out-of-focus light). As the name suggests, this type of confocal does not use a fixed aperture, but rather a series of apertures (circular or linear openings) arranged in a certain spatial array that is spun at high speed. Thus only a small portion of these apertures are within the light path and only a portion of the specimen is being illuminated at any given moment. The collected light is then focused on a high-sensitivity camera that builds up an image until all areas of the field of view have been covered. The spinning disk confocal does not achieve quite the same high degree of axial resolution as a laser scanning confocal, but it does provide for more flexibility in selection of wavelengths and the spinning disk scanning process is substantially faster than the laser scanning process, making it more suitable for detecting physiological events or for facilitating high-throughput imaging studies.

While confocal microscopy is a powerful tool, there are some common pitfalls that the user must consider and potential artifacts that must be recognized. The following points are recommended as best practices for using confocal microscopy:

- Specimen preparation is critical for obtaining accurate images and protocols should be carefully developed and faithfully followed to insure reproducibility. Appropriate controls should be included to ensure specificity of labeling.
- Fluorophores should be chosen that have narrow spectral profiles of excitation and emission and whose peak values are distinctly separate both from each other and from any other fluorophores to be used.
- When imaging, fluorophores should be excited separately and their emission evaluated for potential contamination of signal (bleedthrough) into other detection channels.
- Detection settings in the software should be adjusted in accordance with an objective scale, such as a signal histogram, to ensure that the detections settings use the entire dynamic range of the detector and that no signal (and potential data) is lost at either the high or low ends of the histogram. Oversaturation (making the image too bright and crowding data off the high end of the histogram) is one of the most common user mistakes when using a confocal microscope.
- Users are cautioned against believing everything that appears on the screen when using a confocal microscope. All detections settings should be critically evaluated for the possible production of an imaging artifact. Appropriate controls should be imaged in comparison. The image obtained should be clearer than its appearance by eye down the eyepieces, but there should be no substantial disagreement between visual observation and digital imaging. Let your eyes be the reality check!
- Other sources of analysis should be evaluated when possible and compared to the imaging data for validation.

See also: 6-OH Dopamine Rat Model; Alzheimer's Disease and Parkinsonism; Caspases and Neuronal Cell Death; Dopamine Transporter: Aging and Parkinson's Disease; Dyskinesias: Animal Models; Glial Cell Activation in PD; Glial Cytoplasmic Inclusions; Huntington's Disease; Locus Coeruleus and Norepinephrine; MPTP; Multiple System Atrophy: Animal Models; Neurofibrillary Tangles; Neuroimaging, Parkinson's Disease; Neuronal Ceroid Lipofuscinosis; Neuroprotection in Movement Disorders; Parkinson's Disease: Animal Models; Stereology; Substantia Nigra; Transplantation.

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www.chroma.com – Chroma's 'Find a Filter' utility is a useful tool for determining the optimal filter design for the wavelengths to be detected.

www.olympusmicro.com/ – A broad resource for all forms of microscopy with useful tutorials on fluorescence and confocal microscopy.

www.invitrogen.com/site/us/en/home/brands/Molecular-Probes.html – A useful site for locating suitable optical probes.

Cortical Myoclonus

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Glossary

Epilepsy – A seizure disorder.
Myoclonus – Brief, mostly irregular, focal, multifocal, or generalized muscle jerks that have their origin in the cortex or subcortex in most instances.
Pyramidal – The motor system controlling strength of movement. This two-part neuronal pathway travels from the motor cortex into the subcortex in the internal capsule, then through the brainstem where it crosses at the level of the medulla and travels in the lateral corticospinal tract. At the spinal cord levels, the second cell in this system is located in the anterior horn of the spinal cord and exits as spinal roots, spinal nerves, and finally peripheral nerves to activate muscles. The hallmark of pyramidal tract lesions is weakness.

Clinical Syndrome

The word myoclonus is derived from mŷs for muscle, and clonus is Greek for 'violent, confused motion.' As its name implies, it is characterized by transient, sudden, nonvolitional irregular or rhythmic movements. Although lesions in the peripheral nervous system can lead to this, it is usually considered a central nervous system phenomenon defined by electromyogram (EMG) muscle bursts of 50–300 ms leading to disruption of posture or movement. These characteristics help distinguish it from the other more complex brief involuntary movements like chorea, dystonia, or tics. In certain situations such as tics, irregular amplitude tremor oscillations, or brief fragments of other movement disorders, it might be impossible to differentiate from myoclonus on clinical grounds alone. In these circumstances, electrophysiological techniques become necessary to properly classify these disorders.

Using electrophysiological criteria, Halliday, in 1976, proposed the first classification of myoclonus into three distinct groups: pyramidal, extrapyramidal, and segmental. He characterized the pyramidal type as having EMG activity occurring 15–40 ms after the electroencephalographic (EEG) activity. He postulated the cortex as the site of origin with further propagation via the pyramidal tract. Pyramidal myoclonus is now referred to as cortical myoclonus or cortical positive myoclonus or epileptic myoclonus. In this form of myoclonus, EMG bursts of short duration occur with synchronous agonist/antagonist activation pattern and with EEG correlates consisting of a somatotopically organized cortical discharges typically 20–40 ms before EMG onset. 'Giant' somatosensory evoked potentials (SEPs) and enhanced transcortical reflexes (C-Reflex) are also a part of the electrophysiological features of cortical myoclonus. Cortical myoclonus is found in a variety of acquired, genetic, metabolic, and degenerative disorders.

Pathophysiology

Many excellent reports have studied the pathophysiology of cortical myoclonus using EEG, EMG, transcranial magnetic stimulation (TMS), and magnetoencephalography (MEG) techniques. Most studies suggest an abnormal hyperexcitability of the cortex, in particular, the sensory, motor, and visual cortices. Despite it being largely a cortical phenomenon, the precise pathology remains unclear.

Hyperexcitablity of the motor cortex has been demonstrated using electrodiagnostic techniques. Jerk-locked averaging is a well established technique to study myoclonus. The technique averages EEG activity aligned to EMG onset. In cortical myoclonus, a premyoclonus spike can be detected in the averaged EEG signal prior to the jerks. Refinements in EEG source localization can be ascertained by studying dipole source localization or by using MEG. These studies indicate a source in the motor cortex as well as in the sensory cortex. TMS studies have strengthened the premise of cortical involvement. In these studies, a motor-evoked potential (MEP) can be produced by placing a coil on the scalp and running an electric current through it. The current produces a magnetic pulse that can be directed to a desired location to illicit a motor response. MEP amplitudes are measured in response to the magnetic stimulation. A variant of this technique uses paired pulse stimulation. Two magnetic pulses are generated at varying intervals. A conditioning stimulus 1–6 ms (ISI of 1–6 ms) prior to the test stimulus produces a smaller MEP. In patients with cortical myoclonus, conditioning responses with ISI of 3 and 5 ms exhibit a reduced suppression of the MEP. It is speculated

that these findings suggest an aberrant function in the cortical GABAergic inhibitory circuits.

Sensory cortex hyperexcitability also appears to be important in the pathophysiology of myoclonus. Measuring cortical potentials in response to peripheral sensory stimulation is commonly performed to study the integrity of the central nervous system and the technique is commonly referred to as SEPs. 'Giant' SEPs (P25–P33) are known to occur in patients with cortical myoclonus and suggest hyperexcitability of the sensory cortex. Similar to the TMS paired pulse paradigm, SEP can also be administered in this fashion. SEP suppression is seen at an ISI of $\leq$100 ms in healthy individuals. In some patients with myoclonus, suppression was not observed, and in some cases, facilitation was noted suggesting a dysfunction of the sensory cortical inhibitory circuits leading to hyperexcitability in the cortex.

There is ample evidence to suggest aberrant excitability in the motor and sensory cortices in patients with cortical myoclonus. The underlying pathology though unclear is being studied in great detail using advances in electrodiagnostic techniques. Recent evidence suggests that interhemispheric interactions between the motor cortices appear to be important. The molecular and biochemical abnormalities underlying the hyperexcitablity are yet to be defined.

Treatment

The pharmacological management of cortical myoclonus includes Clonazepam, valproic acid, primidone, and piracetam. Newer agents such as Levetiracetam (an analogue of piracetam) and γ-hydroxybutyric acid (GHB) are also effective antimyoclonic therapies.

See also: Myoclonus; Myoclonus, Epileptic.

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www.movementdisorders.org – Movement Disorder Society.

Cortical Sensory Dysfunction and the Parietal Lobe

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Glossary

Astereognosia – Inability to recognize things by touch.
Exteroception – Perception of stimuli originating outside the body, for example, vision, touch, olfaction.
Interoception – Perception of stimuli originating inside the body, for example, hunger, thirst, visceral sensations.
Proprioception – Perception of the position and movement of body or its parts.
Pseudoathetosis – Involuntary writhing movements due to proprioceptive deficits.
Simultanagnosia – Inability to synthesize visual information into a complete picture.

Introduction

The parietal lobe is part of a sensory system comprising peripheral receptors, neural pathways, and neurons of several supraspinal centers (cerebellum, basal ganglia, parietal lobe) that process visual and somatosensory information. The somatosensory modalities include proprioception (e.g., perception of body and limb positions), interoceptive sensory modalities such as temperature and pain perception, and touch. Classically, touch has been defined as an exteroceptive sense. However, in recognition that touch perception is based on several modalities, the term somatic senses is also commonly used. It is known that the parietal lobes mediate exteroceptive and proprioceptive perception, while interoceptive sensations are also associated with activations of the right insular cortex. This article will focus primarily on the parietal

lobe, and the effect of parietal lobe lesions on cognitive, perceptual, and motor function.

One of the primary roles of the parietal cortex lies in the integration of somatosensory and visual information that is needed for movement planning and control. In addition, specific areas of the parietal lobe are relevant for cognitive processes such as reading comprehension, and logical and mathematical thinking. One of the first comprehensive accounts of parietal lobe function was published in 1953 by the British neurologist Macdonald Critchley whose insights were based largely on the study of patients with parietal lesions. Since then, numerous researchers attempted to correlate behaviors with parietal and subcortical neural activity in humans and animals using an array of psychophysical, electrophysiological, and brain imaging techniques.

Neuroanatomical Subdivisions of the Parietal Lobe

The parietal lobe is a region of the cerebral cortex between the frontal and occipital lobes. Its principal areas include the *primary somatosensory cortex* (PSC) comprising the postcentral gyrus (Brodmann areas 1, 2, 3), the superior parietal lobule (areas 5 and 7), the parietal operculum (area 43), the supramarginal gyrus (area 40), and the angular gyrus (area 39). Two functional zones of the parietal lobe can be distinguished: an anterior zone (Brodmann's areas 1, 2, 3, 43) and a posterior zone which includes the remaining areas. The posterior zone is also known as the *posterior parietal cortex* (PPC).The PPC receives afferent projections from the somatosensory cortex, the premotor and motor cortices. In addition, area 7b of the PPC receives visual, somesthetic, proprioceptive, auditory, vestibular signals, as well as input from oculomotor and cingulate regions. The PPC has efferent projections to the prefrontal area 46, the frontal motor cortical areas (4, 6, and 8), the cingulate gyrus, the basal ganglia, and the cerebellum. It is thought that the close reciprocal connections between prefrontal and parietal areas indicate the importance of this functional loop for the control of spatially guided behavior. This role is underlined by the existence of a major projection known as the *dorsal visual stream* which is believed to encode visual information in an egocentric reference system necessary for planning goal-directed movement.

In addition to distinguish between anterior and posterior parietal zones, a lateralization of functions between the right and left parietal lobes is found. Classically, the dominant (usually left) parietal lobe is involved in language and mathematical processing. Lesions of the left parietal lobe result in anomia, alexia, apraxia, agraphia, acalculia, finger agnosia, and right-to-left disorientation. *Gerstmann's syndrome* is characterized by the latter four features, and is often associated with an angular or a supramarginal gyral lesion. The nondominant (typically right) parietal lobe is thought to be involved in spatial cognition. Lesions may result in contralateral neglect of a part of the body or space, constructional and dressing apraxia, difficulty with cube counting, impaired paper cutting, poor map reading, and astereognosia. When there are bilateral PPC lesions, features of *Balint's syndrome* may be present including *simultanagnosia* (inability to perceive more than one object at a time), *optic ataxia* (incoordination of hand and eye movement), and *optic apraxia* (inability to refixate the eyes voluntarily).

Assessment of Parietal Lobe function

This section reviews some of the most common syndromes and clinical symptoms associated with parietal lobe damage such as apraxia, pseudoathetosis, cortical sensory loss, alien limb, and proprioceptive impairments.

Assessment of parietal function may include *somatosensory thresholds* (e.g., two-point discrimination/tactile sensation), *tactile recognition* (e.g., Sequin-Goddard form board and tactile patterns), *complex visual perceptual tasks* (e.g., Golin incomplete figures and Mooney closure test), *neglect*, *spatial relationships*, language (e.g., speech and reading comprehension using token tests), and *apraxia* (e.g., Kimura box and others discussed later). Another task which appraises frontal and parietal function as it relates to space is the Semmes test of extrapersonal space.

Signs and Symptoms of Parietal Lobe Dysfunction

Neglect

The neglect syndrome, also called hemiagnosia-hemineglect or spatial neglect, is a neurological condition that manifests itself as a deficit in attention to and awareness of one side of the body or extrapersonal space. Most commonly, right parietal lobe damage leads to neglect of left-sided body parts and the left visual field. The impairments in attention to the left side can also occur in the auditory, proprioceptive, and olfactory domains. Right-sided neglect after left parietal damage is rare; likely reflecting the specialization of the left hemisphere for language.

Cortical Sensory Loss

Cortical sensory loss may appear to a patient or a clinician as a symptom due to a peripheral nerve, plexus, or root lesion with clinical symptoms such as numbness or tingling; however, on examination there are no primary sensory findings. There is, rather, impairment in joint position sense and two-point discrimination as well as findings of agraphesthesia and astereognosia.

Pseudoathetosis and Cortical Sensory Dysfunction

Athetosis is a slow writhing movement that is not associated with sensory loss; whereas, pseudoathetosis is clinically indistinguishable from athetosis except for the additional finding of proprioceptive sensory changes. An assortment of different neuropathological lesions, including parietal pathology, can manifest as pseudoathetosis. From Salih's work, lesions in thalamic lemniscal projecting fibers to somatosensory S1 areas 2 and 3a result in altered discriminative sensations, for example, impaired proprioception with relative preservation of other sensory modalities.

Alien Limb Phenomenon

There is controversy as to what constitutes an alien limb, but classically it is thought to include spontaneous movements that are minimally affected by volitional movement and may require restraint by the contralateral hand. Sometimes, pseudoathetosis or simple arm levitation is mistaken as a diagnostic sign of an alien limb.

Proprioceptive Deficits in Parkinson's Disease (PD)

Kinesthesia refers to the conscious awareness of active and passive limb movements and limb or body position. It is often used interchangeably with the terms proprioception or muscle sense. Recent work has shown that individuals with mild to moderate PD have elevated thresholds for detecting changes in limb position, passive motion, and weight perception. In addition, PD patients may exhibit delayed proprioception-related potentials in the somatosensory cortex. While PD is known to affect the basal ganglia, it is also known that the basal ganglia receive massive parietal lobe input. Thus, the observed kinesthetic deficits may be understood as a parietobasal ganglia dysfunction.

Apraxia

Apraxia is the loss of the ability to perform a motor task despite intact motor and sensory functions, and absence of a language disorder. A more specific definition of apraxia as obtained from Zadikoff and Lang and Geschwind and Damasio includes one or all of the following: 'failure to produce the correct movement in response to a verbal command, the failure to correctly imitate a movement performed by an examiner, the failure to perform a movement correctly in response to a seen object, and the failure to handle an object correctly.'

Contextual definitions of apraxia include ideomotor, limb, buccofacial, ideational, limb-kinetic, apraxia of speech and oculomotor apraxia, gait apraxia, and so on. The anatomical bases of these clinically distinct entities are, as expected, quite disparate. For the sake of this discussion, we will focus primarily on ideomotor limb apraxia, ideational, and limb-kinetic apraxia.

Limb-kinetic apraxia is defined as the loss of hand and finger dexterity resulting from the inability to connect or isolate individual movements, and is accompanied by frontal and/or parietal pathology. *Ideomotor apraxia* is an impairment in goal-directed movement, and typically associated with left hemisphere frontoparietal lesions or/and accompanying pathology of deep white matter or parts of the basal ganglia (often striatal) fibers. For example, the person with ideomotor apraxia cannot show how to salute or brush his/her teeth. *Ideational apraxia* is defined as the impairment in knowing what to do, and there are accompanying content errors. The person is unable to create a plan for or appreciate the idea of a specific movement; for example, they cannot pick up a pen and write something. Pathology often involves the left parietotemporal and parietooccipital regions.

Apraxia may be assessed by the *Florida Apraxia Screening Test* (FAST), and the revised version, FAST-R The FAST-R battery consists of a variety of measures such as demonstration of gestures (e.g., how to salute, make a fist) and the use of tools (e.g., scissors, hammer, bottle opener, glass, comb and hair brush, salt shaker, saw, screwdriver, spoon), and signaling to others (e.g., stop, come here, go away, wave goodbye). A variety of errors (content, temporal, spatial) can clarify the degree of impairments. Other means to assess apraxia include the *De Renzi test*, *Goldenberg's test of apraxia* (which assesses impairment in imitation of meaningless gestures of hands, imitation of meaningless gestures of fingers, performance of meaningful gestures on demand, and pantomime of tool use), and the *Kimura box*.

In the realm of movement disorders, there are a variety of conditions that are accompanied by apraxia, the most notable of which is *corticobasal degeneration* (CBD) also (clinically) known as *corticobasal syndrome* (CBS). Other conditions such as PD, progressive supranuclear palsy, Huntington's disease, dementia with Lewy bodies, and multiple system atrophy may also manifest apraxia. On the basis of the above clinical features, we will further discuss CBD/CBS which may prominently feature parietal dysfunction.

Corticobasal Syndrome and Corticobasal Degeneration

CBS and CBD represent clinical and pathological entities, respectively, that are due to brain dysfunction involving the cortex (primarily the parietal lobes) and the basal ganglia; hence, this syndrome was formerly known as corticobasal ganglionic degeneration (CBGD). CBS represents a clinical entity with numerous possible underlying pathologies of which CBD is the most common pathology. Clinical diagnostic criteria proposed for CBS include the presence of all of the following: (1) insidious onset and progressive course; (2) no identifiable cause;

(3) cortical dysfunction (requiring the presence of one of the following: focal or asymmetrical ideomotor apraxia, alien limb phenomenon, cortical sensory loss, visual or sensory hemineglect, constructional apraxia, focal or asymmetric myoclonus, apraxia of speech/nonfluent aphasia); extrapyramidal dysfunction (at least one of the following: focal or asymmetrical appendicular rigidity without prominent and sustained response to levodopa or/and focal asymmetrical appendicular dystonia). Supportive findings from neuropsychological testing, MRI/CT scanning, or positron emission tomography (PET)/single photon emission computed tomography (SPECT) scanning may be helpful in making a clinical diagnosis.

Using diffusion-weighted imaging MRI methods, researchers have distinguished patients with a clinical diagnosis of CBS from other atypical parkinsonian syndromes (100% sensitivity and specificity) based on the presence of hemispheric asymmetry. Another study employing the MRI method, voxel-based morphometry, showed evidence of frontoparietal grey and subcortical grey matter atrophy in individuals who had CBD on autopsy.

The cause of CBS is unknown, and it is usually a sporadic condition. Rarely there have been cases where a genetic mutation or gene linkage has been found. Unfortunately, there is no obvious curative treatment for CBS, and management is primarily symptomatic.

Summary

The parietal lobes are involved in the processing of visual and somatosensory information that is essential for movement planning and spatial cognition. The posterior parietal area is important in the visual guidance of movements of the limbs, head, and eyes along with mental planning of movements. Part of the parietal lobe appears to play a role in mathematical reasoning and reading comprehension. Dysfunction of the parietal lobes may result in features such as cortical sensory loss, apraxia, which may also constitute features of a CBS.

See also: Alien Limb; Apraxia: Upper Limb; Athetosis; Corticobasal Degeneration.

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Cortical Tremor

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Glossary

Myoclonus – Brief, sudden, shock-like, involuntary movements caused by muscular contractions or inhibitions.
Tremors – Rhythmic oscillatory movements.

Clinical Syndrome and Terminology

As a clinical syndrome, the term cortical tremor is most commonly associated with the condition now known as familial cortical myoclonic tremor with epilepsy (FCMTE). FCMTE has previously been referred to by many names, including autosomal dominant cortical

myoclonus and epilepsy, benign adult familial myoclonic epilepsy, familial adult myoclonic epilepsy, familial cortical myoclonic tremor, familial cortical tremor with epilepsy, familial essential myoclonus and epilepsy, familial benign myoclonus epilepsy of adult onset, myoclonic tremor, and heredofamilial tremor and epilepsy. The lack of familiarity with this group of disorders has led not only to confusing names but also to misdiagnosis.

FCMTE was first reported less than 20 years ago. Although 50 Japanese and European families are known to have this malady, it was first described in a Japanese family in 1990 by Ikeda et al. The condition is characterized by fast rhythmic jerks of small amplitude, involving fingers and hands. Because of the postural 9 Hz rhythmicity, with electrophysiological characteristics of cortical myoclonus, this entity was called 'cortical tremor.' The rhythmic movement disorder that is enhanced with the assumption of a posture-like outstretching the hands can easily be confused with other tremor disorders, specially, essential tremor.

FCMTE has several characteristics that distinguish it from other disorders. The tremor movements have a wide range of age of onset, and can occur in children from 10 years of age to late-middle-aged adults. The rhythmic movements are usually the first symptom that brings patients to medical attention. These movements can be provoked by posture, movement, emotional stress, and a lack of sleep, but they can also be present at rest and may involve the head and trunk. Epilepsy is usually the second symptom to appear. In a minority of patients (<20%), epilepsy may precede the tremulous movements. In about 80% of the reported cases, the epilepsy consists of generalized tonic–clonic seizures, but other forms of seizures have also been reported, including absence, myoclonic, and complex partial. The seizures respond well to antiepileptic medications. Mental retardation in children and mild cognitive impairment, night blindness, and migraine headaches in adults have been reported as part of the clinical syndrome.

Pathophysiology

The pathophysiology of cortical tremor is not entirely understood. Cortical hyperexcitability and its responsiveness to antiepileptic medications suggest that GABA receptors may be involved. All the 50 families studied to date show an autosomal dominant pattern of inheritance. The families appear to share a distinct locus within their family and geographical region, but the locus is different in other parts of the world. The Japanese families have an association with chromosome 15, the Italian family with chromosome 2, the Spanish family with chromosome 8, and the Dutch family with chromosomes 2 and 8. It is speculated that this disorder may fall into a class of channelopathies.

Diagnosis

Electrodiagnostic criteria are essential in confirming a cortical disturbance as the origin to the tremor phenomena. The surface electromyographic studies (EMG) demonstrate repetitive, 8–13 Hz frequency burst of 50 ms duration, which can be induced by posture. Polyspike and wave patterns have been reported in 94% of patients and 48% unaffected relatives in routine electroencephalographic studies (EEG). A giant cortical sensory-evoked potential (SEP) can be produced by median nerve stimulation in 84% of patients from one family. The stimulation of the median nerve also demonstrates a long-latency C-reflex response in most of the patients. The jerk-locked back averaging of the EEG triggered by tremor-related EMG bursts reveals a cortical potential preceding the myoclonic jerks in 60% of the patients.

Patients with otherwise typical cortical myoclonus, regardless of their etiology, may experience tremor of the activated limbs when asked to perform an isometric effort. The electrophysiological characterization of their tremor reveals findings similar to those found in patients with FCMTE. This provides further links between FCMTE and cortical myoclonus.

Treatment

Most symptoms of FCMTE can be controlled effectively with antiepileptic medications. Clonazepam, valproate, primidone, phenobarbitol, and, more recently, levitiracetam are very effective in reducing the myoclonic jerks and seizures. Beta blockers provide no benefit in this condition. In individual patients, carbamazepine and phenytoin may also be effective.

See also: Cortical Myoclonus; Myoclonus, Epileptic; Postural Tremor; Tremor; Tremor, Essential (Syndromes).

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Relevant Websites

www.movementdisorders.org – Movement Disorder Society.
www.myoclonus.com – Myoclonus website.

Corticobasal Degeneration

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Glossary

Alien limb – A sign seen in many cases of corticobasal degeneration whereby the arm or leg engages autonomously in complex acts and appears to have 'a mind of its own.'
Corticobasal degeneration – A neurodegenerative disease of later life exhibiting asymmetric signs reflecting dysfunction of both cerebral cortex and basal ganglia.
Tau – A hyperphosphorylated microtubule-associated protein that is typically seen in brain cells of corticobasal degeneration and some other neurodegenerative disorders.

Definition and History

Corticobasal degeneration (CBD) is a degenerative disease of the nervous system. The first reports by Rebeiz and colleagues in 1967 and 1968 called this disorder 'corticodentatonigral degeneration with neuronal achromasia' to describe the pathologic findings in their three cases. Subsequent autopsied cases have not detected involvement of the dentate nucleus, and this portion of the name was discarded. No additional reports of this disease were published until 1985, when Watts and colleagues coined the term 'corticobasal ganglionic degeneration.' Gibb and colleagues added three more autopsied cases in 1989 under the name 'corticobasal degeneration,' a name that has stuck because of its brevity. In 1990, Riley and colleagues detailed the clinical findings in 15 patients with pathologic findings from the two autopsy-verified cases, using the term 'cortical–basal ganglionic degeneration.' This report was influential for the systematic organization of clinical findings into distinct groupings that have been adopted by later authors and remain in use today. It also published the first sets of diagnostic criteria, imaging, electrophysiological findings, and brain biochemistry.

Since this report, CBD has become a well-recognized syndrome in the field of movement disorders. However, as recognition grew, it became simultaneously clear that the classical clinical presentation may accompany other pathologic entities, while the originally described pathologic findings can be associated with atypical syndromes. For this reason, the clinical features of CBD are now known as the 'corticobasal syndrome' (CBS), while CBD is used to refer to the pathologically confirmed disease, somewhat analogous to the relationship between 'parkinsonism' and 'Parkinson's disease.'

Pathogenesis/Pathophysiology

While the specific etiology (or etiologies) is unknown, CBD belongs to a group of degenerative disorders characterized by abnormal intracellular accumulation of hyperphosphorylated microtubule-associated protein 'tau', collectively known as 'tauopathies'. The tau that accumulates in CBD consists exclusively of four-repeat isoforms, the same as in progressive supranuclear palsy. These two diseases also share a common haplotype and genotype profile in the *tau* gene, suggesting a common etiology. However, immunoblot analysis of brain extracts shows distinctive patterns of tau fragments in each disorder, consisting of different amino acid terminals at the carboxyl end of tau. Thus, different intracellular proteolytic processing of aggregated tau may underlie the clinical and pathological differences between the two diseases.

Gross autopsy findings in CBD include cerebral atrophy, often asymmetric and predominating in the medial frontal and parietal lobes, and substantia nigra pallor. Microscopic features include swollen ('ballooned') poorly staining ('achromatic') neurons in the cerebral cortex, most numerous in the superior frontal, precentral, and postcentral gyri. Unlike Alzheimer's or Pick's disease, two other well-known tauopathies, CBD shows no discrete inclusion bodies in cerebral cortical cells, although diffuse or granular tau-positive staining in neurons or glial cells may be present. In fact, tau immunoreactivity is widespread, and predominates in distal astrocytic cellular processes (known as 'astrocytic plaques') rather than in neuronal cell bodies. Astrocytic plaques are most abundant in prefrontal and premotor cortex, and the caudate nucleus. In the substantia nigra, findings include neuronal loss, depigmentation, extraneuronal melanin, and gliosis. Here there may be occasional basophilic neuronal inclusions known as 'corticobasal bodies,' which can be found in other deep nuclei and probably represent tangle-like structures. Degenerative changes in the putamen, caudate nucleus, globus pallidus, and subthalamic nucleus are common though not universal.

The Office of Rare Diseases of the National Institutes of Health of the United States of America has published consensus neuropathologic criteria for CBD diagnosis.

These validated criteria emphasize the importance of tau-immunoreactive lesions in neurons, glia, and cell processes in the neuropathologic diagnosis of CBD. Minimal pathologic features required for a diagnosis of CBD include a combination of (1) cortical and striatal tau-positive neuronal and glial lesions, especially astrocytic plaques and thread-like lesions in both white matter and gray matter and (2) neuronal loss in focal cortical regions and in the substantia nigra.

Epidemiology/Risk Factors

CBD typically begins in the seventh decade. Clinical onset before the age of 55 is unusual. Men are slightly more likely to develop CBD than women. No ethnic or geographic preponderance is known. Data regarding incidence and prevalence of CBD are speculative, in large part due to misdiagnosis. It appears, however, from both clinical and pathologic case series that CBD occurs much less commonly than progressive supranuclear palsy, the disease with which it is most often compared and confused.

Hereditary cases are rare. There have been no documented *tau* mutations in sporadic CBD, but *tau* gene polymorphisms may play an etiologic role. Patients with CBD have a significantly higher prevalence of the H1/H1 genotype in the *tau* gene. Several mutations in the *tau* gene have been associated with hereditary cases of clinical CBS or pathologic CBD. Apart from age and genetics, no other risk factors for CBD have been identified.

Clinical Features and Diagnostic Criteria

The essence of the cortocobasal syndrome is the finding of asymmetric clinical features combining dysfunction in both cerebral cortex and basal ganglia, developing insidiously and gradually progressive. The cerebral cortical manifestations most often encountered are apraxia, cortical sensory loss, and the 'alien limb' phenomenon. The last symptom refers to a limb that engages autonomously in complex acts and appears to have 'a mind of its own.' Basal ganglia manifestations of CBD almost always include akinesia and rigidity, with the latter often pronounced. Another common basal ganglionic feature is dystonia. Clinical manifestations of uncertain localization include an irregular-amplitude action tremor and focal reflex myoclonus, with the former often evolving into the latter. Other manifestations include impaired ocular and eyelid motility, dysarthria, and corticospinal tract signs. All of these features typically present unilaterally and remain highly asymmetric throughout the course. One limb (more often the arm than the leg) or side may be affected for years before there is spread to other body parts. Pain may be prominent, especially if there is severe dystonia. Dementia and aphasia have been increasingly recognized as primary or secondary clinical manifestations of CBD, to the point that they are no longer considered atypical presentations. Their nonspecific nature contributes to the poor accuracy of premortem diagnosis.

Numerous schemes of diagnostic criteria for CBS exist. All incorporate these clinical principles. There are no consensus criteria for clinical diagnosis. The following are the 2002 criteria of Kumar and colleagues.

Mandatory Inclusion Criteria

1. Chronic progressive course
2. Asymmetric at onset (includes speech dyspraxia or dysphasia)
3. Presence of:
   a. 'higher' cortical dysfunction (apraxia, cortical sensory loss, or alien limb) and
   b. movement disorders (akinetic-rigid syndrome resistant to levodopa, plus limb dystonia or spontaneous and reflex focal myoclonus).

Qualifications (Descriptions) of Clinical Features

- *Rigidity:* easily detectable without reinforcement;
- *Apraxia:* more than simple use of limb as object; clear absence of cognitive or motor deficits sufficient to explain the disturbance;
- *Cortical sensory loss:* preserved primary sensation, asymmetric;
- *Alien limb phenomenon:* more than simple *levitation*;
- *Dystonia:* focal in limb; present at rest at onset;
- *Myoclonus:* reflex myoclonus spreads beyond stimulated digits.

Exclusion Criteria

1. Early cognitive disturbances other than apraxias, or speech or language disorders (this may exclude some patients who have CBD pathology, but more often excludes other pathologies);
2. Moderate-to-severe global dementia while the patient remains ambulatory;
3. Responsiveness to levodopa other than mild worsening on withdrawal;
4. Downgaze palsy (including loss of downward optokinetic nystagmus) while the patient remains ambulatory;
5. Typical parkinsonian rest tremor;
6. Severe autonomic disturbances;
7. Sufficient and appropriately located lesions on imaging studies to account for the clinical disturbances.

Differential Diagnosis

The typical CBD patient is aged in their sixties with asymmetric apraxia, akinesia, rigidity, dystonia, and tremor or myoclonus, resulting in the characteristic 'stiff, dystonic, jerky, useless hand.' The highly asymmetric presentation and the cerebral cortical manifestations of the CBS usually distinguish it from every other parkinsonian disorder. However, autopsy studies demonstrate that, not only does CBD present with manifestations different from the classical motor syndrome, but the clinical syndrome (CBS) occurs with disturbing frequency in association with other pathologies. The lack of diagnostic laboratory studies or biological markers compounds the problem, making clinical diagnosis treacherous. Indeed, in one autopsy series, only one of three patients clinically diagnosed with CBS had the characteristic pathologic changes of CBD, and only one of four with histological verification had been correctly identified during life. This poor correlation between CBS and CBD undermines every conclusion based on studies of CBS that was not corroborated by pathologic confirmation, including many of the statements in this chapter.

The greatest source of error leading to inability to recognize CBS is the failure to examine for cerebral cortical dysfunction (cortical sensory loss and apraxia). Other distinctive features of CBS are focal reflex myoclonus, and focal dystonia at rest. Conversely, symmetric presentation, a rest tremor, or responsiveness to levodopa makes CBD an unlikely pathologic diagnosis. The presence of dementia is a potential diagnostic trap. Many CBD patients become demented, and autopsy series indicate that many CBD patients exhibit a predominantly demented presentation. However, patients with the CBS who had dementia represent a disproportionate number of those who turn out to have Alzheimer's or Pick's disease at autopsy. One could exclude patients with early and prominent dementia from a clinical diagnosis of CBS, at the risk of diminished diagnostic sensitivity.

As previously stated, the 'classical' clinical picture (CBS) described is not specific to CBD and has been associated with a variety of other pathologic entities. The most common and difficult false-positive diagnoses have been made in patients with progressive supranuclear palsy who have significant apraxia, and those with Alzheimer's or Pick's disease who have prominent parkinsonian features. The most difficult false-negative diagnosis occurs in a CBD patient with dementia and few or no lateralizing manifestations. Such a patient is much more likely to be diagnosed with Alzheimer's disease. Frontotemporal dementia with parkinsonism linked to chromosome 17 may also produce the CBS; the distinguishing features here are usually the positive family history and young onset.

CBD has more in common with progressive supranuclear palsy than any other disorder, but they do have important clinical and pathological differences. Most striking from a clinical standpoint is the axial distribution of progressive supranuclear palsy versus the unilateral presentation and asymmetric course of CBD. Apraxia or hemidystonia in a patient with progressive supranuclear palsy may lead to a false diagnosis of CBS. Overlap disorders with biochemical and pathological features of both diseases, or combining features of CBD and other disorders, occur surprisingly frequently. Such cases highlight the need for more definitive diagnostic criteria than clinical or pathologic findings.

Diagnostic Workup/Tests

There are no diagnostic tests for CBD. Some laboratory findings may provide supportive data, but it is unclear to what extent they improve diagnostic accuracy. Thus, all diagnostic testing is optional, with relevance determined by the individual patient's clinical presentation.

Anatomic imaging rarely discloses unexpected focal lesions. The most common finding of conventional MRI in CBD patients is asymmetric cerebral atrophy, particularly in parasagittal and paracentral regions, more prominent on the side opposite to that of greater clinical involvement. Hyperintensity in the white matter of affected gyri on T2-weighted, proton density, and fluid-attenuated inversion recovery (FLAIR) images may be found. Basal ganglia MRI abnormalities are far less common than convexity atrophy, but putamenal atrophy has been reported.

Metabolic imaging studies of many stripes may support the clinical impression of involvement of both cerebral cortex and basal ganglia, as well as identify other involved structures. Functional MRI may detect abnormalities in motor and parietal cortex prior to the development of structural abnormalities. Proton magnetic resonance spectroscopy may demonstrate significantly reduced *N*-acetylaspartate/creatine-phosphocreatine ratios in centrum semiovale, and reduced *N*-acetylaspartate/choline in the lentiform nucleus and parietal cortex. Cerebral blood flow (CBF) SPECT scanning with 99mTc-hexamethyl propyleneamine oxime (HMPAO) may show asymmetric frontoparietotemporal cortical, striatal, and thalamic hypoperfusion. Widespread reduction in CBF was observed in frontal, parietal, and temporal cortices, basal ganglia, and thalamus and pontocerebellar regions with 99mTc-ethyl cysteinate dimer (ECD) SPECT scanning. PET with tracers of dopamine storage capacity and oxygen metabolism can demonstrate depressed cortical oxygen metabolism in the superior and posterior temporal, parietal, and occipital associated cortices, as well as in the posterior frontal lobe. Striatal ^{18}F-fluorodopa uptake may be asymmetrically reduced in the caudate nucleus and putamen. ^{18}F-fluorodeoxyglucose studies can demonstrate asymmetric cortical hypometabolism. Imaging defects in anterior

cingulate gyrus, superior parietal lobule, and supplementary motor area appear to correlate with apraxia. PET with PK11195 has demonstrated microglial activation in areas typically involved in CBD.

The characteristic pattern of pathologic lesions in CBD is associated with a variety of deficits on formal neuropsychological testing, most notably in the areas of praxis and executive function. Patients may additionally show any combination of deficits of attention, dynamic motor execution, verbal fluency, explicit learning without retention difficulties, constructional and visuospatial difficulties, acalculia, frontal lobe dysfunction, and nonfluent aphasia. Memory faculties are relatively preserved. Depression may also be a common finding.

CBD has been studied with a multitude of neurophysiological approaches. Ocular motility studies typically show prolonged saccade latency but preserved saccadic velocity and amplitude, in contrast to progressive supranuclear palsy. However, occasional CBD patients exhibit a supranuclear gaze palsy late in the course of their illness. The focal reflex myoclonus of the CBS is produced by two to four short-duration bursts of muscle contraction simultaneously in antagonistic muscle pairs. Back-averaged electroencephalography shows no time-locked cortical discharges. In CBD patients with myoclonus, somatosensory-evoked potentials are normal, while long-latency reflexes are exaggerated. Shortened latency and synchronous activation of additional muscles is consistent with focal reflex myoclonus. Transcranial magnetic stimulation can enhance cortical excitability and increase transcallosal transmission. Its ability to inhibit ipsilateral muscle contraction has been associated with radiologic evidence of corpus callosum atrophy and neuropsychologic deficits of attention and verbal fluency.

Management

The management of CBD is usually a disheartening process. The etiology remains unknown, and thus no curative treatment has been developed. There is no intervention that will alter the progressive nature of the disease, and opportunities for symptomatic relief are limited. Some motor symptoms are amenable to medication therapy, even if only to a modest extent. Levodopa may improve parkinsonian symptoms, although not to the degree one sees in Parkinson's disease. Dystonia may be partially treatable with botulinum toxin injections or clonazepam, and myoclonus with levetiracetam, clonazepam, or valproate. There are no known therapies for any of the cerebral cortical manifestations of CBD.

Nevertheless, there are other opportunities for physicians to provide some benefit to patients and their families. One way in which physicians can improve a patient and caregiver's quality of life is to take on responsibilities beyond the narrow scope of subspecialty care. These might include treatment of depression and other psychiatric needs, filling out forms for various bureaucracies (multiple types of insurance, medical equipment, caregiver absences from work, ambulance transport, etc.), assisting with entry into skilled nursing facilities, and conducting surveillance for infection or other complications of immobility. When there is nothing else to be done, often simply lending a sympathetic ear to caregivers is enough to earn expressions of gratitude.

As with other degenerative diseases that are largely untreatable, one challenge to long-term management of CBD is simply maintaining contact with the patient. It becomes progressively more difficult to provide motivation to return for further evaluation, while both patient and caregivers may grow frustrated and discouraged with the limitations of available treatment, and increasing disability makes travel to the clinic more burdensome. However, it is critical that clinicians do not lose track of patients and miss an opportunity for postmortem examination, which remains mandatory to confirm the diagnosis in every suspected CBD patient.

Prognosis

The most encouraging aspect of the course of CBD that one can share with patients is that the progression occurs slowly, measured in months or years rather than weeks or days. The life expectancy of CBD patients is between 5 and 10 years from onset, although disease courses as short as 2 years and longer than 10 have been reported in autopsy-confirmed cases. Quality of life in the last several years of illness is often quite limited.

See also: Alien Limb; Apraxia: Upper Limb; Basal Ganglia; Dystonia; Myoclonus; Tauopathies.

Further Reading

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Relevant Websites

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Creutzfeldt–Jacob Disease

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Glossary

Ataxia – Inability to coordinate voluntary movements leading to unsteady movements and staggering gait; most often associated with lesions of the cerebellum.
Cellular Prion protein (PrP^C) – A normal protein especially abundant in the brain that by changing shape or conformation may become abnormal and cause sCJD and other prion diseases.
Myoclonus – A sudden twitching of muscles or parts of muscles, without any rhythm or pattern.
PrP^{Sc} types 1 and 2 – Conformationally distinct isoforms of PrP^{Sc} that are associated with phenotypically distinct subtypes of sCJD; together with the methionine/valine polymorphism at codon 129 of the PrP gene, PrP^{Sc} types 1 and 2 determine the five subtypes of sCJD.
Scrapie Prion Protein (PrP^{Sc}) – The abnormal form of PrP^C that may be generated spontaneously in sCJD, by a genetic defect in familial CJD, or by contact of endogenous PrP^C with exogenous PrP^{Sc} in CJD acquired by infection.
Sporadic Creutzfeldt–Jakob disease (sCJD) – The most common type of a group of fatal diseases commonly called prion diseases which affect mainly the brain and are usually characterized by cognitive deterioration and loss of motor skills resulting in jerky movements.

Definition and History

Creutzfeldt–Jakob disease (CJD) is the most frequent phenotype of a group of fatal illnesses called transmissible spongiform encephalopathies or prion diseases. Its incidence is about 1 per 1 000 000 cases of the general population per year; and it is unique in having three etiologies: sporadic or idiopathic, genetically determined, or acquired by infection.

Alfons Maria Jakob in 1920 first reported three patients with progressive dementia associated with cortical, striatal, and spinal degeneration. Hans Gerhard Creutzfeldt reported a similar case in the same year. The eponym 'Creutzfeldt–Jakob disease' (Creutzfeldt–Jakobsche Krankheit) was coined by Walther Spielmeyer in 1922. Of the eight cases originally presented – seven by Jakob and one by Creutzfeldt – only three cases reported by Jakob are now accepted as CJD. Friedrich Meggendorfer is credited as having first described a familial case of CJD in 1930, a case which was later confirmed by genetic analysis. Kuru, a prion disease acquired by cannibalism, was discovered in 1957. The disease was observed to have features comparable to scrapie, a transmissible disease of sheep. These similarities led to a series of experiments designed to test the transmissibility of kuru and CJD, and the term transmissible spongiform encephalopathies (TSE) was thereafter applied to this entire set of diseases. The contemporary era of TSE dates from 1982, when the discovery of the prion protein provided the foundations for the protein only or prion hypothesis.

Pathogenesis

The key tenet of the prion hypothesis is that the prion protein (PrP^C) is converted into an isoform named scrapie prion protein (PrP^{Sc}), a prion which has a different conformation and is pathogenic. This central pathogenetic event is shared by all three forms of prion diseases. In sporadic CJD (sCJD), the PrP^{Sc} is believed to be formed randomly, perhaps as a lapse in the so-called quality control mechanism whereby cells detect and eliminate abnormally conformed proteins. In the genetically determined or familial CJD (fCJD), the formation of PrP^{Sc} results from a mutation in the PrP gene which encodes for an abnormally conformed and unstable PrP with the propensity to convert into PrP^{Sc}. Finally, CJD acquired by infection arises from contact between exogenous PrP^{Sc} and endogenous PrP^C, which requires that the two isoforms be compatible so that they can interact; it is this interaction that triggers the conversion of PrP^C to PrP^{Sc}. For example, in variant CJD (vCJD), the form of CJD acquired by eating prion-contaminated beef, the first critical requirement is that there be an affinity between the bovine PrP^{Sc} and the human PrP^C, which makes it possible for the two PrP isoforms to interact and for the human PrP^C to undergo the first conversion into PrP^{Sc}. Therefore, while the exogenous PrP^{Sc} acts as the primer for the initial human PrP^C conversion, the newly formed human PrP^{Sc} induces the autocatalytic reaction, which leads to propagation of the prion infection.

The pathogenetic mechanism of prion disease in general and of prion diseases individually, can only be fully understood if key characteristics of PrP^C and PrP^{Sc} are appreciated. PrP^C is a well conserved protein of the central nervous system (CNS) and other tissues of mammals as well as of other species. In humans, in its mature form PrP^C is a relatively small protein of 209 amino acids (residues 23–231) and accounts for ~0.01% of all brain proteins. PrP^C is processed in cells as a secretory protein. Most of the PrP^C carries a glycolipid anchor by which it is attached to the external surface of the cell plasma membrane (**Figure 1**). This site thus exposes the PrP^C to interaction with any extracellular ligand, the exogenous PrP^{Sc} of course being of special relevance. PrP^C also carries two sites of nonobligatory *N*-glycosylation that engender the diglycosylated, monoglycosylated and unglycosylated PrP^C glycoforms. Structurally, human PrP^C includes an N-terminal flexibly disordered 'tail' (23–124) and a globular domain (125–228). The globular domain contains three α-helices located at residues 144–228 and interspersed with two short anti-parallel β-sheets at residues 128–131 and 161–164.

Overwhelming evidence indicates that when PrP^C converts to PrP^{Sc} the β-sheet regions expand at the expense of the adjacent α-helical segment(s). With the expansion of the β-sheet component, PrP^{Sc} may acquire at least five

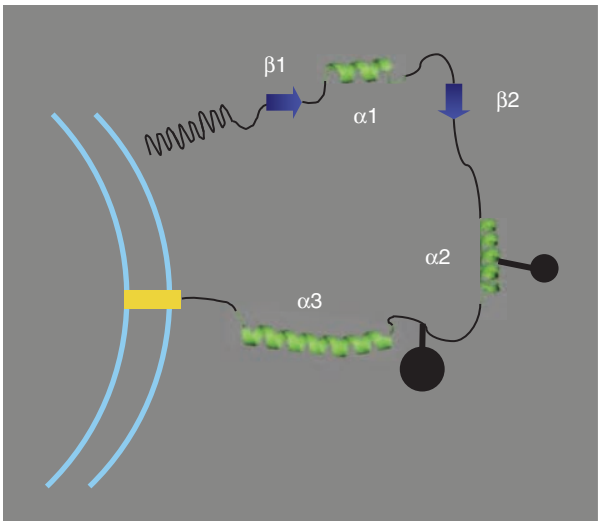

Figure 1 PrP^c on the cell surface. PrP^c is attached to the plasma membrane of the cell and hangs in the extracellular space. The cell plasma membrane is represented by the two curved blue lines. The yellow block represents GPI anchor. The two blue arrows represent the two β-strands. The three green ribbons identify the α-helixes. The N-linked glycans at residues 181 and 197 are shown as black lollipops. The PrP^c structure is based on the NMR study of recombinant human PrP.

distinctive molecular attributes: (1) insolubility in detergents, (2) propensity to aggregate, (3) acquisition of various degrees of resistance to digestion with proteases, which may result in (4) generation of PrP^{Sc} fragments of different sizes and/or with different ratios of the three glycoforms, and finally, (5) acquisition of various degrees of infectivity and pathogenicity. A sixth feature is the PrP^{Sc} amino acid sequence, which of course reflects that of the mother PrP^C. Cumulatively, these characteristics (and probably others not yet identified) play a key role in determining what are called prion strains, which in human prion diseases comprise distinct species of PrP^{Sc} each of which is associated with a distinct disease phenotype. Although all the molecular features designated above are measurable and important, only two have been demonstrated as the most consistent in their association with distinct disease phenotypes, and thus, have played a significant role in the current understanding of CJD: first, the sequence of the PrP^{Sc} as determined by codon 129 of the PrP gene and second, the size of the PrP^{Sc} protease-resistant fragment.

The PrP gene has several polymorphisms, the most common and best known of which is the methionine (M)/valine (V) polymorphism at codon 129. In the general Caucasian population, 52% of individuals are M homozygous (MM), 36% are heterozygous (MV) and 12% are V homozygous (VV). This polymorphism modifies the phenotype in human prion diseases. Therefore, subjects who are MM at codon 129 (129MM) (i.e., they carry exclusively the PrP isoform with M at the amino acid

position 129) present with a sCJD phenotype which is different from that of 129VV subjects.

As for the PrP^{Sc} size, extensive analysis of the protease-resistant fragment of PrP^{Sc} (hereafter identified as $rPrP^{Sc}$) has revealed that the great majority sCJD patients have either one of two types of $rPrP^{Sc}$, which are easily distinguishable by their electrophoretic mobility; these are referred to as type 1 and 2. Again, sCJD patients carrying $rPrP^{Sc}$ type 1 are likely to have a disease phenotype different from those carrying type 2. The difference in electrophoretic mobility that results in a relative molecular weight of 21 kDa and 19 kDa for types 1 and 2, respectively (when referred to the mobility of the unglycosylated isoform) stems from distinct major sites of PrP^{Sc} cleavage following treatment with proteinase K (PK), the commonly used protease in $rPrP^{Sc}$ analyses: amino acid residue 82 for type 1 and residue 97 for type 2. The finding that the same protease cleaves two protein isoforms having the same amino acid sequence at two different cleavage sites indicates that the two isoforms have distinct conformations which generate different proteolytic fragments. This conclusion was recently born out by duplication of types 1 and 2 in bioassays and in vitro, and by direct conformation assay. Therefore, the finding that the primary and the secondary structures of PrP^{Sc} (i.e., the amino acid sequence and the conformation) are determinants of the disease phenotype as well as of the major prion strains is compatible with the protein-only hypothesis according to which all that is required for PrP^{Sc} to replicate itself while retaining diversity is encrypted in the protein structure rather than in nucleic acids.

Shortly after the original description of CJD, variants of the original form were proposed reflecting the heterogeneity of the clinical and histopathological features of sCJD. In addition to the original CJD, referred to as typical or myoclonic, at least six additional variants were subsequently recognized, including Heidenhain or visual, amyotrophic, dyskinetic, thalamic, cerebellar or ataxic, corticostriatal, and panencephalopathic. More recently, two additional variants, the cognitive and affective, have been recognized. It is obvious that diagnosis of a rare disease for which there is no definitive clinical diagnostic test, and which may moreover manifest in nine different presentations poses a herculean task for clinicians. However, now this task is facilitated through the identification of fairly accurate phenotypic determinants such as the PrP patient's genotype and the PrP^{Sc} type, both of which now allow for classification of CJD subtypes on the basis of molecular features rather than objective clinical or histopathological characteristics.

In 1999, we used the combination of the genotype at codon 129 (identified as MM, MV, and VV) and the PrP^{Sc} type 1 or 2 to distinguish five phenotypes in sCJD, along with a sixth phenotype that we named sporadic fatal insomnia (sFI). These six phenotypes are easily distinguishable by clinical and histopathological features such as type, severity, and topography of the lesions along with the pattern and distribution of the PrP immunostaining.

Clinical and Histopathological Phenotypes

sCJDMM(MV)1

sCJDMM1 and MV1 are phenotypically indistinguishable and are therefore grouped together as sCJDMM (MV)1.

Prevalence

This subtype accounts for about 70% of all cases of sCJD.

Clinical features

The mean age at onset of symptoms is 65 years (range 42–91); the average disease duration is 4 months with a range of 1–36 months. The most common presentations (70% of cases) include cognitive impairment; less common presentations include ataxia, mental signs, and visual signs (field defects, distortion, cortical blindness). Unilateral onset of neurological signs occurs in about 25% of cases. Ataxia, myoclonus, and pyramidal signs are usually evident as the disease progresses. In about 80% of the cases, the EEG shows periodic sharp wave (PSW) complexes within the first 3 months of disease. The detection of the 14–3–3 protein in the cerebrospinal fluid (CSF) has a sensitivity of about 95%. MRI shows T2-weighted cortical and basal ganglia involvement in up to 58% of the cases; however, with diffusion-weighted imaging (DWI) the percentage increases to 75%. Cerebellar and thalamic hyperintensity is usually not observed.

Histopathology

The most common and defining characteristics are moderate fine spongiform degeneration (SD) (**Figure 2(a)**) and astrogliosis in most gray matter structures but more pronounced in the cortex than in basal ganglia and thalamus, and more prominent in the occipital than in the frontal cortex. The hippocampal gyrus is spared. SD is prominently present in the entorhinal cortex. The cerebellum shows moderate to minimal SD in the molecular layer and no atrophy of the cortex. The substantia nigra (SN) is not affected.

PrP immunohistochemistry

There is a fine punctate (synaptic) immunostaining pattern occasionally intermixed with small clusters of larger granules or a 'coarse' pattern (**Figure 2(d)**). The staining intensity matches the severity of the SD. The cerebellar molecular layer shows the distinct pattern of 'brush stroke.' The dentate nucleus and the SN commonly are unstained.

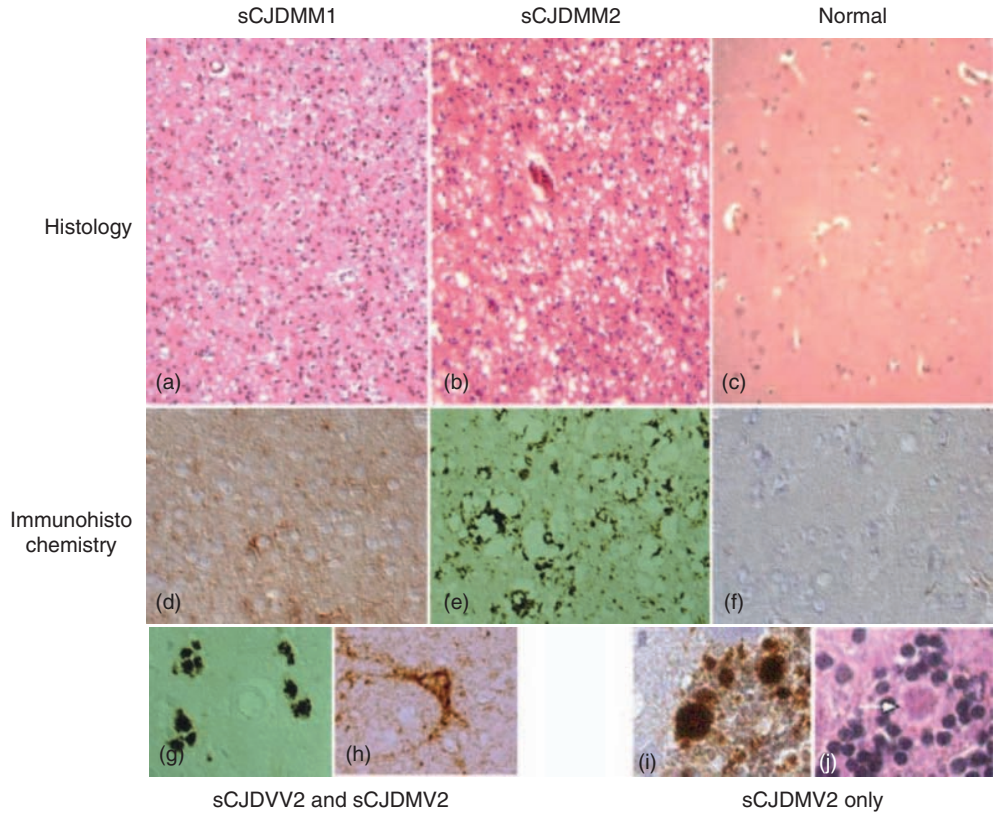

Figure 2 Histopathology and immuno-histochemistry of sCJD subtypes. Histopathology (Hematoxilin and eosine) shows spongiform degeneration (SD) in two sCJD subtypes with a remarkable difference in vacuoles size: fine (SD) is seen in sCJDMM1 (a) while large/confluent vacuoles are characteristic of sCJDMM2 (b). The normal cerebral cortex shows no SD (c). Immuno-histochemistry discloses fine punctate (synaptic) immunostaining pattern of PrP immunoreactivity in sCJDMM1 (d), while coarse staining with characteristic perivacuolar PrP-immunoreactivity in commonly seen in sCJDMM2 sub-type (e). The control, non prion disease brain shows no PrP immustaining (f). Plaque like (g) and perineuronal (h) PrP-immunoreactivity is the characteristic staining of both MV2 and VV2 sub-types; while kuru plaques, shown in immunohistochemical (i) and histopathological (j) preparation, are seen exclusively in MV2 cases. Characteristic histo-pathological and immune-histochemical features make the sCJD subtypes distinguishable at histological examination.

sCJDVV1

Prevalence

This subtype accounts for about 1% of all cases of sCJD.

Clinical features

The mean age at onset is 37 years (range 19–55) and the average disease duration is 21 months (range 10–49), which identifies this subtype as early onset. Presentation is characterized by dementia mainly of the frontotemporal type. Myoclonus, pyramidal signs, and ataxia eventually appear as the disease progresses. EEG shows no PSW complexes. The 14–3–3 test is positive in 100% of cases. MRI shows signal increase in the cerebral cortex in 100% and in <30% in basal ganglia.

Histopathology

The hallmarks are the severity of the SD and astrogliosis along with the presence of 'ballooned' neurons. The severity of SD is similar in the basal ganglia and cerebral cortex, where it is more pronounced in the frontal than in the occipital lobes; less prominent in the thalamus. The SD distribution in the hippocampal formation is similar to that of sCJDMM(MV)1. The cerebellum and the SN are virtually spared.

PrP immunohistochemistry

The staining (with antibody 3F4) is extremely light and free of the cluster of larger granules or 'coarse' patterns. The cerebellar cortex and SN are usually unstained.

sCJDMM2

Prevalence

This subtype accounts for about 5% of all cases of sCJD.

Clinical features

The mean age at onset is 65 years (range 49–77), and the average disease duration is 16 months (range 9–36). The presentation is dominated by cognitive impairment of the focal type (aphasia, apraxia, spatial disorientation,

frontal signs) in one-third of the cases. As the disease progresses, myoclonus, and pyramidal signs also become common; and parkinsonism and seizures are present in about 30% of the cases. Ataxia is uncommon. The EEG never shows PSW complexes. The 14–3–3 test is positive in 75% of cases. MRI demonstrates cerebral cortical hyperintensity, whereas in the thalamus the signal is generally unchanged.

Histopathology

The hallmark of this subtype is the much larger and often confluent vacuoles of SD (**Figure 2**(**b**)), easily distinguishable from those of all the other sCJD subtypes, although fine SD may also be present. The cerebral cortex in the various lobes is similarly affected but the hippocampal gyrus is spared. Basal ganglia and thalamus are less affected while cerebellum and SN are spared.

PrP immunohistochemistry

The two dominant staining patterns consist of round loose plaque-like deposits, along with staining of the rims of the large vacuoles (**Figure 2**(**e**)). The staining is very intense in the cortex and subcortical nuclei; the cerebellum shows occasional clusters of plaque-like staining in the molecular layer while the SN is unstained.

sCJDVV2 and sCJDMV2

The phenotypes of these two subtypes are very similar and are therefore reported together.

Prevalence

sCJDVV2 accounts for about 16%, and sCJDMV2 for about 9% of all sCJD.

Clinical features

The mean age at onset is about 60 years (range 41–81); the average disease durations are 17 months (range 5–72) for sCJDMV2 and 6 months (range 3–18) for sCJDVV2. Ataxia is the invariable presenting sign in both subtypes. Cognitive impairment is always present and is often preceded by mental signs in sCJDMV2 cases while it is observed in just one-third of sCJDVV2 patients. As the disease progresses, myoclonus and pyramidal signs affect the majority of patients. Aphasia and apraxia are common in sCJDMV2, but absent in sCJDVV2 patients. In both subtypes, the EEG shows PSW complexes in $<10\%$ of the cases and the sensitivity of the 14–3–3 test is $<80\%$. MRI thalamic hyperintensity is common (up to 86% on DWI), allowing for differentiation of sCJDMV2 from sCJDVV2.

Histopathology

The SD is of the fine type and exhibits similar distribution in the two subtypes. The cortex is much less affected than the basal ganglia and thalamus and the frontal is more affected than the occipital lobe. The hippocampal gyrus shows extensive SD. The cerebellum has SD in the molecular layer and the SN is also affected. The difference between the two subtypes resides in the cerebellum. In contrast to sCJDVV2, sCJDMV2 shows no atrophy of the granule cell layer and contains kuru plaques in the superficial zone of the granule cell layer (**Figure 2**(**l**)).

PrP immunohistochemistry

In addition to the fine punctate immunostaining, there are scattered plaque-like aggregates and characteristic perineuronal staining made of small granules dotting the surface of the neuronal cell body and processes (**Figure 2**(**g**) and (**h**)). The intensity of the immunostaining is related to the severity of the lesions. The hippocampal gyrus and the SN are immunostained. The immunostaining pattern of the cerebellum is distinct in the two subtypes. Although in both subtypes the granule cell layer is heavily and preferentially stained, the staining predominantly exhibits tight aggregates in sCJDMV2 and loose plaque-like formations in sCJDVV2.

sCJD with co-occurrence type 1 and 2 (sCJD1–2)

Clinical features

PrP^{Sc} types 1 and 2 may coexist in up to $\sim$40% of cases with sCJD. Type 1 appears to be better represented than type 2 in MM sCJD subjects, while type 2 is more evident in VV subjects. The clinical and histopathological phenotypes reflect those of the predominant PrP^{Sc} type. For example, sCJDMM1–2 subjects with predominant type 1 are likely to have a phenotype similar to that of the sCJDMM1 subtype.

Diagnostic Tests

This section provides a synopsis of diagnostic tests. The EEG consistently shows the characteristic PSW complexes only in sCJDMM(MV)1. The 14–3–3, a widely used CSF test commonly based on Western blot, is helpful in the differential diagnosis of sCJD from other rapidly progressing dementia conditions. With some exceptions, the great majority of studies report an overall sensitivity of 90% or more and a specificity of 50% or less. Therefore, the 14–3–3 test over-diagnoses sCJD. The sensitivity varies according to the sCJD subtype: it is over 95% in sCJDMM1 and around 80% in sCJDMV2 and sCJDVV2. MRI should be used along with the 14–3–3 test to rule out focal brain destructive conditions that often results in a positive 14–3–3. Other CSF tests include tau, neuronal specific enolase and S100 and are the other protein markers most frequently used. Tau, the most studied, has a slightly overall lower sensitivity of 80–90% and a higher specificity of 70–80% than those of 14–3–3 (**Table 1**).

MRI plays an increasingly important role in the diagnosis of sCJD, and might become the test of choice in

Table 1 sCJD subtypes: phenotypic features

Subtype	*Prevalence (%)*	*Clinical features*	*Diagnostic test*	*Histopathology*
MM(MV)1	70	*Onset*: 65 years (42–91); *duration*: 4 months(1–36) *presentation*: cognitive impairment, ataxia, mental and visual signs; *later stage*: myoclonus, ataxia, and pyramidal signs	*EEG*: PSW in 80% of cases 14–3–3: 95% positivity *MRI*: cortical and BG signal increase in up to 58% of cases (75% with DWI)	Widespread fine SD and minimal astrogliosis more pronounced in cortex, especially occipital and entorhinal, than BG and thalamus; hippocampal gyrus and SN not affected; fine punctuate immunostaining with occasional small clusters of larger granules matching in intensity the severity of the SD; 'brush stroke' pattern in cerebellar molecular layer; dentate nucleus and the SN are unstained
VV1	1	*Onset*: 37 years (19–55); *duration*: 21 months (10–49) *presentation*: dementia of frontotemporal type; *later stage*: myoclonus, pyramidal signs, and ataxia	*EEG*: No PSW 14–3–3: 100% positivity *MRI*: signal increase in cerebral cortex in 100% and BG in 30% of cases	Severe SD and astrogliosis with 'ballooned' neurons; SD similar in BG and cerebral cortex, more severe in frontal lobe; thalamus affected; SD distribution in hippocampus similar to sCJDMM(MV)1; cerebellum and SN spared; immunostaining very light and cluster-free; cerebellum and SN unstained
MM2	5	*Onset*: 65 years (49–77); *duration*: 16 months (9–36) *presentation*: cognitive impairment; *later stage*: myoclonus, pyramidal signs, seizures; ataxia uncommon	*EEG*: No PSW 14–3–3: 75% positivity *MRI*: increased cerebral cortical intensity; no thalamic abnormalities	SD with much larger and confluent vacuoles; fine SD sometime present; cerebral cortex similarly affected; hippocampal gyrus spared; BG and thalamus less affected; cerebellum and SN spared. Two immune staining patterns: (1) round loose 'plaque-like' deposits; (2) staining of large vacuole rims; occasional plaque-like staining in cerebellar molecular layer; SN unstained
VV2 MV2	16 9	*Onset*: 60 years (41–81); *duration*: 6 months (3–18) [sCJDVV2], 17 months (5–72) [sCJDMV2] *presentation*: ataxia in all cases; cognitive impairment often with mental signs in 100% sCJDMV2 and in 30% of sCJDVV2 cases; *later stage*: myoclonus and pyramidal signs; aphasia and apraxia common in sCJDMV2, absent in sCJDVV2	*EEG*: PSW in 10% of cases 14–3–3: 80% positivity *MRI*: thalamic hyperintensity in up to 86%; DWI different in sCJDVV2 and sCJDMV2	Fine SD in deep cortical layers less severe than in BG and thalamus; frontal more affected than occipital lobe; extensive SD in hippocampal gyrus, moderate in cerebellum; SN affected. sCJDMV2: kuru plaques in cerebellum with no atrophy; sCJDVV2: atrophy no kuru plaques. Fine punctuate, scattered plaque-like and perineuronal immunostaining; patterns often laminar in the cortex; tight aggregates cerebellar immunostaining in sCJDMV2; loose plaque-like in sCJDVV2

sCJD. Hyperintensity of the basal ganglia in T2-weighted images is characteristic. Emerging, and more sensitive, techniques such as FLAIR (fluid-attenuated inversion recovery) and DWI have demonstrated cortical signal increase, thus increasing overall MRI sensitivity and specificity in specialized centers to over 90%.

Treatment

The first drug studies of CJD were undertaken almost 40 years ago and since then dozens of drugs have been tested. Yet no effective treatment has been found. Nevertheless four compounds have been (or are currently being) studied with sufficient rigor and in an adequate number of patients.

Quinacrine, once widely used antimalarial drug, was found to block formation of PrP^{Sc} in infected cell cultures. A recent patient-preference trial on all forms of CJD showed acceptable level of tolerance but no effect on the clinical course of CJD. Flupirtine maleate, a centrally acting nonopioid analgesic, has been tested in a randomized double-blind study of subjects with the diagnosis of probable CJD. Treated patients showed a significantly slower rate of cognitive deterioration but no significant difference in survival time. Administration of doxycycline, a member of the tetracycline group, to sCJD patients under compassionate treatment has been reported to more than double survival compared to untreated sCJD subjects. A phase II, multicenter, randomized, double-blind study is ongoing.

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See also: Ataxia; Electroencephalography (EEG); Kuru; Myoclonus; Variant Creutzfeldt–Jakob Disease.

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Cyanides

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Chemistry and Exposure Information

Hydrocyanic acid is one of the most rapidly acting poisons, and it is therefore used especially as a suicidal or homicidal agent. Cyanide intoxication also occurs accidentally during fumigation, including fire inhalation, electroplating, and gold or silver ore extraction. Free hydrocyanic acid or cyanogenetic glycosides are produced by choke–cherry trees and other plants, and accidental poisoning is due to the ingestion and chewing of the toxic

seeds. Cyanides are general protoplasmic poisons producing asphyxia by inhibiting the action of energy-generating respiratory enzymes throughout the body. Benzyl cyanides inhibit dopamine beta hydroxylase, the synthetic enzyme for the neurochemical, norepinephrine. They also induce a brief stimulation of the central nervous system that is rapidly replaced by a paralyzing action. In addition, cyanides interact with the dopamine metabolite, 3,4-dihydroxyphenylacetaldehyde (DOPAL), to generate a biologically active compound (cyanohydrin adduct) that may contribute to its neurotoxicity.

Clinical Signs of Intoxication

Within 10 min of the ingestion of lethal doses of cyanide, victims lose consciousness, exhibit generalized convulsions, and die within 2–5 min. Most often, the toxic effects appear more slowly with some agitation, salivation, anxiety, confusion, and nausea. These symptoms are accompanied by vertigo, headache, unsteady gait, and a feeling of stiffness in the lower extremities. Seizures may develop and appear to relate to a depletion of the energy generating compound, adenosine triphosphate (ATP). Breathing is stentorian; the face is flushed and then cyanotic; and the pupils are dilated. Respiration frequently ceases before the heart stops, and death usually ensues within 15 min to 1 h. Recovery may occur when treatment is instituted rapidly. If patients survive the first hour, they usually recover completely, although some experience weakness, unsteady gait, headache, difficulty in speaking, and drowsiness. There is a high degree of individual susceptibility to cyanide intoxication, but some patients have survived even after the ingestion of 6 g of potassium cyanide, although as little as 0.13 g can be lethal.

After the inhalation of gaseous hydrocyanic acid, the victim develops nausea, vomiting, and difficulty in breathing. Unconsciousness supervenes, and within 10 min, respiratory failure and death may occur. Survivors typically have parkinsonian features, with masked facial expression, severe hypophonia, bradykinesia of limbs and trunk, and unsteady gait due to postural reflex compromise. Tremor is not always present and can have a mixed rest/postural/kinetic character. Some patients have additional cognitive alterations and some have added cerebellar features of poor coordination and slurred speech, which superimpose on parkinsonian hypophonia. MR scans show damage to the globus pallidus, putamen, midbrain, and cerebellum. The evidence of hemorrhagic necrosis develops within 6 weeks of intoxication and cystic degeneration is a late finding. The sensorimotor cortex can also be involved in pseudolaminar necrosis. ^{18}F-fluoro-dopa positron emission tomography scans can reveal a symmetrical reduction of activity in two anatomical areas, the caudate nucleus and putamen. Glucose metabolism scans show regional reductions in the putamen, temporo-parieto- occipital cortex, and cerebellum. With chronic potassium cyanide exposure, MR spectroscopy and SPECT may be more useful in documenting abnormalities when the standard MR scan does not reveal extensive abnormalities. Cyanide intoxication can also cause a different syndrome without parkinsonism: cerebellar dyssynergia, ataxia and accompanying malaise, weakness, visual disturbances, and muscle pains. Vertigo and unusual periods of fluctuating consciousness have also been observed. Finally, chronic cyanide intoxication caused by a long-standing ingestion of the cassava root has also been linked to tropical amblyopia and tropical ataxic neuropathy. Cassava is the tuberous root of the shrublike plant *Manioc palmatea*, and this plant contains a high concentration of glycoside, which is metabolically transformed into cyanide by the action of hydrolase activated by handling, heating, or bruising the tubers. Farmers and subjects in close contact with cassava have been affected most frequently. Clinically, this chronic intoxication is manifested by optic atrophy, bilateral nerve deafness, and spinal cord damage with weakness and loss of vibratory and touch sensation and diffuse polyneuropathy involving distal nerves. The lower limbs are most frequently involved and show marked weakness and wasting. In terms of signs of movement disorders, an occasional patient reveals cerebellar findings of staggering gait, poor coordination, and slurred speech. In an area of Mozambique, where an epidemic of spastic paraparesis developed in association with cassava ingestion, high urinary thiocyanate and decreased inorganic sulfate excretion were documented. These findings suggested a high cyanide exposure and have further added evidence to the hypothesis that cyanides may relate to the pathogenesis of some types of spinal ataxia and peripheral nerve lesions heretofore considered to be idiopathic or of unknown cause.

In the 1970s, the anticancer drug, laetrile, was used in many areas of the world, and at its height, an estimated 20 000–50 000 people used the drug on a yearly basis. The drug induced many cases of cyanide toxicity, most notably, a mixed neuropathy–myelopathy with ataxia and dyssynergia occurring in some patients. The toxicity of laetrile related to cyanide release during the metabolism of amygdalin, a major component of the drug.

Patients usually recover spontaneously from poisoning due to cyanide gas inhalation if they can be brought into open air before respiration ceases. Artificial respiration is imperative if there is interruption of breathing. For specific treatment, the National Poison Center network recommends sodium nitrite, amyl nitrite, and sodium thiosulfate, with close attention to blood pressure.

See also: Parkinson's Disease: Definition, Diagnosis, and Management.

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Cylinder Test (Paw Reach Test)

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Glossary

6-OHDA – 6-Hydroxydopamine, a neurotoxin that induces selective degeneration of catecholamine neurons, frequently used following injection into the vicinity of midbrain dopamine neurons to induce an animal model of Parkinson's disease.

L-dopa – L-dihydroxyphenylalanine, the active precursor for the neurotransmitter dopamine, and the prototypical drug for treatment of Parkinson's disease.

MCAO – Middle cerebral artery occlusion, a frequently used method to induce focal stroke in the brain of experimental animals.

The cylinder test was introduced in the mid-1990s by Timothy Schallert as a simple and sensitive test of spontaneous limb use for applications in rat lesion models of Parkinson's disease. The test turns out to be useful for assessing the sensorimotor consequences of a range of unilateral lesion models, in particular when induced by stereotaxic injection of toxins or focal ischemia. The test relies on the spontaneous tendency for rodents, when placed in a novel environment, to explore by rearing to look around. When tested in a confined space, the rats will place their forepaws against the wall to maintain stability and place their paws back on the floor to balance as they descend. A normal rat will typically use both paws equally, with the splaying of the digits as the paw contacts the wall, but unilateral brain damage typically yields impairments in the use of the contralateral limb, with the forearm held loose or against the body and the paw more clenched.

The Cylinder Test

The cylinder test (**Figure 1**) involves placing the animal into a transparent Perspex cylinder ~20 cm in diameter and 30 cm high (sufficient to allow free rearing and turning but to avoid the animal climbing out). An angled mirror is placed behind the cylinder so that the animal's movements can be observed at all angles. Typically, the rat is placed into the cylinder and movements video recorded for a fixed period, say 5 min, for subsequent analysis in terms of the number and duration of rears, number and duration of left and right paw contact with the wall surface, and whether the animal uses one or both paws for weight bearing when it descends from rearing.

The simplest outcome measure is to express the time or number of wall contacts with the ipsilateral paw as a ratio of total time or contacts with both paws. For some purposes, such as tracking recovery of function or effects of experimental therapeutics, this simple ratio measure is the most practical. For other purposes, such as comparing

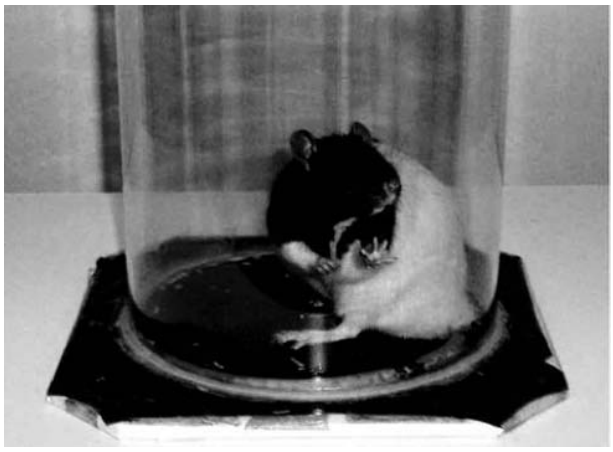

Figure 1 Rat in the cylinder test. Note that as the rat rears, it typically places one or both paws against the cylinder wall to stabilize its balance. In this example, the animal is placing with the left paw and holding back the right paw, which is a characteristic posture following lesions in the left basal ganglia or nigrostriatal pathway.

the profile of deficits after different lesions, Schallert advocates using a combination of measures involving both simultaneous and independent use of the two limbs for contacting the wall when rearing, for weight shifting, for regaining center of balance while turning, and both simultaneous and independent use of the two limbs for landing. Providing an even more fine-grain analysis, Whishaw and colleagues have used Eshkol–Wachman movement notation to characterize in detail horizontal movements, vertical movements, head scanning, turning, forelimb progression during a vertical scan, and weight shifting on the hind limbs during vertical progression.

Although most experimental work using the cylinder test has been undertaken in rats, a few studies have successfully adapted the test to mice and small monkeys (marmosets).

Key Results

Unilateral lesions at multiple levels of the motor systems of the brain are seen to produce asymmetries in limb placing in the cylinder test, including lesions in the nigrostriatal pathway, the striatum, the somatosensory and motor areas of neocortex, and focal ischemia by middle cerebral artery occlusion (MCAO) affecting the striatum and the sensorimotor cortex, the rubrospinal tract, and cervical spinal cord. Although all lesion types have somewhat similar effects in reducing the use of the contralateral limb for placing, stabilization, and balance as the animals rear to explore their environment, and for landing after a rear, considerable differences have been recorded in the degree of spontaneous recovery. Although several of the lesion syndromes routinely exhibit significant or complete recovery and return of bilateral limb use in cylinder exploration, deficits may be long-lasting, in particular after nigrostriatal and cervical lesions.

The cylinder test has been widely used for the investigation of novel therapeutic strategies, in particular in MCAO models of stroke. Thus, for example, conventional Parkinsonian treatments such as L-dopa or dopamine receptor agonists can produce improved limb use in the cylinder test in the acute period following lesion, although longer-term recovery is confounded by competition from the abnormal involuntary movements induced by chronic treatment with L-dopa. A number of studies have reported good functional benefit in the cylinder test by viral transfection of trophic molecules such as glial cell line-derived neurotrophic factor (GDNF) providing neuroprotection of the intrinsic system against acute toxin-induced degeneration, whereas recovery in cell transplantation studies have in most cases proved more disappointing on this functional measure, clearly illustrating the different mechanisms of neuroprotection and repair provided by these alternative strategies. There is, however, evidence that recovery following cell replacement may be promoted by environmental enrichment.

See also: 6-OH Dopamine Rat Model; Parkinson's Disease: Animal Models.

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Cystatin B

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Glossary

Allele – One member of the different forms of a gene.
Alternative splicing – Variation in the splicing of RNA in which the exons of the primary gene transcript are separated and reconnected to produce a variety of structurally different RNA molecules, which when translated result in different protein isoforms.
Cathepsin – An enzyme that degrades polypeptides and contains either a cysteine or an aspartic acid amino acid in the enzyme's active site.
Cysteine protease: – An enzyme that degrades polypeptides and contains a cysteine amino acid in the enzyme's active site.
Dodecamer repeat – A stretch of DNA that consists of 12 structural units of DNA, the nucleotides, and that occurs in more than one consecutive copy on the DNA strand.
Founder effect – The loss of genetic variation when a new colony is formed by a very small number of individuals from a larger population.
Northern blot analysis – A molecular biological method to study gene (RNA) expression that is based on detection of RNA molecules with hybridization probes after size separation by gel electrophoresis.

Introduction

Unverricht–Lundborg disease (EPM1; OMIM 254800) is an autosomal recessively inherited disorder and the most common single cause of progressive myoclonus epilepsy worldwide. Mutations in the CSTB gene (*CSTB*) encoding Cystatin B, a cysteine protease inhibitor, are responsible for the primary defect in the majority of EPM1 patients. Gene identification in EPM1 has made possible molecular diagnostics in the majority of patients, elucidation of the cellular function of the CSTB protein, and studies of the EPM1-associated disease mechanisms, which are reviewed here.

The Cystatin B Gene

The *CSTB* gene contains three exons with a ubiquitously expressed mRNA of approximately 0.8 kb in northern blot analysis. Two potential transcription start sites are located 67 and 78 nucleotides downstream of the dodecamer repeat element in the promoter. *CSTB* is alternatively spliced with at least five isoforms of unknown physiological significance, some of which show tissue specificity.

EPM1-Associated *CSTB* Gene Mutations

Ten mutations have been reported to underlie EPM1 (**Table 1**). The most common of these is an unstable expansion of a polymorphic 12-nucleotide, dodecamer, repeat (5′-CCCCGCCCCGCG-3′), in the promoter region of *CSTB*. Control individuals have two or three copies of the repeat, whereas EPM1-associated alleles contain between 30 and approximately 125 copies. This mutation is found in approximately 90% of the disease alleles worldwide and in homozygous form in the majority of the patients, especially in populations with a founder effect. So far, only one EPM1 patient without the expansion mutation has been described. The dodecamer repeat expansion mutation seems to show no correlation between the number of repeats and either disease severity or the age of onset.

In vitro studies have indicated a significantly reduced *CSTB* promoter activity in the presence of the expansion mutation. Compatible with these data, the expansion results in a significant downregulation of *CSTB* mRNA expression in vivo with less than 10% of expression from that in controls. Consequently, the CSTB protein expression and its inhibitory activity are also significantly reduced in cells of EPM1 patients.

The other EPM1-associated *CSTB* mutations change single amino acids, affect splice sites, or predict truncated proteins (**Table 1**). With the exception of the p.G4R substitution mutation, these mutations have been reported to occur in compound heterozygous form with the repeat expansion. All three reported amino acid substitution mutations are likely to affect the interaction of the CSTB protein with its target cysteine proteases. Alternatively, they may change the stability or life span of the inhibitory effect of CSTB. *CSTB* mRNA and protein expression data suggest that reduced CSTB expression is the primary pathological consequence in the majority of EPM1 mutations, with a possible exclusion of the amino acid substitution mutations.

The Cystatin B Protein

Human CSTB protein consists of 98 amino acids comprising a molecular weight of approximately 11 kDa and it

Table 1 Mutations in *CSTB* underlying Unverricht–Lundborg disease

Mutation	*Position of mutation in gene/type*	*Predicted consequence on protein*	*No. of patients*[a]/Country of origin
Dodecamer repeat expansion	5′UTR/Expansion	Reduced CSTB expression	>200; Various
c.10G>C	Exon 1/Missense	p.G4R	1; Morocco
c.67–1G>C	Intron 1/Splice site	p.delV23_K56	>10; Various
c.149G>A	Exon 2/Missense	p.G50E	1; Finland
c.168G>A	Exon 2/Splice site	Aberrant splicing?	1; Japan
c.168+1_18del	Intron 2/Deletion	p.delV23_K56 and p.V57EfsX28	1; Italy
c.169–2A>G	Intron 2/Splice site	Aberrant splicing?	1; France
c.202C>T	Exon 3/Nonsense	p.R68X	>10; Finland, Sweden
c.212A>C	Exon 3/Missense	p.Q71P	1; The Netherlands
c.218_219delTC	Exon 3/Deletion	p.L73fsX3	<10; Various

[a]Reported in the literature or known to the author.

is widely expressed in different tissues and cell types. CSTB belongs to family 1 of the cysteine protease inhibitor superfamily, the cystatins, which are small molecular weight single polypeptide chain proteins that do not contain carbohydrate side chains or disulphide bonds. CSTB inhibits in vitro several lysosomal cysteine proteases, cathepsins, by tight, reversible binding and thereby contributes to their activity. The main function of cathepsins is nonselective degradation of intracellular proteins, but they also participate in antigen processing and apoptosis. Decreased inhibitory activity of CSTB, through reduced gene and protein expression, has been shown to correlate with enhanced activity of cathepsins B, L, and S in EPM1 patient cells, providing in vivo evidence for cathepsins being regulated by CSTB.

Cytoplasmic, lysosomal, and nuclear localization has been reported for wild-type CSTB protein with somewhat controversial results between different studies, possibly due to the different cellular models and antibodies used. In proliferating human primary myoblasts and in differentiated nonproliferating myotubes, CSTB localization seems to be dependent on the differentiation status of the cells with only cytoplasmic localization in myotubes but both lysosomal and nuclear localization in myoblasts. Available data suggest that CSTB is attached to the outer side of the lysosomal membrane rather than within the lysosome, although this would need to be experimentally verified.

Amino acid substitution mutations that are likely to express a structurally and functionally altered protein in patients have been utilized in cellular expression studies to give insight into the physiological function of CSTB. Such mutant proteins, when transiently expressed in cells, fail to associate with lysosomes implying that the lysosomal association is essential for the physiological function of CSTB and that a loss of this association contributes to the molecular pathogenesis of EPM1. As all the three amino acids that are known to be altered in patients likely affect binding of CSTB to cathepsins, it may be that the loss of lysosomal association is a consequence of altered binding to cathepsins: a hypothesis, which awaits experimental verification.

Cystatin B-Deficient Mice – A Model for EPM1

The Cystatin B-deficient mice with targeted disruption of the mouse *Cstb* gene mimic the human phenotype reasonably well. The mice develop myoclonic seizures during sleep by one month of age and progressive ataxia by six months of age. No tonic–clonic seizures, photosensitivity, or spike-wave complexes in EEG have been observed in the mice. The genetic background has a clear impact on the clinical outcome, implying that genetic factors influence the phenotype.

The neuropathological hallmark in the *Cstb*-deficient mice is a severe progressive loss of cerebellar granule cells due to apoptotic death. There is a less marked neuronal apoptosis in the hippocampal formation and entorhinal cortex in young animals and a widespread cortical and white matter gliosis in older mice. In addition, the superficial neurons of the prosubiculum in the cerebral cortex display prominent cellular atrophy, which is similar in seizure-prone and seizure-resistant mouse backgrounds. These data suggest that CSTB has an endogenous neuroprotective role and that EPM1 should be classified as a primary neurodegenerative disorder, with specific neuronal populations affected and both neuronal death and dysfunction contributing to the phenotype.

The *Cstb*-deficient mouse model has been utilized in studies aiming at understanding the related disease mechanisms. Studies in hippocampal slice preparations from these mice have revealed latent hyperexcitability,

which may be due to a loss of GABAergic cells and a subsequent loss of inhibition, and which may relate to EPM1 onset. Moreover, *Cstb*-deficient mice have an increased susceptibility to kainate-induced seizures. They show a shorter latency to seizure onset, more severe seizures and a more severe neuronal damage compared with wild-type littermates. As CSTB expression also increases in response to hippocampal kindling, it can be hypothesized that CSTB acts as a physiological safeguard and that loss of its activity not only triggers neurodegeneration but also makes neurons more susceptible to prolonged seizure-induced cell death contributing to disease progression in EPM1. Finally, cerebellar granule neuron degeneration is reduced in *Cstb*-deficient mice from which the *Cathepsin B* gene is also genetically removed, with no effect on the ataxia and seizure phenotypes. It is thus likely that cathepsin B is one contributor to the apoptotic phenotype resulting from CSTB deficiency.

Conclusion

Loss-of-function mutations in *CSTB* are the primary defect in EPM1. Available evidence implies lost lysosomal association of CSTB as an important contributing factor to the disease pathogenesis. Moreover, cathepsins, especially cathepsin B, are likely to have a role in the molecular pathology of EPM1. CSTB seems to have an endogenous neuroprotective role with different neuronal populations having different sensitivity to CSTB deficiency. The physiological function and the disease mechanisms of EPM1 remain to be elucidated.

See also: Lafora Disease; Mitochondrial Encephalopathies; Myoclonus, Epileptic; Unverricht–Lundborg's Disease.

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D

Deep Brain Stimulation

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Introduction

Deep brain stimulation (DBS) is an outgrowth of stereotactic lesion surgery for Parkinson's disease (PD) that began in the 1940s. With advances in technology, brain mapping, neurosurgical technique, and brain neurophysiology, DBS was developed to relieve symptoms of tremor, rigidity, and bradykinesia in patients with PD. Since its introduction as an effective treatment for tremor in the 1990s, DBS has been successfully applied to several other neurological and psychiatric disorders.

To date, tens of thousands of patients with essential tremor (ET), PD, and dystonia have been successfully implanted, worldwide, with DBS devices to control symptoms of tremor, rigidity, dystonia, bradykinesia, and drug-induced dyskinesias. A single electrode controls symptoms on the opposite body side, and DBS can be performed on one or both sides of the brain. DBS has proven more effective at suppressing tremor than any medical treatment to date. For individuals with advanced PD complicated by wearing off motor fluctuations and dyskinesias, DBS can yield important benefits in symptom control and quality of life that are not achievable by medication adjustment alone.

In addition to neurological applications, DBS is being investigated as a treatment for chronic pain, depression, obsessive–compulsive disorder (OCD), and Tourette syndrome (TS).

To date, there is no evidence that DBS modifies disease or prevents disease progression. DBS remains a treatment approach that works by suppressing the symptoms, and is used only for those symptoms that do not adequately respond to medication.

This article will briefly review the development of DBS as a neurosurgical treatment, the technical aspects of DBS, electrophysiology, and application to several common neurological and psychiatric disorders, with an emphasis on movement disorders: PD, tremor, and dystonia.

DBS Components and Techniques

The deep brain stimulator device consists of three parts: an electrode with a linear tetrad of platinum iridium ring contacts, an extension wire, and a programmable implantable pulse generator (IPG), or battery. Guided by neuroimaging studies and intraoperative neurophysiological mapping, the stimulating electrode is inserted under local anesthesia through a skull burr hole into a deep brain structure. The electrode is anchored at the skull, and connected by a lead extension that is threaded subcutaneously through the muscles of the neck, and attached to the IPG, or battery, implanted in the chest wall below the clavicle.

The DBS electrode can be interrogated and programmed percutaneously using a handheld device placed over the IPG. Various electrical settings can be manipulated: the configuration of contacts in the quadripolar electrode, the voltage amplitude, pulse width, and frequency. In theory, the device allows more than 40,000 combinations of electrical parameters but in clinical practice, assuming accurate electrode placement, therapeutic results are produced by a limited set of readily identifiable settings. The device provides only stimulation, and has no sensing capability that might allow more sophisticated synchronization with brain electrophysiology.

Development of DBS

The origins of DBS began over a 100 years ago with the development of the first stereotactic apparatus by Horsley and Clark for brain surgery in animals. Innovative neurosurgeons began to treat abnormal involuntary movements, including chorea, dystonia, and tremor, by excising parts of the human cortex. It was American neurosurgeon Meyer who made the seminal observation in the 1940s

that lesioning parts of the basal ganglia could successfully reduce tremor *without resulting in weakness or paralysis*. In the ensuing decades, neurosurgeons created different lesions in many areas of the basal ganglia, including the globus pallidus, caudate, thalamus, subthalamic nucleus (STN), and ansa lenticularis to reduce the symptoms of dystonia, tremor, rigidity, and chorea.

Microelectrode recording for brain mapping was developed by Narabayashi in the 1960s. The use of intraoperative stimulation of brain targets in preparation for ablative surgery revealed that high-frequency stimulation of the thalamus could suppress tremor on the opposite side of the body. As an alternative to lesion surgery, high-frequency stimulation of deep brain structures was first introduced in the 1970s. In 1991, Benabid reported that continuous high-frequency stimulation of the ventral intermediate (VIM) thalamus produced long-term tremor suppression.

DBS was shortly thereafter applied to the surgical targets previously shown by lesion techniques to be most effective for controlling movement disorder: VIM thalamus for tremor, globus pallidus interna (GPi) for PD and dystonia. On the basis of DeLong's research that a lesion of the STN could reverse the signs of experimental parkinsonism in a primate, this nucleus was targeted for stimulation in patients with PD. DBS proved to be safe and efficacious at all three target sites: VIM thalamus, GPi, and STN. The technique was approved by the FDA as a standard therapy for treating essential tremor (1997), PD tremor (1997), advanced PD (2002), and dystonia (2003).

Electrophysiological Effects of DBS

On the basis of observation that DBS replicated the effect of ablative surgery in the thalamus, globus pallidus, and STN, it was initially assumed that DBS worked by suppressing electrical activity in brain structures through neuroinhibition. It seems more likely that DBS exerts a variety of effects on brain tissue, with different actions on white matter tracts and cell bodies. No electrophysiological model currently accounts for all of the effects and consequences of DBS in brain tissue, which can be influenced by lead location, electrode configuration, and firing rate. At a subcellular level, electrical stimulation appears to activate or inhibit nerve terminals by changing electrical thresholds for voltage-dependent channel function and release of neurotransmitter. Effects on individual nerve fibers may include the orthodromic activation of cortical structures, or the antidromic activation of cerebellar fibers and other components of the basal ganglia. Through its local effects at the point of stimulation, DBS can bring about immediate and long-term widespread changes in neuronal network activity and cerebral blood flow. As noted, the current brain electrode is purely stimulating, and has no recording or monitoring function that might enable selective stimulation effects.

DBS Applications in Neurology and Psychiatry

To date, only three neurological applications of DBS are clearly defined: PD, ET, and dystonia. In addition, several successful minor applications of DBS to movement disorders have been reported in small series, including VIM stimulation to suppress the tremor of multiple sclerosis and GPi stimulation for myoclonus-dystonia.

An outgrowth of sustained neurosurgical innovation for the treatment of PD and dystonia, the neurological applications of DBS are supported by many decades of empirical ablative surgery. In addition, DBS exploits the existing knowledge of neuroanatomy and neurophysiology within brain circuitry that is well-defined by radiolabeling experiments and functional imaging.

By contrast, the neuropsychiatric applications of DBS have a different history, and are not supported by a wealth of experience of neurobiological understanding. Unlike movement disorders, psychiatric illness does not appear to result from a focal neuroanatomical or biophysiological deficit, such as the degeneration of nigral dopamine-containing cells in PD.

There are few animal models of psychiatric disease. Many of the cognitive and behavioral aspects of psychiatric disease cannot be studied in animals, and may be unique to humans. The brain substrate of psychiatric disorders, including depression and OCD, is not conceptualized as closely connected neuronal structures but instead comprises vast networks of cognitive, emotional, behavioral, and motoric brain circuitry. The best studied model is one that proposes five separate but entwined cortico-striato-thalamocortical loops that link the basal ganglia, limbic system, and frontal cortex.

Patient selection is not well defined in the application of DBS to psychiatric disease, and randomized long-term follow-up studies are lacking. Moreover, the surgical approach to psychiatric illness is freighted with substantial ethical concerns. As a result, in 2009, DBS treatment of psychiatric illness does not stand on the same firm ground of extended clinical practice, empirical observation, and scientific understanding that characterizes the treatment of tremor and PD.

Neurological Disorders

Parkinson's Disease

DBS of the STN, GPi, and VIM thalamus are used for treating the symptoms of PD. The effects of DBS at these

targets vary, and the outcome of surgery depends critically on patient selection and accurate electrode placement. STN and GPi DBS have the broadest antiparkinsonian effects, and are the targets of choice for patients with advanced disease complicated by wearing off motor fluctuations and dopaminergic dyskinesias.

The antiparkinsonian effect of STN and GPi DBS can generally be predicted by the response to individual doses of levodopa: if a patient experiences a temporary relief of rigidity, bradykinesia, or tremor from levodopa, DBS will yield a similar response. For patients with parkinsonism that does not respond, even temporarily, to individual doses of medication, DBS is unlikely to succeed. In randomized comparison, DBS at both sites produces comparable efficacy, and carries equivalent risk of complication. Both target sites are effective at reducing dyskinesias but GPi stimulation appears to suppress dyskinesias *directly*, whereas the reduction in dyskinesias following STN stimulation is attributed in most cases to reducing medication intake postoperatively.

VIM thalamic stimulation is reserved for the treatment of tremor-predominant PD and patients with medication-refractory tremor. A subset of individuals with PD experiences disabling tremors that do not respond to even suprathreshold doses of levodopa, but their tremors can sometimes be controlled by VIM DBS. The primary limitation of this target site is that it has few effects on bradykinesia or rigidity: for individuals with generalized parkinsonism, VIM stimulation will not be adequate to control all the motor symptoms of their disease.

Long-term studies of DBS are in progress. The largest series provide 5-year follow-up that document long-term reductions of tremor, bradykinesia, and rigidity, with concomitant long-term improvements in quality of life. However, PD is a progressive neurodegenerative disease, and many patients develop long-term complications of speech impairment, postural instability, gait freezing, truncal flexion, and dementia – symptoms that do not respond to DBS.

Since its introduction as a standard therapy for advance PD, a consensus has emerged regarding patient selection (see **Table 1**). Individuals most likely to benefit from DBS are those with a clinically definite diagnosis of idiopathic PD and a robust response to individual doses of levodopa. Ideal candidates for surgery are in good physical and psychological health, have no significant medical complications, do not experience frequent falls or dementia, and have a good social or family support network.

Table 1 Patient selection for DBS in Parkinson's disease

Good candidate for DBS	*Poor candidate for DBS*
Typical PD, with tremor	Atypical parkinsonism
Good response to individual doses of levodopa	Poor response to levodopa
Dyskinesias	Dementia or apathy
Wearing off motor fluctuations	Depression or anxiety
Good general health	Severe medical illness
Strong family and social support network	Poor social support

Individuals who are not suitable candidates for DBS surgery are those with atypical forms of parkinsonism, such as multiple system atrophy (MSA) or progressive supranuclear palsy (PSP), patients who do not respond to levodopa, and patients with dementia, frequent falling due to freezing or retropulsion, psychosis, depression, and a poor network of social or family support.

In the past decade, the literature of DBS treatment for PD has matured from a simple assessment of short-term efficacy and complication rates to deeper issues relating to patient selection, timing of surgery, and new targets. In many series, the best outcomes of DBS were observed in young patients. Nonetheless, there is no strict exclusion on the basis of age if the other features indicating a favorable prognosis are present. Patients over 70 years are more likely to experience early falling, cognitive decline, and medical illnesses, however, and the long-term results of DBS in the older cohort are not likely to last as long.

The potential risks and complications of DBS surgery fall into three categories: (1) intraoperative complications, (2) adverse effects due to electrical stimulation, and (3) hardware-related breakdown and malfunction. The most serious potential complications of DBS include intraoperative hemorrhage or stroke caused by brain mapping or electrode insertion. At major centers with substantial experience using DBS, the risk of these serious complications is estimated at less than 5% per electrode insertion. Additional serious complications include infections of the implanted apparatus, seizure, and postoperative confusion. Individuals with preexisting dementia are considered at risk for postoperative cognitive impairments, most often in the domains visuospatial processing, executive function, verbal fluency, and attention. Infections of the apparatus may begin at any part of the hardware, but most frequently result from skin erosion at the battery implant in the chest. Infection may require removing part of the hardware or explanation of the entire apparatus, in combination with antibiotic therapy.

Complications of stimulation tend to occur during programming, and are reversible. Temporary shocking or tingling sensations, muscular spasms or contractions, speech difficulties, balance problems, unusual cephalic sensations, dizziness, and visual disturbances can all occur during stimulation. Acute, reversible feelings of sadness and despair can be triggered by DBS, as can impulsivity and euphoria, depending on the location of the contacts and the device settings. Both STN and GPi stimulation can induce dyskinesias that are similar to dopaminergic dyskinesias. Finally,

some individuals treated with DBS have become chronically depressed and committed suicide in the months and years following surgery.

Potential problems with DBS hardware include unexpected deactivation, premature battery failure, and fracture of the extension lead, or disruption of its connections sites. In addition, the lifespan of the battery ranges between 3 and 5 years under normal usage, and must therefore be replaced periodically.

The primary limitations of DBS as a treatment for PD are (1) surgical risk, (2) its lack of effect on disease progression, and (3) its relatively restricted application to those individuals with the ideal set of clinical criteria. DBS does not slow or halt disease progression, and it is not effective for some of the most disabling aspects of the disorder, including dementia, postural instability, and gait freezing. Recognizing these limitations, clinical investigators are searching for additional brain targets to help medication-resistant symptoms and signs of PD, such as the zona incerta. Stimulation of one experimental target, the pedunculopontine nucleus (PPN), is currently being investigated for its effect on gait freezing.

Dystonia

Dystonia, a rare disorder of twisting postures, is classified into primary and secondary forms. The prototype primary dystonia is caused by a gene mutation in the *TorsinA* gene, and designated DYT1 dystonia. Primary dystonia is for the most part a nonsymptomatic disorder, although some individuals may manifest behavioral disturbances, such as anxiety or OCD. Affected individuals typically experience the onset of dystonia during childhood.

Secondary forms of dystonia are those disorders caused by a variety of inherited or acquired conditions, including hypoxia, trauma, vascular events, and metabolic and genetic disorders, such as Wilson's disease or pantothenate kinase deficiency (PKAN). Affected individuals with secondary dystonia often experience neurological impairments in multiple systems, manifesting as developmental delay, seizures, spasticity, neuropathy, parkinsonism, and ataxia. With the exception of dopa-responsive dystonia, most dystonic disorders tend to be resistant to medical therapy.

GPi DBS has been effective for primary dystonia, including DYT1 dystonia. The stimulation is required bilaterally, and has been successfully performed even in small children. Pallidal stimulation has also been used in several other dystonic syndromes, including tardive dystonia and various metabolic disorders, such as myoclonic dystonia. The reported short-term results of GPi stimulation in metabolic disorders, such as Lesch-Nyhan disease and PKAN, document symptomatic relief of dystonia, but the underlying neurodegenerative disease remains untreated and is progressive.

Essential Tremor

ET, one of the most common movement disorders, typically presents with action tremors of the hands. The disorder is progressive, often familial, and may result in generalized, disabling tremors that can affect all manual activities. ET can cause tremors of the face, voice, neck, legs, and trunk. Some patients with ET develop an associated rest tremor, and manifest a tremor-predominant form of PD. Other individuals develop a tremor disorder with features of cerebellar disease, including ataxia and dysarthria.

Thalamic DBS is effective for suppressing tremors in patients with even advanced ET. The procedure can be performed unilaterally or bilaterally. Potential adverse effects of VIM stimulation, especially when performed bilaterally, include dysarthria and ataxia.

Psychiatric Disorders

Depression

The neuronal substrate of depression is not clearly defined but involves several cortical, subcortical, and limbic networks. On the basis of functional neuroimaging studies indicating abnormal hyperactivity of the subgenual cingulate gyrus (Brodmann area 25, or Cg25) in sadness and depression, Mayberg proposed stimulation of this brain region as a treatment for severe depression. Her influential case report of bilateral cingulate DBS in six patients with medication-refractory and electroconvulsive therapy (ECT)-resistant depression demonstrated a dramatic and sustained mood improvement in four patients. Antidepressant effects in responders were associated with a marked reduction in local cerebral blood flow, as well as network effects in limbic and cortical sites, measured using positron emission tomography.

The effectiveness of Cg25 in a few individuals with depression supports the concept that activity in a widespread limbic-cortical circuit can be modified therapeutically by electrical stimulation delivered at a single point. The Mayberg report ignited widespread interest in treating depression using DBS, and large-scale clinical trials are underway.

Additional targets for treating depression include the ventral striatum/nucleus accumbens region, associated with reward mechanisms, and the inferior thalamic peduncle. As noted, the treatment of depression using DBS is fraught with ethical complexity, as the ability for a severely depressed individual to provide informed consent may be compromised by his emotional state. Moreover, the rare complication of suicide among individuals who undergo DBS is more likely to occur in severe, medication-resistant depression.

Obsessive–Compulsive Disorder

OCD is a common psychiatric disorder in which patients experience disabling, repetitive, purposeless urges and thoughts that interfere with scholastic, occupational, and social functioning. The disorder can be severely debilitating and refractory to all forms of conventional treatment, including therapy and medication. Like depression, the neurobiological substrate of OCD is considered to involve interconnected cortico-striato-thalamocortical loops that modulate neuronal activity between parts of the orbitofrontal and anterior cingulate cortices, as well the medial, dorsomedial, and anterior thalamic nuclei. Preliminary applications of DBS to OCD have targeted the anterior limb of the internal capsule, with limited benefits overall but some improvement in individual patients.

Tourette Syndrome

TS is a complex neuropsychiatric disorder characterized by the presence of chronic motor and vocal tics that begin in childhood or adolescence. Individuals may also manifest severe behavioral disturbances that include attentional deficits, hyperactivity, OCD, anxiety, impulsivity, disinhibition, aggression, personality disorder, and substance abuse. The treatment of TS must be aimed at the clinical issues causing the most disability and distress, which vary from patient to patient, and may fluctuate over time. One individual may experience severe, uncontrollable tics, while for a different patient, hyperactivity or obsessive–compulsive behaviors may be the most significant clinical features.

The application of DBS to TS is described in a small clinical literature, consisting mainly of case reports and small series that show reductions in tics and OCD symptoms. The brain targets for DBS in Tourette are not well-defined but for tic suppression, the most frequently stimulated brain targets are the internal segment of the globus pallidus (GPi) and the centromedian-parafascicular complex and ventral oral nuclei of the thalamus. No target has been compared to any other, and a global picture of the effects of DBS on all aspects of the disorder has not yet emerged. The application of DBS to TS requires a careful multidisciplinary approach that involves neurology and psychiatry. There is no clear concensus regarding patient selection but those with severe personality disorders or substance abuse addiction are not considered as suitable candidates.

Other Disorders

DBS is used in the treatment of a growing variety of other neurological, psychiatric, and medical disorders that do not overlap with the subspecialty of movement disorders. DBS has long been used to control pain syndromes, and the current stimulating electrode is an outgrowth of spinal stimulation technology for chronic back pain. DBS of the periaqueductal gray (PAG) region and somatosensory thalamus has improved intractable pain in patients suffering from neuropathic pain and painful dysesthesias, back pain, phantom limb pain, central pain syndromes, and intractable cluster headache.

Epilepsy has long been a focus of neurosurgical treatments and technology, including surgical removal of epileptogenic brain tissue, transcranial magnetic stimulation, and vagus nerve stimulation. In addition, direct stimulation of medial temporal lobe structures in temporal lobe epilepsy has been explored as a potential DBS application.

The neurobiology of obesity implicates brain appetite and satiety centers of the lateral hypothalamus and ventromedial hypothalamus, as well as the nucleus accumbens, all potential DBS targets for the treatment of morbid obesity. By exerting direct effects on the brain's reward centers, DBS may offer a theoretical advantage over bariatric surgery and other weight-reducing approaches that do not curb the desire to eat.

Conclusions

The successful application of DBS to neurological and psychiatric disease resulted from the convergence of innovation in several fields during the latter half of the twentieth century: medical engineering, neurosurgery, neuroradiology, and neurophysiology. Improvements in stereotactic surgical technique, reductions in surgical morbidity, advances in brain mapping and neuroimaging, and refinements in medical engineering lead have resulted in successful treatment for PD tremor, rigidity, bradykinesia, and dyskinesias, as well as ET and dystonia. In recent years, medication-resistant depression, OCD, TS, and other conditions have become the focus of DBS therapy. To date, DBS have proven effective at suppressing symptoms but it does not modify disease mechanisms, or prevent underlying progression. It seems likely that new applications and brain target sites will be discovered, even as the technology becomes more sophisticated, effective, and physiologically compatible with brain circuitry.

See also: Pallidotomy for Parkinson's Disease; Subthalamic Nucleus; Surgery for Movement Disorders, Overview, Including History; Thalamotomy.

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Dementia with Lewy Bodies

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Glossary

α-synuclein – A presynaptic protein that is abnormally distributed in axons and neuronal cell bodies in DLB and a major component of Lewy bodies.
Cholinesterase inhibitor – A drug which blocks the degradation of acetylcholine to increase cholinergic neurotransmission in the brain. Donepezil and galantamine inhibit acetylcholinesterase while rivastigmine additionally inhibits butyrylcholinesterase. Galantamine is additionally an allosteric modulator of nicotinic receptors.
Lewy body (LB) – An eosinophilic intracytoplasmic inclusion body, characteristic of Parkinson's disease and dementia with LBs.
Lewy body dementia – A 'catch all' term encompassing dementia associated with Parkinson's disease and dementia with Lewy bodies.
Neuroleptic sensitivity – A potentially life-threatening adverse reaction to antipsychotic drugs described in dementia with Lewy bodies and characterized by sedation, immobility, rigidity, postural instability, falls, and increased confusion.

Definition and History

Dementia with Lewy bodies (DLB) is a primary neurodegenerative dementia, characterized by a variable combination of fluctuating cognition (FC), neuropsychiatric disturbance, and Parkinsonism. Autonomic dysfunction and sleep disorders may also be prominent features, with the former contributing to falls. Through a combination of dementia and, frequently, extrapyramidal features, DLB bridges the worlds of movement disorders, dementia, and geriatric psychiatry.

The first case reports of DLB appeared in 1961, when Okazaki published a report of two patients, aged 69 and 70 years, presenting with dementia who died shortly afterward with severe extrapyramidal rigidity. Autopsy showed Lewy body (LB) pathology in the cerebral cortex. With the advent of antiubiquitin immunocytochemical staining methods, the frequency and distribution of cortical LBs could be defined more easily, and the clinico-pathological boundaries of DLB began to emerge. More recently, α-synuclein antibodies have revealed even more extensive pathological changes in DLB and have demonstrated a neurobiological link with other synucleinopathies, Parkinson's disease (PD), and multiple system atrophy.

The nature of functional disability differs between Alzheimer's disease (AD) and DLB, with additional impairments in mobility and self-care in DLB being mainly attributable to extrapyramidal motor symptoms. Consideration of these is important in assessment and management. Furthermore, patients with DLB have a poorer quality of life and consume more resources than patients with AD, thereby, making the impact of this dementia syndrome even more striking. Exquisite, not infrequently fatal, sensitivity to neuroleptic drugs and encouraging trial results for cholinesterase inhibitor drugs highlight the importance of an accurate diagnosis of DLB.

Pathogenesis/Pathophysiology

Etiology and Pathophysiology

The etiology of DLB is unknown. Triplication of the α-synuclein gene can lead to a DLB-like phenotype in some families, presumably through a dose-effect, but this mechanism is not a common cause of DLB. A higher

frequency of mutations in the *GBA* gene, which encodes glucocerebrosidase, has been found in several case-control series of DLB and PD. Such mutations may represent a risk factor for LB disorders, although the relatively small sample sizes for DLB cases to date have yielded widely differing mutation frequencies (3.5–23%). The ε4 allele frequency is elevated in DLB, similar to that found in AD, and the presence of this allele is associated with a more rapid progression of cognitive impairment. There are subtle differences in the ApoE4 allele frequencies between AD and DLB, with a higher ε2 allele frequency and a reduced frequency of the ε4/4 genotype in DLB. Differences in the ApoE4 frequencies may account for some of the differences between the two diseases in terms of clinical presentation and pathology, but it is unlikely that one single genetic determinant accounts for the differences between DLB and AD.

The presynaptic protein α-synuclein is a major component of cortical and subcortical LBs and neurites. α-synuclein antibodies label greater numbers of cortical and hippocampal CA2/3 LNs and intraneuronal inclusions than ubiquitin, including fine granular and diffuse deposits and LBs, indicating that the accumulation of α-synuclein precedes its ubiquitination. The presence of other neuronal proteins within LBs may provide further clues to their formation. Cytoskeletal proteins, such as neurofilaments and microtubules may become trapped within the α-synuclein fibrillary aggregates. The presence of ubiquitin, a cofactor in the ubiquitin–proteasome system of intracellular proteolysis, and catalytic enzymes may constitute part of a cell stress response to eliminate abnormal and damaged proteins from cells. Chaperone proteins, such as parkin (a ubiquitin-protein ligase), torsin A, and heat shock proteins (e.g., HSP70), known to participate in refolding misfolded proteins and/or directing proteins toward degradation have been also localized in brain stem and cortical LBs and neurites. These findings, together with the evidence that the ubiquitin–proteasome pathway is impaired, could indicate that altered protein handling leads to accumulation of damaged α-synuclein within LBs and to neuronal degeneration. Lysosomal-mediated autophagy may provide a 'back-up' mechanism for the overloaded ubiquitin–proteosomal system. Induction of autophagy may represent a potential therapeutic target to assist with clearance of the abnormal protein load.

Pathology

High LB loads and cortical senile plaque counts are found in the majority of patients with DLB. There is no evidence of significant neocortical tau pathology, paired helical filaments, or neurofibrillary tangles in 80–90% of DLB cases. Whether DLB is considered to be a variant of AD depends upon the pathological definition of AD applied. When using the 1996 DLB criteria (which required only the presence of LB for the pathologic diagnosis) and the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria for AD (a definition of AD that is heavily dependent upon plaque density), 77% of cases would fulfill both pathological diagnoses. By contrast, 80–90% of cases would *fail* to fulfill definitions of AD reliant upon numbers of neocortical neurofibrillary tangles. These findings, together with clinical studies showing higher clinical diagnostic accuracy for DLB patients with low-burden AD pathology, have led to a revision of neuropathological criteria for diagnosing DLB. This combines the National Institute on Aging (NIA)/Reagan criteria and the modified Consensus DLB guidelines, based on semiquantitative assessment of α-synuclein pathology. The revised criteria acknowledge that a pathological diagnosis of both diseases should be made on a probabilistic basis, taking into account the extent and the contribution of the different pathological findings (**Table 1**). A diagnosis of DLB therefore becomes less likely as AD-related pathology, staged by NIA/Reagan criteria, increases.

Clinicopathological Correlations

The severity of cognitive impairment in DLB is positively correlated with the density of cortical LBs in frontal and temporal lobes and with the density of LNs in the hippocampal CA2 field, though not with LB density in anterior cingulate cortex. Profound neuronal loss and extensive LB/α-synuclein pathology in the nucleus basalis of Meynert is also likely to contribute to the dementia.

Table 1 Assessment of likelihood of LB and Alzheimer pathologies to be associated with DLB clinical syndrome

	Alzheimer type pathology		
Lewy body pathology	*NIA/Reagan low (BST 0–II)*	*NIA/Reagan intermediate (BST III–IV)*	*NIA/Reagan high (BST V–VI)*
Brain stem predominant	Low	Low	Low
Limbic (transitional)	High	Intermediate	Low
Diffuse neocortical	High	High	Intermediate

Modified from McKeith I, Dickson D, Lowe J et al. (2005) Diagnosis and management of dementia with Lewy bodies. Third report of the DLB Consortium. *Neurology* 65: 1863–1872.
DLB, dementia with Lewy bodies; BST, Braak stage; NIA, National Institute on Aging.

FC shows no correlation with LB density in either neocortical, paralimbic, or nigral areas. In patients with DLB and well-formed visual hallucinations, high LB densities are found in the amygdala and parahippocampus, with early hallucinations relating to higher densities in parahippocampal and inferior temporal cortices. Depression, frequently reported in DLB, appears not to be associated with cortical and subcortical LBs. DLB cases with parkinsonism have neuronal loss in the ventrolateral tier of the substantia nigra similar in severity to that seen in PD, in contrast to only mild or moderate neuronal loss in DLB cases without parkinsonism.

Epidemiology

Between 15% and 20% of all cases of the elderly with dementia reaching autopsy have DLB, making it the second most common cause of degenerative dementia after AD. Prevalence estimates for DLB, depending on case criteria, range from 0% to 5% with regard to the general population, and from 0% to 30.5% of all dementia cases. DLB incidence has been estimated at 0.1% a year for the general population and 3.2% a year for all new dementia cases.

Clinical Features and Diagnostic Criteria

Cognitive Impairment

The characteristic syndrome of DLB may be summarized as a 'dysexecutive–visuoperceptual' dementia. There is, however, heterogeneity of cognitive deficits within the LB dementia spectrum, with 56% and 55% of patients with Parkinson's disease dementia (PDD) and DLB, respectively, having a so-called 'subcortical' cognitive profile compared with only 33% of patients with AD. Conversely, 30% of patients with PDD and 26% of those with DLB are classified as having a 'cortical' profile, according to the Dementia Rating Scale. DLB is characterized by increased variability in performance on cognitive tasks, within and between patients and when compared to age-matched controls and patients with AD. This variability is particularly evident in executive and attentional tasks.

Simple global measures of performance (e.g., the mini-mental state examination, MMSE) are usually equivalent to those of patients with AD of comparable severity, perhaps reflecting the insensitivity of these measures to attentional impairments. Patients with DLB tend to perform better than patients with AD on verbal memory and orientation tasks. Performance on visual tasks, particularly recognition tasks, is consistently more impaired than in AD. These differences are more pronounced in the earlier disease stages.

Rate of progression, as evidenced by change in global cognitive measures such as the MMSE or Cambridge Cognitive Examination (CAMCOG), is equivalent to or faster to that seen in AD and vascular dementia, with a decline of 4–5 MMSE points per year.

Fluctuating Cognition

Fluctuating cognition (FC) occurs in 80% or more of people suffering from DLB, 30–60% of individuals with vascular dementia, and 20% of people with AD. It may present in several ways, depending upon the severity and diurnal pattern. Carers of patients with DLB describe spontaneous, periodic, and transient episodes of fluctuation, affecting functional abilities quite different from the more prolonged, situation-dependent variability seen in AD. In PDD, attention is the single strongest cognitive predictor of activity of daily living status, matching the strength of the effects of motor functions. Evaluation of FC requires careful questioning of patients and carers. Several clinical scales have been validated to quantify FC in DLB such as The Clinician Assessment of Fluctuation Scale and The Mayo Fluctuations Composite Scale. In the latter instrument, informant endorsement of three of four questions (Does the patient experience excessive daytime sleepiness? Do they sleep more than 2 h during the day? Do their words occasionally come out jumbled? Are there times when they stare into space for long periods?) has a positive predictive value of 83% for a diagnosis of DLB versus AD. FC may also be an important determinant of poor prognosis, according to a retrospective analysis of 243 autopsy-confirmed cases of DLB and PDD.

Psychiatric Symptoms

At least 80% of patients with DLB experience neuropsychiatric symptoms, such as visual hallucinations, auditory hallucinations, delusions, delusional misidentification, and depression. Visual hallucinations are the most common symptom, with a mean frequency of 50% (range, 13–80%) in prospective studies, compared with 20–30% of AD patients with AD. The person with DLB typically sees adults, children, or animals of normal size, sometimes with accompanying auditory hallucinations, which are far less frequent in AD. Tactile hallucinations are uncommon, but do occasionally occur. Delusions have a frequency of 55–70% in DLB with common themes being paranoid ideation, such as spousal infidelity, and 'phantom boarder' (believing strangers are living in the house). Major depression occurs in 19% of DLB cases at presentation, with nearly 50% of patients experiencing depressive symptoms at some stage of their illness.

Extrapyramidal Features

Parkinsonian features at presentation in DLB have been reported in 10–78% of cases, while 40–100% of patients display extrapyramidal signs at some stage of their illness. Differences are most likely to represent ascertainment bias and the variable definition of clinical phenomenology. Significant parkinsonism is more frequent in DLB than in AD or vascular dementia. A postural instability–gait difficulty (PIGD) motor phenotype is overrepresented in DLB (and dementia associated with PD) compared with PD patients with no dementia. In one cross-sectional study, 69% of 26 patients with DLB were classified as PIGD phenotype, compared with only 30% of 38 patients with PD. The involvement of brainstem cholinergic nuclei, notably the pedunculopontine nucleus, may be responsible for the expression of this phenotype. Reduced rest tremor, greater symmetry of signs, myoclonic jerks, and a reduced response to levodopa have all been reported in DLB, although these features have not been universally confirmed.

Sleep Disorders

Rapid-eye-movement (REM) behavior disorder (RBD), characterized by loss of normal skeletal muscle atonia during REM sleep with resultant motor activity and 'acting out of dreams,' affects up to 80% of patients with DLB. This is similar to other synucleinopathies such as PD or multiple system atrophy, but contrasts with AD, where RBD is relatively uncommon. Intriguingly, RBD may precede the onset of other features of DLB by several years (mean of 11, range 5–23 years in one series), suggesting pathological involvement of sites remote from those mediating cognitive and motor impairments. Interviewing the bed-partner using the Mayo Sleep Questionnaire has high sensitivity (92%) and specificity (100%) for the diagnosis of RBD, although video polysomnography remains the 'gold standard' diagnostic test.

Autonomic Features

Autonomic dysfunction with cardiovascular instability or orthostatic hypotension may occur in DLB and may contribute to recurrent falls. Over one-third of patients with DLB suffer more than 20 falls per year. The abnormal cardiovascular autonomic function, which may predate the onset of parkinsonism and dementia by several years, or develop with other clinical features. Orthostatic hypotension and carotid sinus hypersensitivity are common in DLB and associated with burden of hyperintense lesions on magnetic resonance imaging (MRI) brain scanning. Patients with DLB have impaired sympathetic and parasympathetic function on autonomic testing, and also reduced cardiac uptake of ^{123}I-*meta*-iodobenzylguanidine (^{123}I-MIBG), a marker of postganglionic myocardial sympathetic innervation (see below).

Urological symptoms and urodynamic abnormalities are common in DLB and result not only from dementia and immobility but also from central and peripheral somato-autonomic dysfunction. Urgency and urge incontinence are more frequent in DLB cases compared with AD, with up to 90% of DLB patients affected. This may relate to greater subcortical pathology in DLB, leading to disinhibition of pontine micturition centers. Other autonomic symptoms include constipation, erectile dysfunction, and dysphagia.

Consensus Criteria for DLB

Consensus clinical diagnostic criteria were first published in 1996 and subsequently updated in 1999 and, most recently, in 2005 (**Table 2**). The central feature of DLB is a dementia syndrome typically characterized by prominent attentional, executive, and visuospatial deficits. A diagnosis of 'probable DLB' requires the presence of two or more of three core clinical features (fluctuating attention and alertness, recurrent visual hallucinations, Parkinsonism), together with the variable presence of suggestive or supportive features. RBD, severe neuroleptic sensitivity and abnormal dopamine (DA) uptake on single photon emission computed tomography (SPECT) or positron emission tomography (PET) imaging comprise 'suggestive features.' They have similar diagnostic weighting to core features but require further validation before being considered sufficient for a diagnosis of probable DLB in the absence of core features. Features considered as supportive of a diagnosis of DLB (listed in **Table 2**) lack specificity because they may also occur in a variety of other disorders.

Differential Diagnosis

Possible differential diagnoses for DLB include AD, vascular dementia, delirium secondary to systemic or pharmacological toxicity, prion disease, or other neurodegenerative syndromes (e.g., progressive supranuclear palsy and progranulin mutations). The most common diagnostic difficulty encountered is in discriminating DLB from AD. Consensus guidelines for the clinical diagnosis of DLB have been shown to have prospective diagnostic accuracy at least as good as those for AD. It is recommended that they are applied as early in the disease course as possible, when their discriminatory ability may be greatest. The inability of moderately cognitively impaired patients with DLB to copy pentagons accurately has been reported to have a sensitivity of 88% and a specificity of 59% compared with AD, suggesting this may be a useful and simple clinic-based screening test. Extrapyramidal signs are highly suggestive, because parkinsonism is uncommon in early AD or vascular

Table 2 Revised criteria for the clinical diagnosis of DLB

1. *Central feature (essential for a diagnosis of possible or probable DLB)*
   Dementia defined as progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention, executive function, and visuospatial ability may be especially prominent
2. *Core features (two core features are sufficient for a diagnosis of probable DLB, one for possible DLB)*
   FC with pronounced variations in attention and alertness
   Recurrent visual hallucinations that are typically well formed and detailed
   Spontaneous features of parkinsonism
3. *Suggestive features (if one or more of these is present in the presence of one or more core features, a diagnosis of probable DLB can be made. In the absence of any core features, one or more suggestive features is sufficient for possible DLB. Probable DLB should not be diagnosed on the basis of suggestive features alone)*
   REM sleep behavior disorder
   Severe neuroleptic sensitivity
   Low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET. imaging
4. *Supportive features (commonly present but not proven to have diagnostic specificity)*
   Repeated falls and syncope
   Transient, unexplained loss of consciousness
   Severe autonomic dysfunction, e.g., orthostatic hypotension, urinary incontinence
   Hallucinations in other modalities
   Systematized delusions
   Depression
   Relative preservation of medial temporal lobe structures on CT/MRI scan
   Generalized low uptake on SPECT/PET perfusion scan with reduced occipital activity
   Abnormal (low uptake) MIBG myocardial scintigraphy
   Prominent slow wave activity on EEG with temporal lobe transient sharp waves
5. *A diagnosis of DLB is less likely*
   In the presence of cerebrovascular disease evident as focal neurologic signs or on brain imaging
   In the presence of any other physical illness or brain disorder sufficient to account in part or in total for the clinical picture
   If parkinsonism only appears for the first time at a stage of severe dementia
6. *Temporal sequence of symptoms*
   DLB should be diagnosed when dementia occurs before or concurrently with parkinsonism (if it is present). The term Parkinson's disease dementia (PDD) should be used to describe dementia that occurs in the context of well-established Parkinsonian disease. In a practice setting the term that is most appropriate to the clinical situation should be used and generic terms such as LB disease are often helpful. In research studies in which distinction needs to be made between DLB and PDD, the existing 1-year rule between the onset of dementia and parkinsonism DLB continues to be recommended. Adoption of other time periods will simply confound data pooling or comparison between studies. In other research settings that may include clinicopathologic studies and clinical trials, both clinical phenotypes may be considered collectively under categories such as LB disease or α-synucleinopathy

Modified from McKeith I, Dickson D, Lowe J et al. (2005) Diagnosis and management of dementia with Lewy bodies. Third report of the DLB Consortium. *Neurology* 65: 1863–1872.

dementia, while the presence of visual hallucinations and visuospatial/constructional dysfunction may also have good predictive value for the diagnosis of DLB. Care must be taken in attempting to interpret motor signs in the demented patient, however. To the inexperienced clinician, paratonic rigidity ('Gegenhalten') may be mistaken for lead-pipe or cog-wheel rigidity, while ideomotor apraxia can be misinterpreted as bradykinesia. A short-stepped, hesitant 'glue gait' may occur in vascular dementia, although arm swing is usually relatively preserved (in contrast with the LB dementias).

The DLB Consortium recommended that if a patient has had motor symptoms of PD for more than 1 year prior to the diagnosis of dementia, then a diagnosis of PDD is most appropriate. If mental symptoms occur within 12 months of onset of motor disability, then a primary diagnosis of DLB is more appropriate. This approach is also consistent with recent guidelines for the clinical diagnosis of PDD. It should be remembered, however, that attempts to draw absolute boundaries between DLB and PDD, such as the 12-month rule, are only arbitrary conventions designed to help in clinical practice and research. These dementias share similar underlying neurodegenerative pathologies, including abnormal α-synuclein deposition and formation of Lewy neurites/bodies. PDD and DLB are therefore likely to represent a spectrum of LB syndromes. In some situations, for example, pathological studies and clinical trials, it may be more appropriate to consider both PDD and DLB under a common term such as 'LB dementias.'

Diagnostic Investigations

Clinical examination and investigations should establish the presence of cognitive, psychiatric, and neurological signs

and exclude hematological, biochemical, or pharmacological causes. The EEG is usually abnormal in DLB, with a greater degree of background slowing compared with AD, but this is too nonspecific to be of use in an individual case. Transient slow wave (delta) activity can be seen in the temporal lobes of 50% of DLB cases (compared with 18% in AD) and is associated with FC. Other studies have shown no significant EEG differences between DLB and AD. EEG spectrum studies using Fourier analysis have suggested variable changes in power spectra and coherence, but these findings require further confirmation.

Analysis of cerebrospinal fluid (CSF) proteins (total tau, phosphorylated tau, amyloid) is currently confined to research studies and does not add to diagnostic accuracy in the individual patient. Levels of β-amyloid 1–40 or 1–42 do not distinguish DLB from AD, although recent studies suggest that other β-amyloid peptides (e.g., the ratio of beta 1–42 to beta 1–38) may have greater discriminatory value. An oxidized α-helical form of β-amyloid, thought to be formed as a result of interaction between β-amyloid peptides and α-synuclein, may be significantly increased in DLB. CSF neurofilament proteins and serpins do not differentiate DLB from AD.

Imaging

Structural neuroimaging

The use of computed tomography (CT) is normally restricted to the exclusion of other significant comorbidities such as chronic subdural hematoma or cerebrovascular disease.

On MRI of the brain, the main structural imaging change noted in DLB is relative preservation of the hippocampus and medial temporal lobe compared to the reduction seen in AD. This may at least partly account for the relative preservation of mnemonic function in DLB. Although hippocampal volume is reduced by only 15% compared to controls, and considerably less than the 40% reduction seen in AD, these differences are based upon group studies and, overall, have low diagnostic sensitivity (40%). Other MRI changes reported for DLB include atrophy of the putamen and basal forebrain, with relative preservation of cortical grey matter compared to patients with AD. No consistent pattern has emerged from studying the rate of volume loss over time using serial MRI. White matter lesions are increased in DLB, as in AD although the effects on cognitive function have not yet been determined. In summary, structural MRI can highlight group differences in DLB compared with AD, but these changes lack sufficient sensitivity to be diagnostically useful in an individual patient.

Functional neuroimaging

PET studies of glucose metabolism and SPECT investigations using blood flow markers such as Tc-HMPAO demonstrate many similarities to the patterns seen in AD, limiting the diagnostic value of these investigations. Biparietal hypoperfusion in DLB is more extensive than in patients with AD, matched for age and dementia severity, particularly in Brodmann area 7, an area that mediates important aspects of visuospatial function. Occipital hypometabolism on PET and hypoperfusion on PET and SPECT are strongly associated with DLB and localize to primary visual cortex as well as visual association areas (Brodmann areas 17–19). A sensitivity of 90% and specificity of 80% has been reported for occipital hypometabolism in separating DLB from AD, although only 11 DLB cases were examined in the study that led to this conclusion. In a larger SPECT study, occipital hypoperfusion had reasonable specificity (86%) in distinguishing DLB from AD and controls, although sensitivity was suboptimal at 64%.

Labeling of muscarinic acetylcholine receptors using ^{123}I-iodo-quinuclidinyl-benzilate (QNB) shows variably increased binding in the LB dementias, but the diagnostic value of this finding is uncertain and the ligand is not currently widely available.

A key neurochemical finding in DLB is the loss of dopamine transporter (DAT) in the caudate and putamen, reflecting the loss of nigrostriatal dopaminergic afferent projections. Several SPECT and PET ligands are now available to permit in vivo imaging of the DAT density. Changes may be quantified by visual inspection, semi-quantitative or automated quantitative techniques. A large, multicenter phase III trial of (123)I-2β-carbomethoxy-3β-(4-iodophenyl)-*N*-(3-fluoropropyl)nortropane (FP-CIT) SPECT compared DLB and non-DLB dementia (predominantly AD). Abnormal scans had a sensitivity of 77.7% for detecting clinically probable DLB, with a specificity of 90.4% for excluding non-DLB dementia and an overall diagnostic accuracy of 85.7%. Because of the robust nature of this and several other smaller studies, abnormal DAT activity in the basal ganglia on FP-CIT SPECT scanning has now been incorporated into the Consensus Criteria for DLB as a suggestive feature.

FP-CIT SPECT binding may be more evenly reduced across the striatum in DLB, compared with PD, due to greater loss in the caudate head, while there is also a relative lack of asymmetry in DLB cases. Reduced DA D_2 receptor density in basal ganglia using ^{123}I-iodobenzamide has been reported in DLB but use of this ligand cannot be recommended for diagnostic purposes.

^{11}C Pittsburgh Compound B (PIB) PET has recently been used to study in vivo β-amyloid burden in DLB and other degenerative dementias. In general, cortical PIB binding appears to be markedly elevated in AD, regardless of disease severity. In DLB, PIB binding may be generally lower than in AD and more variable. Areas of significant tracer increase in DLB have been reported to be cortical

association areas, cingulate, and striatum. Interestingly, cortical PIB binding in PDD may not be increased compared with normal age-matched controls.

Cardiac imaging

As described above, autonomic dysfunction is common in DLB. Cardiac scintigraphy, using ^{123}I-MIBG, permits some quantification of postganglionic sympathetic innervation. The use of ^{123}I-MIBG scintigraphy has demonstrated in three studies that a reduction in cardiac uptake has high sensitivity and specificity for a diagnosis of DLB compared to AD, although larger multicentre studies are required to confirm the utility of this finding. Furthermore, several common, comorbid problems encountered in the elderly patient may confound interpretation of ^{123}I-MIBG scans include diabetes and ischemic heart disease.

Management

General Considerations

Establishing an accurate and timely diagnosis is fundamental to planning management and treatment interventions in DLB. Identifying and evaluating the significance of key symptoms is a useful approach to take, while a problem list of cognitive, psychiatric, and motor disabilities should be established, in addition to the usual assessments of function, risk, and carer burden.

The importance of educating patients and carers about the nature of the symptoms of DLB cannot be overemphasised. A range of 'nonpharmacological' strategies may be effective, several of which may be delivered by the carer after appropriate training. Strategies for cognitive symptoms include orientation and memory prompts and attentional cues. For psychiatric symptoms, options include explanation, education, reassurance, and targeted behavioral interventions. Motor impairments may benefit from physiotherapy and mobility aids, although there is currently no solid evidence base for these suggestions. Patient and carer support associations may also provide important resources and written material.

Symptomatic Drug Treatments

There are no disease-modifying pharmacological therapies yet available for DLB and only symptomatic treatments are currently available. There is often a therapeutic 'tension' as the treatment of one symptom may potentially exacerbate another, underlining the need to prioritize problems, and only to treat with drugs if absolutely required. For example, patients treated with antipsychotic medication, especially those with high D_2 receptor antagonism, frequently experience an exacerbation of parkinsonian symptoms. More significantly, ~50% of DLB patients who receive neuroleptics experience life-threatening adverse effects, termed neuroleptic sensitivity and characterized by sedation, immobility, rigidity, postural instability, falls, and increased confusion. Deterioration can be rapid, and patients are unable to maintain adequate fluid and food intake. The reaction is associated with a poor outcome and a two- to threefold increase in mortality.

Because of the risk of neuroleptic sensitivity, the use of antipsychotic agents in the DLB patient should not simply be a 'knee-jerk' response. Factors exacerbating psychosis, such as intercurrent infection, should be identified and excluded. The use of anticholinergics to manage urinary symptoms should be avoided if at all possible. If relevant, gradual dose reduction or even withdrawal of antiparkinsonian drugs should be considered, at least on a trial basis. If there is still no improvement, or severity of symptoms necessitates more urgent action, then a cautious trial of an antipsychotic agent may be considered. Even the newer 'atypical' antipsychotics may be associated with neuroleptic sensitivity, especially as the dose is increased. Until more robust clinical trial data are available specific recommendations are limited, but overall, atypical antipsychotics are probably safer than traditional agents in DLB. Low dosing may be more important than the use of any specific drug. Although trial data are lacking, cholinesterase inhibitors may actually prove to have greater antipsychotic potential in DLB than many existing atypical antipsychotic agents. Other novel antipsychotic drugs, which operate via alternative neurochemical systems, such as pimavanserin (ACP-103), are currently being evaluated in the LB dementias.

Functional impairment in DLB is related to the severity of Parkinsonism. 3,4-Dihydroxyphenylalanine (L-dopa) is generally well tolerated in DLB patients and can produce worthwhile benefit, although motor responsiveness is generally less than that observed in PD. Younger DLB cases may be more likely to respond to dopaminergic treatment. The use of L-dopa was not associated with adverse cognitive or neuropsychiatric effects after 3 months of treatment in one study.

Clonazepam may be effective in suppressing the motor features of RBD but does not restore REM-sleep atonia. The drug may be associated with excessive daytime drowsiness, so the lowest possible dose should be used (0.25 mg nocte initially) if treatment of RBD proves to be necessary. Melatonin may also be beneficial in patients who fail to respond to clonazepam or who are unable to tolerate therapeutic doses. Further work is needed to investigate the role of cholinesterase inhibitors as a treatment approach for RBD.

Cholinesterase inhibitors

Open label studies of cholinesterase inhibitors (ChEIs) in DLB patients have shown improvements in both cognitive and noncognitive symptoms with donepezil, rivastigmine,

and galantamine without significant deterioration in motor function. Moreover, treatment efficacy has been demonstrated for up to 96 weeks. Apathy, anxiety, impaired attention, hallucinations, delusions, sleep disturbance, and cognitive test performance are the most frequently cited treatment–responsive symptoms in DLB patients treated with ChEIs. A retrospective comparative analysis of donepezil, rivastigmine, and galantamine suggested that there was no compelling evidence to recommend one ChEI over another. Open label studies have also helped guide clinical practice to date, in the absence of more rigorous data. Thus, in patients with advanced DLB, a further increase from 10 to 15 mg of donepezil daily, while carefully monitoring for adverse events, may be a strategy to treat recurrent neuropsychiatric symptoms. If ChEIs are to be discontinued in DLB, this should be done gradually (over several weeks). The use of ChEIs does not significantly influence the ability of 123I-FP-CIT SPECT to distinguish DLB from AD, despite the fact that there have been reports of these drugs reducing radioligand binding to the DAT receptor in animal studies.

A multicenter, randomized placebo-controlled trial of rivastigmine included 120 patients with a clinical diagnosis of probable DLB and MMSE score of greater than 10. Participants received up to 12 mg day^{-1} of rivastigmine or placebo for 20 weeks. A four-item subscore of the neuropsychiatric inventory (NPI-4, the sum of scores for delusions, hallucinations, apathy and depression) was used as the primary efficacy measure. Approximately twice as many patients taking rivastigmine (63.4%) than placebo (30.0%) showed at least a 30% improvement from baseline on their NPI-4 scores (p=0.001), with psychotic features resolving almost completely in over half of the treated patients. These symptoms rapidly reemerged during a 3-week wash-out period. Nonsignificant improvements were also seen at 20 weeks in MMSE score and clinical global change-plus rating, in favor of the rivastigmine-treated group. Parkinsonian signs did not worsen on treatment, although an emergent tremor was noted in four rivastigmine-treated patients. Predominant adverse effects were cholinergic in nature and the frequency of nausea (37%), vomiting (25%), anorexia (19%), and somnolence (9%) was significantly higher in the rivastigmine-treated patients. Most adverse events were rated as either mild or moderate, however, and only 7 of 59 patients receiving the ChEI withdrew for this reason (not significantly different from the placebo-group).

The presence of visual hallucinations in DLB may predict a good treatment response to rivastigmine, as evidenced by improved attention measures on computerized assessment system. Similar results were obtained from a later double-blind study of rivastigmine in PDD. Donepezil also improves power of attention, continuity of attention and reaction time variability (a measure of FC) in the LB dementias. Approximately 25% of DLB patients will have treatment-resistant visual hallucinations. The presence of delusions may predict this resistance, according to one small observational study.

Neurochemical postmortem studies have shown that DLB cases with visual hallucinations have lower levels of cortical choline acetyltransferase, particularly in temporoparietal regions, compared with DLB patients without visual hallucinations. This may allow greater clinical improvements to occur, with cholinergic replacement therapy having a more marked effect upon a lower neurochemical baseline. Interestingly, cognitive reaction time (calculated by subtracting simple from choice reaction times), does not seem to be improved by rivastigmine. Such variability in the responsiveness of different cognitive parameters to ChEIs may give an insight into their neurochemical basis. Thus, it may be postulated that failure to improve choice reaction time by cholinomimetic therapy is because this is also dopaminergically mediated, perhaps via loss of mesocortical dopaminergic projections.

Finally, there is some evidence that the use of ChEI drugs antemortem may be associated with less cortical β-amyloid deposition. The clinical relevance of this finding is unknown, although a variety of biologically plausible mechanisms may be invoked to account for this observation. The data are certainly not robust enough at present to classify ChEIs as 'disease modifying' however.

Memantine

Open label studies for the noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist memantine have given conflicting results for DLB, with some reporting benefit and others significant worsening that was reversed upon discontinuation of the drug. A randomized-controlled trial of memantine in PDD and DLB has recently completed recruitment and the results of this study will hopefully resolve whether this drug has a place in the management of DLB.

Prognosis

Cognitive test scores seem to decline by a mean of 10% per annum, a rate similar to that of AD. Extrapyramidal features worsen by 10% per year, although the decline is probably more rapid in the earliest disease stages. Neuropsychiatric features, particularly hallucinations, tend to be present from the onset and to persist throughout the disease course.

A prospective study comprising 315 participants confirmed that while DLB increased the risk of mortality compared with AD (hazard ratio 1.88, 95% confidence limits 1.4–2.5), there was no difference in the rate of cognitive decline. This suggests that 'noncognitive' factors play a significant role in determining death in DLB.

Survival time after dementia diagnosis was 7.3 years for DLB versus 8.5 years for AD. Men with DLB had a shorter survival time than women in this study. DLB cases overall had a similar risk of institutionalization and survival in long-term care facilities compared with AD.

A retrospective analysis of 243 autopsy-confirmed cases of DLB and PDD revealed a median survival of 5 years from symptom onset. Male gender was again associated with shortened survival in this analysis. Additionally, older age at onset, FC, and visual hallucinations at onset predicted shorter survival. Associated Alzheimer pathology also shortened survival. These features are presumably the selected out DLB cases from the pooled LB dementia group.

See also: Cholinesterase Inhibitors in Parkinson's Disease; Dementia, Movement Disorders; Hallucinations and Movement Disorders; PARK1, Alpha Synuclein; Psychosis in Parkinsonism; REM-behavior Disorder.

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Dementia, Movement Disorders

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Glossary

Atypical parkinsonism – Parkinsonian disorders that share features of Parkinson's disease (e.g., bradykinesia, rigidity, gait/postural impairment) but exhibit other atypical features such as rapid progression, poor response to dopaminergic therapy, early falls, oculomotor abnormalities, early autonomic failure, pyramidal and cerebellar signs, hallucinations, early cognitive impairment, and apraxia; examples include progressive supranuclear palsy, corticobasal degeneration, and multiple system atrophy.

Cortical dementia – Dementia syndromes characterized by greater deficits in memory,

language, and higher cortical functions; examples include Alzheimer's disease, Pick's disease.
Executive function – A descriptive term comprising a broad range of cognitive processes, including planning, initiating, and monitoring behavior. Executive functions include working memory, abstract reasoning, problem solving, and mental flexibility.
REM behavior disorder – A sleep disorder or more specifically, a parasomnia, manifested by enactment of dream behavior and maintenance of muscle tone during REM sleep; may be an early manifestation of neurodegenerative disease.
Subcortical dementia – Dementia syndromes characterized by greater deficits in executive function, attention, and processing speed; related to disruption of frontal–striatal circuitry; examples include Parkinson's disease, Huntington's disease, and progressive supranuclear palsy.
Synucleinopathy – A neurodegenerative disorder with accumulation of α-synuclein in the brain; examples include Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy.
Tauopathy – A neurodegenerative disorder with tau-positive inclusions on neuropathology; often present with dementia and/or parkinsonism; examples include progressive supranuclear palsy, corticobasal degeneration, frontotemporal dementias.
TDP-43 – Or transactive response (TAR)-DNA binding protein 43 – a protein normally expressed in the nucleus; functions as a transcriptional repressor and splicing regulator.
Wisconsin Card Sorting Test – A neuropsychological test of executive functions (i.e., conceptualization, set shifting, and set maintenance); requires subjects to sort cards according to one criterion (color, form, number) that they must figure out based on the examiner's feedback on whether their response is correct or not. After 10 consecutive correct responses, the examiner shifts the rule without telling the subject and the subject must deduce the new rule.

Introduction

Dementia, generally defined as the presence of cognitive impairment in more than one cognitive area that reflects a significant change from previous level of function and significantly interferes with social, occupational, or other daily functioning, can occur as a main feature of several movement disorders. It may precede the onset of motor features in some movement disorders or occur primarily with advanced disease in others. Dementia may be the core feature in some movement disorders, but in others, may be secondary to greater motor dysfunction. Clinically, the cognitive deficits in movement disorders often manifest themselves as impaired executive function, attention, working memory, and processing speed, thereby suggesting frontal–subcortical involvement or a subcortical dementia. However, in other movement disorders, greater episodic memory and cortical deficits can be seen. In this article, movement disorders associated with dementia or cognitive impairment will be reviewed and grouped by the movement disorder phenomenology. Since many of these movement disorders are discussed in greater detail in other articles, this article will focus specifically on the dementia or cognitive features of only selected movement disorders, their related clinical features, pathogenesis, and treatments.

Dementia, Parkinsonism

Parkinson's Disease (PD)

History

In his *Essay on the Shaking Palsy* (1817), James Parkinson wrote that 'the senses and intellects were uninjured.' Of course, since his case series consisted of six patients of whom only three were examined personally, it is not surprising that he concluded that cognition was spared. About 50 years later, observations by the French neurologists Trousseau and Charcot revealed that cognition indeed was affected. Nonmotor features such as cognitive impairment and dementia are now widely recognized in PD as common and potentially disabling complications.

Clinical features

Cognitive dysfunction in PD encompasses a broad spectrum of clinical deficits and severity, affecting both nonmemory and memory domains and ranging from mild impairment to severe dementia. PD cognitive impairment and dementia (PDD) prototypically reflect a subcortical syndrome with greater executive dysfunction, attention and visuospatial deficits, and fewer abnormalities in memory and other cortical domains. The cognitive profile of mild to moderate PDD is generally marked by these features, although there is greater heterogeneity and cortical profiles in some. Memory, particularly declarative memory, is less impaired, and typically aphasia, apraxia, or agnosia are lacking. Recent diagnostic criteria for PDD reflect the greater emphasis on nonmemory cognitive domains and on behavioral features (e.g., apathy, mood disturbances, hallucinations, delusions, and excessive daytime sleepiness) that frequently accompany PD.

Many studies demonstrate that PDD differs from Alzheimer's disease (AD). For example, compared with AD

patients, PDD patients perform worse on measures of executive function, attention, and visuospatial function. However, the PDD patients typically perform better on verbal memory tests and have a better performance on recognition or cued components of verbal tests than on free recall. Greater hallucinations, fluctuations, REM behavior disorder, excessive daytime sleepiness, and depression have been reported in PDD compared with AD. Some PDD patients, however, may exhibit significant memory impairment, global deficits, and a severe dementia more similar to AD; cortical cognitive profiles or global impairment was identified in about 30% of their PDD patients by Janvin et al. In terms of cognitive phenotype, PDD may be more similar to dementia with Lewy Bodies (DLB) than to AD, although whether PDD and DLB represent distinct entities or a spectrum of Lewy body disorders is often debated.

Nondemented PD patients also exhibit cognitive dysfunction, as characterized by a milder phenotype of many cognitive deficits seen in PDD. Patient complaints typically include slowed processing, difficulty with multitasking or planning, decreased attention and concentration, and sometimes, word finding trouble. Nondemented PD patients may have difficulty in tasks that require cognitive sequencing, planning, or set maintenance or shifting to novel stimuli (i.e., executive functions). PD patients generally have more difficulty with internally generated cued behavior and benefit from external cues. Decreased information content of spontaneous speech, impaired comprehension of complex sentences, and impaired verbal fluency may occur and represent frontal lobe functions of concept formation, set shifting, attention, and working memory.

Many risk factors have been proposed for PDD but often with inconsistent results. In longitudinal studies, the most consistent risk factors for PDD have been older age, more severe parkinsonism (particularly postural instability and gait disturbance), and mild cognitive impairment at baseline. Other factors such as older age at disease onset, education, male gender, depression, and hallucinations have not been consistently found. Genetic features such as the APOE4 genotype also yield conflicting results in PDD.

Epidemiology

Prevalence estimates of PDD are about 40%, although epidemiologic studies vary in ascertainment methods, sample populations, and neuropsychological criteria used. Systematic review of PD prevalence studies by Aarsland et al. estimates that PDD accounts for 3–4% of dementia in the population, occurring in about 150–500/100 000 in those over age 65. Longitudinal studies demonstrate the cumulative prevalence of PDD. In a longitudinal, community-based study in Norway by Aarsland et al., PDD was present in 26% at baseline, 52% at 4 years, but in 78.2% at 8 years. Another longitudinal study of PD in Sydney by Hely et al. reported cognitive decline in 84% and dementia, as defined by impairment in short-term memory and two other cortical areas, sufficiently severe to affect occupational and social functioning, in 48% at 15-year follow-up. Subsequently, 20-year data from the Sydney study reported that 83% of the surviving patients were demented; once dementia was diagnosed, the median survival was 54 months. Community-based series reveal incidence rates of PDD ranging from 95.3 to 112.5 per 1000 person-years of observation with an increased relative risk (RR) of almost six times compared with normal, age-matched controls. PDD is associated with increased morbidity and mortality. More recently, studies have focused on the epidemiology of milder cognitive impairment in PD. In a community, population study identifying new cases of parkinsonism in the United Kingdom, Foltynie et al. found that 36% of their PD cases who had cognitive tests were cognitively impaired but not demented. Application of modified Petersen's criteria (1999) for mild cognitive impairment to PD cohorts have revealed about 20–50% with PD mild cognitive impairment.

Pathogenesis/pathophysiology

The neuropathology of PDD remains somewhat controversial but overall, PDD has three main pathological hallmarks that may act individually or collectively: brainstem degeneration, cortical and limbic Lewy bodies, and concomitant AD pathology.

In the six progressive stages of PD pathology described by Braak et al., stage 3 involves the presence of Lewy bodies and Lewy neurites in the substantia nigra, pedunculopontine nucleus, raphe nuclei, and basal forebrain nuclei, perhaps reflecting the earliest pathological correlates of PDD. Increased counts of Lewy bodies and Lewy neurites in the entorhinal, hippocampal, and amygdalar regions of the temporal mesocortex and in prefrontal and high-order sensory association neocortical areas occur in Braak's PD stages 4–6. Mini-mental State Examination (MMSE) scores correlate with these stages; in Braak's cohort of 88 PD patients, at stage 3, 75% had a MMSE score <25. Increased cortical Lewy bodies and Lewy neurites correlate with greater PDD severity and lower MMSE score. Overall, AD pathology was low in the PD cohort but others, including Jellinger and colleagues have found greater AD pathology with concomitant neurofibrillary tangles (NFT) and neuritic plaques in the entorhinal cortex, hippocampus, and cortical regions.

The neurochemistry and neuroanatomy underlying PD cognitive dysfunction likely represents complex interactions among the dopaminergic, cholinergic, serotoninergic, noradrenergic, and glutaminergic systems and frontal–subcortical and cortical regions. Cholinergic deficits may be more pronounced in PDD than AD; there is decreased ChAT activity in the cerebral cortex of PDD and neuronal loss in the nucleus basalis of Meynert. Use of cholinesterase inhibitors in dementia is rooted in the involvement of the cholinergic system in learning, memory, and attention.

Dopaminergic deficits also impact on cognition through frontal–striatal pathways, influencing specific circuits such as the prefrontal cortex, particularly the dorsolateral prefrontal cortex, which plays a critical role in executive function and working memory; the anterior cingulate, which is involved in attention, response initiation, inhibition, and apathy; and the lateral orbitofrontal cortex, which contributes to decision making, reward, impulse control disorders (ICD), and mood.

Treatment

Dopaminergic medications used to treat PD motor symptoms exert variable effects on PD cognition. Studies have reported no change in cognitive slowing or reward-associated learning, whereas others have demonstrated improvement in alertness and arousal, working memory, planning tasks, cognitive flexibility, and apathy. However, some have reported worsening in tests with choice reaction times and increased sleepiness. Anticholinergics worsen cognition and should be avoided in older PD and those with cognitive impairment.

The first report of cholinesterase inhibitors in PDD was published as early as 1996 with a small open label study of tacrine. Subsequently, donepezil, rivastigmine, galantamine, and memantine have been studied; however, sample sizes have been relatively small and treatment durations, often less than 12 weeks. To date, the largest trial has been with rivastigmine, a dual cholinesterase inhibitor, published by Emre et al. in 2004. The trial enrolled 541 mild-moderate PDD patients of whom 410 completed; rivastigmine (or placebo) was given as 3–12 mg day^{-1} over 24 weeks. PDD patients treated with rivastigmine had a statistically significant mean improvement in their Alzheimer's Disease Assessment Scale (ADAS-cog) score (2.1 points), compared with a 0.7 point worsening in those receiving placebo, as well as a statistically significant improvement in the Alzheimer's Disease Cooperative Study-Clinician's Global Impression of Change (ADCS-CGIC) compared with the placebo group. The most frequent adverse events were nausea, emesis, and tremor.

Dementia with Lewy Bodies (DLB)

History

The first report of DLB by Okazaki et al. in 1961 featured two patients with dementia and a marked rigidity who had cortical Lewy bodies. Over the years, advances in immunostaining for ubiquitin and α-synuclein have improved identification of Lewy bodies and Lewy neurites. Consensus criteria for the clinical and pathological diagnosis of DLB were published initially in 1996 by McKeith et al., and most recently revised in 2005. The revised criteria incorporate additional information on clinical features such as REM behavior disorder and neuroleptic sensitivity, functional imaging studies demonstrating reduced striatal dopamine transporter activity, and pathological guidelines for the regional distribution of Lewy bodies and Lewy neurites and evaluation of concomitant AD pathology. The distinction between DLB and PDD remains a subject of debate and research interest. Although DLB and PDD may represent a spectrum of Lewy body disease, the '1-year rule,' as applied in the literature as well as this section, defines DLB as a dementia syndrome with the later development (after at least 1 year) of parkinsonism.

Clinical features

The central feature of DLB is a dementia defined as a progressive cognitive decline that significantly impacts on normal social or occupational function. The clinical cognitive deficits are largely subcortical in nature with predominant executive dysfunction, attentional deficits, and impaired visuospatial abilities. Prominent or persistent memory impairment may not necessarily be present in the early stages but typically occurs with disease progression. Thus, the cognitive profile of DLB encompasses both subcortical and cortical impairments. In contrast to AD, DLB patients perform worse on measures of executive function, verbal fluency, and visual perception and constructional praxis, but better on tests of naming and verbal memory. MMSE score, however, does not reliably discriminate between DLB and AD. As such, the cognitive deficits of DLB are more similar to those found in PDD. The annual rate of cognitive decline in DLB, as measured by global cognitive tests such as the MMSE, may be faster than that of PDD and AD.

Other core features in the DLB diagnostic criteria include fluctuating cognition with pronounced variation in attention and alertness, recurrent visual hallucinations, and spontaneous features of parkinsonism. Furthermore, suggestive features such as REM behavior disorder, severe neuroleptic sensitivity, and low dopamine transporter uptake in the basal ganglia on functional neuroimaging and supportive features such as repeated falls and syncope, severe autonomic dysfunction, hallucinations in other modalities, delusions, depression, and specific neuroimaging and electrophysiologic correlates have been proposed; these neuropsychiatric, motor, and autonomic features are discussed in other articles.

Pathogenesis/pathophysiology

DLB is characterized by widespread Lewy bodies, especially in cortical and limbic regions. The density of cortical and limbic Lewy body pathology positively correlates with the severity of cognitive impairment in DLB. Cholinergic degeneration in the basal forebrain is apparent. Amyloid pathology also may be seen in DLB as detected on neuropathology and with neuroimaging studies using amyloid tracers such as Pittsburgh Compound B, but its contribution to the clinical symptoms is unclear. NFT are present in some DLB, but the low burden of AD pathology in DLB

cases suggests that AD does not fully explain the dementia of DLB. In fact, the likelihood that the observed neuropathology explains the DLB clinical phenotype is directly related to the severity of Lewy-related pathology and inversely related to the severity of concurrent AD-type pathology. At postmortem investigation, distinction between DLB and PDD may be difficult due to the presence of diffuse abnormalities. However, neuronal loss in the substantia nigra and possibly the striatum may be greater in PDD. Other factors that may contribute to the pathogenesis of dementia in DLB include age, genetics (APOE4 genotype, extra copies of the α-synuclein gene), regional distribution of pathology (temporal and frontal lobe), and degree of amyloid burden and AD pathology.

Treatment

Cholinesterase inhibitors have been reported to improve neuropsychiatric symptoms in DLB without significant motor side effects. Initial open-label studies with donepezil, galantamine, and rivastigmine were followed by a large, multicenter, randomized, double-blind, placebo-controlled trial of rivastigmine by McKeith et al. in 2000. This trial included 120 probable DLB patients (92 completed) who received rivastigmine (up to 12 mg day^{-1}) or placebo for 20 weeks, followed by a 3-week rest. Analysis of the 92 observed cases revealed a greater improvement in neuropsychiatric symptoms, as measured by the Neuropsychiatric Inventory-4 (measuring delusions, hallucinations, apathy, and depression), in the rivastigmine group compared with the placebo group. MMSE score and clinical global change score improved in the rivastigmine group, but this did not meet statistical significance. Performance on computerized cognitive assessments was faster and better in the rivastigmine treated group, particularly on attentional tasks. After drug discontinuation, differences between the two groups tended to disappear. Side effects included tremor, nausea, emesis, and somnolence and were greater in the rivastigmine group. Given concern for neuroleptic sensitivity and worsened parkinsonism, it is important to note that rivastigmine did not appear to worsen parkinsonism. To date, memantine use in DLB has been reported only in case reports or small studies, with conflicting results, including worsening of hallucinations and psychosis in some.

Progressive Supranuclear Palsy (PSP)

History

Although descriptions of the clinical features of PSP may have been noted by Charcot and Dutil in the late nineteenth century, the disease was first reported in 1963 by Steele, Richardson, and Olszewski as a new syndrome characterized by parkinsonism, marked vertical gaze paresis, dementia, and axial rigidity. Diagnostic criteria, proposed in the 1990s, for probable PSP require the presence of a gradually progressive disorder with an age of onset of 40 or later, vertical supranuclear ophthalmoparesis, and prominent postural instability with falls in the first year of symptoms (with the presence of the first criterion plus either of the latter two for possible PSP). None of the proposed diagnostic criteria specifies cognitive or behavioral features. Early cognitive impairment with apathy, abstract thought impairment, decreased verbal fluency, imitation behavior, or frontal release signs are recognized as part of probable PSP but perhaps overshadowed by prominent motor and balance disturbances.

Clinical features

The cognitive deficits in PSP typically reflect frontal–striatal pathology and represent a subcortical dementia. Cognitive impairment may be mild but is often present on neuropsychological testing. In the first year, 20–50% of cases may have cognitive slowing, and cognition declines as the disease progresses. The initial presentation of cognitive and behavioral symptoms may result in a diagnosis of dementia other than PSP. The hallmark of cognitive impairment or dementia in PSP is a dysexecutive syndrome with deficits in planning, processing, solving problems, forming concepts, social cognition, and verbal fluency. In addition, there may be perseveration, reflecting set shifting and concept formation problems. PSP patients have greater difficulty with verbal fluency than PD or AD, in some studies. In addition, PSP patients perform poorly on tasks such as the Wisconsin Card Sorting Test, Trail Making Test, and Luria sequence. They may have impaired problem-solving abilities, proverb interpretation, similarities, abstract concepts, and picture arrangement. Similar to other subcortical dementias, declarative memory function is less affected in PSP. Although PSP patients may have impaired immediate and delayed recall on memory tests such as the California Verbal Learning Test, when the encoding of items is controlled by use of a semantic category cue and recall performed with the same semantic cues, the recall performance improves. This suggests that the problem is not one of mesial temporal lobe memory function but rather encoding or retrieval.

In addition, behavioral disturbances may be prominent features in PSP. These behaviors include apathy, disinhibition, depression, anxiety, and perseveration. Apathy may be the initial symptom and unrelated to depression. Frontal lobe reflexes such as grasp, imitative, and utilization behaviors may occur. PSP patients may be unable to stop an automatic motor program once it has been started. Dubois et al. have termed this the 'applause sign,' which can be tested at bedside by asking the patient to clap three times consecutively. PSP patients clap several more times, indicating faulty frontal–striatal pathways and inhibition. The 'applause sign' discriminates PSP from frontotemporal dementia (FTD) and PD, correctly identifying 82% of the PSP versus FTD patients and 75% of the PSP versus PD patients.

Pathogenesis/pathophysiology

The neuropathology of PSP reveals midbrain and mild frontal atrophy, findings that also may be apparent on structural neuroimaging in vivo. Histopathological findings include neuronal loss and gliosis affecting mostly subcortical structures. However, abundant NFT and/or neuropil threads especially in the striatum, pallidum, subthalamic nucleus, basis pontis, dentate nucleus, and prefrontal cortex are the primary hallmark of PSP, and pathological tau in PSP is characterized by the four repeat isoform. The subcortical distribution and ultrastructure of NFT in PSP differ from those found in AD. NFT and tufted astrocytes can be found in premotor and motor cortices as well as dentate granule hippocampal cells, which may correlate with aging and dementia. The prefrontal areas, however, demonstrate relatively little NFT or neuronal loss. It has been suggested that the cognitive dysfunction seen in PSP relates to subcortical tau pathology, disruption of frontal pathways (e.g., dorsolateral prefrontal cortex, anterior cingulate, and orbitofrontal cortex), and basal forebrain cholinergic projecting neurons. Dementia, however, does not clearly correlate with ChAT activity. Striatal pathology may disrupt output from the striatopallidal complex to the frontal lobes, thereby contributing to the cognitive impairment in PSP. Serotonergic and noradrenergic systems seem to be relatively unaffected in PSP.

Treatment

Pharmacological agents studied in PSP cognitive impairment are based on the cholinergic hypothesis and damage to cholinergic striatal, basal forebrain, and brainstem neurons. Two randomized, double-blind, controlled trials with the cholinergic agents physostigmine and RS-86 showed mild or no efficacy in PSP. In a randomized, double-blind, placebo-controlled crossover trial, Litvan et al. studied donepezil 10 mg day^{-1} in 21 PSP patients over 6 weeks with a 1-month washout period. There was no significant difference in global cognitive measures, MMSE, NPI total, the Selective Reminding Test, or attention tests. Although Double Memory Test scores improved while taking donepezil, motor function and activities of daily living/mobility scores worsened, thus suggesting minimal cognitive benefit and risk of motor worsening. Fabbrini et al. found no cognitive benefit in a small, open-label study of donepezil in six PSP patients, but did not report motor worsening. Future treatment strategies in tauopathies may include inhibitors of tau phosphorylation and aggregation, increased tau clearance, antitau directed immunotherapy, or interference of tau splicing but these remain to be seen.

Corticobasal Degeneration

History

In 1967, Rebeiz et al. described the syndrome known as corticobasal degeneration (CBD) in three patients with a progressive asymmetric parkinsonian syndrome with apraxia and pathological features of contralateral frontoparietal atrophy, neuronal loss, and 'ballooned neurons.'

Clinical features

Like PSP, CBD is a 4-repeat tauopathy with features of parkinsonism and cognitive impairment or dementia. Although there may be overlap, CBD tends to present either with progressive asymmetric rigidity and apraxia, sometimes accompanied by dystonia, myoclonus, cortical sensory loss, and alien limb phenomenon or with a predominant dementia syndrome. These two different presentations of CBD explain why sometimes these patients are referred to movement disorders specialists, and other times, to dementia clinics. In the more common, motor variant, dementia is relatively uncommon but develops in about 25%. In these patients, neuropsychological findings typically demonstrate impaired executive function, verbal fluency, praxis, and visuospatial functioning, thereby reflecting the frontal–striatal, frontal, and parietal circuitry. Learning and memory are less affected. Compared with AD patients, CBD patients performed worse on tests of attention, praxis, and motor function; however, they performed better on tests of immediate recall. Depending on the hemispheric lateralization, language may be variably affected in CBD. The apraxias associated with CBD are discussed in other articles.

The dementia syndrome of CBD shares features with fronto-temporal dementia and primary progressive aphasia. In these cases, CBD presents with early and severe cognitive impairment with frontal lobe features (executive dysfunction and poor attention) that progresses to a more generalized dementia with cortical features involving memory, language, and behavioral disorders (e.g., personality changes, inappropriate behavior, repetitive or compulsive activities); this may be accompanied by parkinsonism, corticospinal involvement, and incontinence. The different dementia presentations of CBD depend on the underlying cortical localization. When the lateral dominant frontal lobe is affected, early symptoms may be orofacial apraxia and speech impairment. When the superior temporal gyrus is involved, the presentation resembles primary progressive aphasia. Language difficulty may be seen in CBD, most commonly problems with language expression, including trouble with finding words or naming. In some patients, reading, writing, and calculation abilities may be impaired. Differential diagnosis may include FTD and parkinsonism linked to chromosome 17 (FTDP-17), depending on the family history and possibly, the age of onset.

Pathogenesis/pathophysiology

Neuropathology of CBD reveals asymmetric parietofrontal or frontotemporal cortical atrophy; these findings may be apparent on structural and functional neuroimaging studies during life. Neuronal loss is prominent in those affected

cortical gyri. Microscopically, tau-positive astrocytic plaques and thread-like inclusions are found in gray and white matter, including the superior frontal gyrus, superior parietal gyrus, pre- and postcentral gyri, and striatum. The selective involvement of cortical regions in CBD and subcortical structures correlates with the motor, cognitive, and behavioral signs and symptoms of CBD. Achromatic, ballooned neurons are commonly associated with CBD. Similar to PSP and other tauopathies, tau is thought to be an important factor in the pathogenesis of CBD, with hyperphosphorylation of tau contributing to the disruption of microtubule binding. Clinical and genetic studies demonstrate overlap among PSP, CBD, and FTDP-17.

Treatment

To date, there are no specific treatments for the dementia of CBD. Lessons from treatments studied in the FTDs may be informative. Future studies may explore tau-related interventions.

Parkinsonism–Dementia Complex of Guam

History

The parkinsonism-dementia complex (PDC) of Guam, a term introduced by Hirano et al. in 1961, comprises a family of diseases marked by clinical and pathological features of amyotrophic lateral sclerosis (ALS), parkinsonism, and dementia. In the 1940s, the Chamorro population in Guam, the largest of the Mariana islands in the Western Pacific, was noted to have an increased prevalence of motor neuron disease. Subsequently, another neurodegenerative condition, characterized by the onset of parkinsonism and dementia in middle-age, was identified in the Chamorros, some of whom also had the ALS syndrome themselves or in their family history. The Chamorros called this syndrome *lytico-bodig*: *lytico* for the progressive paralysis that resembled ALS and *bodig* for the parkinsonism, sometimes occurring with dementia. Between 1940 and 1965, this syndrome was a leading cause of death in adult Chamorros. Similar phenotypes to the Guamanian lytico-bodig have been recognized in isolated villages in the Kii peninsula of Japan and in western Papua New Guinea. Over the years, the ALS/PDC syndrome has been a source of great interest for epidemiological, environmental, and genetic studies.

Clinical features

In the ALS/PDC syndrome, there is a range of clinical phenotype from a more prominent motor neuron/ALS presentation to parkinsonism and dementia. In the ALS phenotype, the age of onset is about 46 years with a mean range from 20 to 70 years, with a male predominance; the mean disease duration is 4 years. In those with the parkinsonian-dementia phenotype, the age of onset is in the 50–60s, with a greater male–female ratio compared with the ALS cases. Parkinsonian features include bradykinesia, rigidity, tremor, flexed posture, and shuffling gait; loss of smell, drooling, sweating, and sleep disturbances have been reported. Progressive cognitive dysfunction includes mental slowness, personality changes, memory impairment, and mood disorders, leading to a severe dementia. Pigmentary retinopathy may occur in about 50%. About 45% have a positive family history of ALS or PDC. Over the years, decreased incidence of the ALS/PDC syndrome along with an increase in the onset age has been reported, although this is not well understood. Treatment is symptomatic with rehabilitative therapies and levodopa, if indicated.

Pathogenesis/pathophysiology

Gross pathological features of the ALS/PDC syndrome include prominent cerebral atrophy including the temporal and frontal lobes, hippocampus, and rostral brainstem tegmentum. NFT are seen in the mesial temporal lobe, basal ganglia, and locus ceruleus and demonstrate a different laminar distribution from those in AD, with more tangles in the superficial cortical layers. NFT have been found in nondemented Chamorros at higher frequencies than in Western populations. The tangles contain insoluble tau composed of 3-repeat and 4-repeat, in contrast to the 4-repeat isoform found in PSP. Lewy bodies and plaques have been typically absent. Anterior horn cells demonstrate degeneration and ubiquitin positive inclusions. More recently, Hasegawa et al. and Geser et al. reported TDP-43, transactive response (TAR)-DNA binding protein 43, which has been found in frontotemporal lobar degeneration with ubiquitinated inclusions (FTLD-U) and ALS, in dystrophic neurites, neuronal and glial inclusions in ALS/PDC. In addition, some of the tangles, astrocytes, and oligodendroglial coiled bodies in ALS/PDC have stained positively with antibodies to LRRK-2, a protein associated with genetic forms of PD and microtubule protein kinase function.

Theories related to the ALS/PDC syndrome have included environmental factors such as calcium and/or magnesium deficiency and the cycad hypothesis among others; however, much debate about the pathogenesis of this syndrome remains. The original cycad hypothesis by Whitting (1963) proposed that the disease related to environmental exposure to the toxins from *Cycas micronesica*, a Guamanian false sago palm from which fading flour was made. Possible explanations for the cycad toxicity included consumption of the cycad nut itself, which contains β-Methylamino-L-alanine (BMAA) toxin as well as increased toxin exposure by consumption of the Guamanian flying fox, which has higher concentrations of the BMAA toxin. Decreasing incidence of ALS cases may parallel the decline in the flying fox population in Guam. The cycad theory has remained controversial.

Dementia, Chorea

Huntington's Disease

History

In his paper 'On Chorea' (1872), George Huntington described features of a hereditary chorea in eastern Long Island, New York noted also by his father and grandfather. Besides the hereditary nature, presence of chorea, and adult onset, Huntington described neuropsychiatric disturbances with 'a tendency to insanity and suicide' and wrote that with disease progression 'the mind becomes more or less impaired, in many amounting to insanity.'

Clinical features

Huntington's disease (HD), an autosomal dominant neurodegenerative condition caused by a polyglutamine (CAG) expansion in the *huntingtin* gene on chromosome 4, is characterized by a triad of chorea, dementia, and behavioral disturbances. The cognitive impairment of HD generally represents a subcortical syndrome with frontal–striatal deficits resulting in impaired executive function, processing speed, attention, and concentration. Cognitive inflexibility, difficulty with switching 'sets,' and perseveration may occur. Early cognitive changes are frequently accompanied by behavioral disturbances such as depression, anxiety, irritability, and apathy. The cognitive and psychiatric features may be significant indicators of functional status. Since the average age of onset for HD is 35–40 years and many HD patients may still be working at the time of disease manifestation, impairment in executive functions (e.g., planning, sequencing, organizing, and carrying out multistep or complex tasks) can significantly affect occupational performance. HD patients are impaired on tests of executive function, attention, and mental flexibility such as Symbol Digit Modalities Test, verbal fluency tasks, Trail Making Test Part B, and Stroop Interference Test. As the disease advances, dementia progresses with greater executive dysfunction and memory impairment, although aphasia and agnosia are not typically present. Although HD patients may have mild to moderate memory impairment, the memory deficits relate more to faulty encoding and retrieval processes than to a storage defect. Comparison of AD and HD patients on immediate and delayed recall memory tests highlights this distinction. Similar to other subcortical dementias, HD patients perform better on recognition and with semantic cues than on recall. In contrast to mildly demented AD, HD patients also exhibit impaired motor skill learning and probabilistic learning. Cognitive changes in asymptomatic *HD* gene carriers have been variably reported and await further study.

Pathogenesis/pathophysiology

Neuropathology studies in HD reveal marked caudate and putamen atrophy as well as some cortical atrophy. Medium spiny neurons projecting from the striatum to the external pallidum are preferentially lost. Intraneuronal inclusions, representing huntingtin protein aggregates, are prominent in the striatal and cortical neurons. The exact mechanism by which the CAG repeat expansion causes disease is not fully understood but likely involves a toxic gain of function. The *HD* gene is expressed in neuronal tissues such as the striatum, cortex, substantia nigra, cerebellar Purkinje cells, angular gyrus of the parietal lobe, thalamus, and hypothalamus. The subcortical cognitive deficits in HD are generally thought to reflect disruption of frontal–striatal loops. There is also associated neuronal degeneration in frontal and temporal lobes that may contribute to dementia.

Treatment

Studies of pharmacological agents for HD cognition also have focused on the cholinesterase inhibitors, donepezil, and rivastigmine. In a randomized, double-blind, placebo-controlled study of donepezil 10 mg day^{-1} administered to 30 nondemented HD patients, Cubo et al. did not detect any significant improvement in cognition (as measured by the ADAS), chorea, or quality of life. A small open-label study with donepezil in HD patients with moderate to severe cognitive change was hampered by its open-label design, small sample, and large drop-out rate. De Tommaso et al. evaluated rivastigmine in a small, open-label, randomized controlled study of 21 HD patients (14 treated with rivastigmine), finding a small, although probably not clinically meaningful, but statistically significant improvement in MMSE score of 1 point. Overall, these studies, despite methodological issues, suggest that cholinesterase inhibitors have little effect on cognitive and motor symptoms in HD, although further rigorous study is needed.

Dementia, Tremor

Fragile X-associated Tremor-Ataxia Syndrome

History

In recent years, Fragile X-associated Tremor-Ataxia syndrome (FXTAS) has been identified as a newly recognized neurodegenerative disorder. The story of this entity began with clinical observations of progressive neurological disorders in the grandfathers of children with fragile X mental retardation syndrome. The grandfathers, who were later found to harbor premutations of 55–200 CGG repeats in the fragile X mental retardation 1 (*FMR1*) gene, developed variable presentations of neurological features that included action tremor, gait and limb ataxia, parkinsonism, polyneuropathy, autonomic dysfunction, and dementia, beginning in their 50–60s. Many of these patients were previously diagnosed as having essential tremor (ET), parkinsonism, or multiple system atrophy.

Additional clinical, radiological, pathological, and genetic features in both male and female premutation carriers have been described.

Clinical features

In addition to tremor, ataxia, and parkinsonism, cognitive deficits are common in males with FXTAS. The initial cognitive deficits relate to executive dysfunction, although a generalized dementia with more cortical features may occur, particularly with advanced disease. Cognitive deficits may already be apparent at the time of diagnosis with tremor, ataxia, or parkinsonism. The rate of cognitive decline appears to be variable but awaits further study. Dementia has been reported to develop in at least 50% of cases. Diagnostic criteria for FXTAS recently proposed by Berry-Kravis et al. also incorporate moderate to severe working memory deficits and executive dysfunction as a minor clinical criteria.

Overall, the cognitive deficits described include impairment in attention, executive function, and working memory as well as declarative and procedural learning. Similar to other frontal subcortical dementias, the executive dysfunction of FXTAS manifests itself as impairment in planning, processing, and achieving goal-directed behavior. Grigsby and colleagues have shown in several studies that individuals with FXTAS have lower scores on WAIS-III Performance (nonverbal IQ), measures of executive function, and processing speed, compared with age- and education-matched controls. In addition, males with FXTAS perform worse than controls on MMSE, tests of executive function, working memory, declarative memory, processing speed, temporal sequencing, and visuospatial function; Grigsby et al. noted that language and verbal comprehension were spared. A retrospective, chart review comparing neuropsychological tests of language, phonemic fluency, and digit span in FXTAS patients with dementia matched by age, education, gender, and dementia stage to patients with AD did not reveal any significant differences between the two patient groups. With more advanced disease, greater impairment in declarative memory can be seen. Visuospatial function, constructional praxis, and language appear to be largely unaffected in FXTAS.

Although most of the literature focuses on male FXTAS patients, progressive cognitive decline has been reported in some female FXTAS carriers with impaired executive function, judgment, perseverations, and memory. Since FXTAS is less common in females, true estimates of the prevalence and characteristics of cognitive impairment and dementia in female FXTAS carriers remain to be seen.

Pathogenesis/pathophysiology

Genetic studies have identified that FXTAS is due to a premutation in the *FMR1* gene with CGG repeat lengths of 55–200, whereas Fragile X mental retardation is caused by a full mutation with expansion lengths >200 CGG repeats. In contrast to the Fragile X mental retardation in which the CGG repeat expansions lead to methylation and transcriptional silencing of the *FMR1* gene, levels of FMR1 mRNA are elevated in premutation carriers, thereby, suggesting a possible toxic 'gain of function' mechanism. Neuropathology in mice and humans demonstrates eosinophilic, ubiquitin-staining, intranuclear inclusions in neurons and astrocytes throughout the brain, including frontal regions and hippocampus. The hippocampal and frontal cortex inclusions may underlie some of the cognitive dysfunction, and also possibly mood disturbances, seen in FXTAS.

Treatment

To date, pharmacological treatments for the cognitive dysfunction associated with FXTAS have focused on those agents already approved for AD and PDD, namely cholinesterase inhibitors, but controlled trials are lacking. Anecdotal reports suggest that the cholinesterase inhibitors (e.g., donepezil, galantamine, rivastigmine) and the NMDA antagonist, memantine, may be helpful, although rigorous trials are lacking. In a questionnaire study of different medications used by FXTAS patients, Hall et al. reported that 2/6 patients on venlafaxine and 3/9 patients on cholinesterase inhibitors reported 'slowing of cognitive decline.' Since increased tremor has been reported with cholinesterase inhibitor use, including in the PDD studies, this side effect should be monitored. In addition, medications that may be used to treat tremor, parkinsonism, and ataxia (e.g., benzodiazepines, primidone, amantadine, and dopaminergic agents) can cause sedation and confusion, particularly in the elderly and those with baseline cognitive impairment. As a result, these agents should be started with low doses and increased gradually, while monitoring for side effects.

Essential Tremor

Clinical features

Although the hallmark of ET is an action tremor, recent studies suggest a more heterogeneous clinical and pathological phenotype of ET. Reported nonmotor features have included executive dysfunction and memory impairment similar to AD. Population-based studies have examined the association between ET and dementia. In a Spanish population study, Benito-León et al. sought to determine whether ET is associated with prevalent dementia. The authors identified all persons with dementia and ET in central Spain (as part of the Neurological Disorders in Central Spain Study), finding 31 of 273 ET cases (11.4%) to have dementia as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn (DSM-IV) compared to 204 of 3382 non-ET controls (6.0%). Adjusting for age, stroke, and education, the ET cases with tremor onset after age 65 years were 70% more likely to be demented than

controls (OR = 1.70, 95% CI = 1.04–2.76). Another study by the same group assessed the risk of incident dementia in ET, following 3891 nondemented ET cases and controls prospectively (mean duration of follow up, 3.2 years). Based on DSM-IV criteria, 16 or 206 ET cases (7.8%) developed incident dementia compared to 145 of 3685 controls (3.9%) (adjusted RR 1.66, 95% CI = 0.99–2.80). ET cases with tremor onset after age 65 years were twice as likely to develop dementia.

Pathogenesis/pathophysiology

Furthermore, postmortem studies of ET patients demonstrate mixed pathologies. A subset of ET cases have demonstrated brainstem Lewy bodies (including the locus ceruleus). Other ET cases exhibit cerebellar changes with Purkinje cell loss, increased torpedoes, and Bergmann glia. In a series of 33 postmortem ET cases, higher CERAD plaque scores were uncommon and none of the cases or controls met NIA-Reagan pathological criteria for AD; however, further examination of the pathology and cognitive status is needed. The findings of dementia in ET also appear to be distinct from the Fragile X Tremor-Ataxia syndrome with FMR1 premutations, which can manifest itself as the middle-age onset of a combination of tremor, parkinsonism, ataxia, and dementia.

Dementia, Ataxia

Dementia may accompany several different ataxia syndromes, including FXTAS (discussed under section 'Dementia, Tremor'), spinocerebellar ataxia type 17 (SCA17), dentatorubral-pallidoluysian atrophy (DRPLA), and Creutzfeldt–Jacob disease (discussed in other Encyclopedia articles), among others. Although cognitive impairment can be evident in other ataxias such as the autosomal dominant spinocerebellar ataxias type 1, 2, 3, 6, or 21, this section highlights SCA17 and DRPLA as ataxias associated with prominent dementia syndromes. Clinically, cognitive dysfunction in the cerebellar disorders typically resembles a dysexecutive syndrome and may be accompanied by affective symptoms; as such, it has been termed a 'cerebellar cognitive affective syndrome.' The exact mechanism of cognitive dysfunction in cerebellar syndromes is not fully elucidated but implicates the cerebrocerebellar, cortico-striatal-thalamocortical, and frontal circuitry.

Spinocerebellar Ataxia Type 17 (SCA17)

Clinical features

SCA17 is an autosomal dominant neurodegenerative disorder characterized by cerebellar gait ataxia and dementia with the development of limb ataxia, bradykinesia, and hyperreflexia over several decades. The age of onset ranges from 19 to 48 years, with a mean onset age of 33 years. The cognitive features reported in SCA17 have included slowed thinking, impaired memory, and intellectual decline. Intellectual deterioration has been reported in up to 80%. Cognitive symptoms also frequently occur early in the disease course; presenting symptoms vary with some pedigrees manifesting greater initial dementia, ataxic, DRPLA-like, HD-like, or parkinsonian phenotypes. In 1999, Koide et al. described a 14-year-old Japanese female with progressive ataxia and intellectual deterioration beginning at age 6 years, who was found to have a de novo expansion of the CAG of the TATA-binding protein (*TBP*) gene. Subsequently, deterioration of intellectual function or dementia, sometimes at the onset, was found in other SCA17 pedigrees. Other studies have reported similarities to HD due to the presence of dementia, psychiatric disturbances, and chorea. Besides the cognitive decline, psychiatric symptoms, ranging from depression or personality changes, to aggression, hallucinations, or psychosis, may occur.

Pathogenesis/pathophysiology

SCA17 is caused by expansion of a CAG/CAA repeat coding for a polyglutamine stretch of the *TBP* gene on chromosome 6q27. TBP is a general transcription initiator factor; proposed pathogenetic mechanisms of the CAG repeat expansion include effects on transcriptional initiator factor or promoting toxic functions. Brain MRI reveals marked cerebellar atrophy and mild cortical atrophy. Positron emission tomography (PET) and single photon emission computed tomography (SPECT) imaging studies performed on two unrelated SCA17 patients by Minnerop et al. demonstrated a significantly reduced glucose metabolism in the putamen, a reduced dopamine transporter activity in the basal ganglia, and a pronounced reduction in the putamen. A MRI voxel-based morphometry study by Lasek et al. in 12 patients with SCA17, six of whom had dementia, revealed gray matter atrophy in the cerebellum, basal ganglia, and frontal and temporal lobes, compared with normal controls. The neuropsychological test scores correlated with atrophy of the nucleus accumbens, whereas personality changes correlated with frontal cortex and limbic region atrophy. Neuropathology reveals moderate cerebellar degeneration, neuronal intranuclear inclusions, and mild to moderate changes in the basal ganglia and cortical regions. The widespread cortical and subcortical involvement depicted on imaging and pathological studies likely underscores the cognitive deterioration and other neurological manifestations.

Dentatorubral–Pallidoluysian Atrophy

Clinical features

DRPLA is an autosomal dominant ataxia with phenotypic similarities to the spinocerebellar ataxias, progressive

myoclonic epilepsies, and HD, depending on the age of onset. Clinical features of ataxia and dementia are present regardless of the age of onset. Inverse correlation between age of onset and CAG repeat length and anticipation, particularly with paternal transmission, occur. The age of onset is variable, ranging from childhood to late adulthood but on average, symptoms occur around age 30. Patients with symptom onset at age less than 20 share a phenotype with progressive myoclonic epilepsy, as seizures and myoclonus are present in addition to ataxia and dementia. Those patients with the symptom onset after age 20 are more likely to resemble either spinocerebellar ataxias or HD due to chorea and psychiatric symptoms. Cognitive features are generally similar to a subcortical dementia with psychomotor retardation, executive dysfunction, and mild memory deficits. Psychiatric symptoms include mood disorders, apathy, irritability, childish behavior, and occasionally hallucinations or psychosis. DRPLA is relatively common in Japan with a prevalence rate of 0.2–0.7 per 100 000 and is present in the United States as a variant, Haw River syndrome that has been reported in African-American kindred in North Carolina.

Pathogenesis/pathophysiology

DRPLA is caused by a polyglutamine CAG repeat mapped to chromosome 12p and encoding a cytoplasmic protein, atrophin-1. Mutant DRPLA proteins with polyglutamine expansions likely act by toxin 'gain of function.' Neuropathological examination reveals degeneration in the dentate, red nucleus, subthalamus, and globus pallidus and accumulation of atrophin-1 in neuronal nuclei. Other neuropathological studies have not found neuronal loss in the nucleus basalis of Meynert or clinico-pathological correlation between dementia and this cholinergic structure. Rather, the widespread degeneration in cortical, subcortical, and cerebellar regions may be responsible for dementia.

Conclusion

Dementia and milder cognitive impairment are common features in movement disorders and can have a profound effect on the patient and the caregiver, morbidity, and mortality. Although predominantly characterized as subcortical dementia syndromes with hallmarks of executive dysfunction, attentional difficulties, and visuospatial disturbances, some of the dementias present as more cortical profiles with memory, language, and praxis affected or evolve into a mix of cortical and subcortical deficits as the disease progresses. Unfortunately, at this stage, pharmacological treatments to address symptoms are limited, and disease-modifying treatments are lacking. Providing supportive care for the patient and the caregiver, addressing safety issues and driving, and managing behavioral issues such as psychosis are essential components in the care of the demented patient. Further understanding of the underlying pathophysiology of these dementia/movement disorder syndromes may yield improved treatments.

See also: Alzheimer's Disease and Parkinsonism; Cholinesterase Inhibitors in Parkinson's Disease; Cognitive Assessments and Parkinson's Disease; Creutzfeldt–Jacob Disease; Dementia with Lewy Bodies; Dentatorubropallidoluysian Atrophy; Executive Dysfunction; Frontotemporal Dementia-Parkinsonism; Huntington's Disease; MMSE - Mini-Mental State Examination; Parkinson's Disease: Definition, Diagnosis, and Management; SCA17; Tauopathies.

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Dentatorubropallidoluysian Atrophy

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Glossary

Anticipation – The symptoms occur earlier with successive generations.
ATN 1 gene – A gene, located on chromosome 12, that codes for a protein called atrophin 1. A mutation in this gene, due to an expansion in the CAG repeating sequence, results in DRPLA.
Autosomal dominant – A hereditary condition that is passed on from parent to child and does not 'skip' generations. One copy of the abnormal gene is enough to cause the condition.
CAG repeat – A repeating genetic sequence of three nucleotides cytosine, adenosine, and guanine that codes for the amino acid glutamine.
Chorea – An involuntary movement disorder characterized by brief, rapid movements. Can affect the arms, legs, trunk, and face.
Dentatorubropallidoluysian atrophy (DRPLA) – Also known as dentatorubropallidoluysian atrophy. An autosomal dominant neurodegenerative disorder characterized by ataxia, myoclonus, and dementia.
Myoclonus – Involuntary, rapid, lightning type of abnormal movements.

Definition and History

Dentatorubropallidoluysian atrophy (DRPLA) is a rare autosomal dominant neurodegenerative disorder characterized by cerebellar ataxia, myoclonic epilepsy, choreoathetosis, and dementia. The age of onset and clinical presentation depend on the size of the expanded CAG mutation in mutated gene. The condition was originally described in the Japanese population in the 1970s.

Pathology

In autopsies of affected brains in DRPLA, a combined degeneration of the dentatorubral and pallidoluysian systems of the central nervous system is seen. There is a pronounced neuronal loss also in the globus pallidus, striatum, and subthalamic (Luys body), red, and dentate nuclei in addition to Purkinje cell degeneration. Autopsy study of the white matter lesions showed diffuse myelin pallor, axonal preservation, and reactive astrogliosis in the cerebral white matter.

Epidemiology

Most cases originate from Japan, where its prevalence is 0.2–0.7 per 100 000. While rare outside Japan, it has been described in individuals and families of European and other Asian descent. In the United States, families of African descent have been described, the condition being referred to as the Haw River syndrome.

Genetics

DRPLA is an autosomal dominant disorder with high penetrance. The genetic mutation has been characterized as an expansion of a CAG repeat in the ATN1 gene on chromosome 12p13. This gene produces a 190 kDa protein known as Atrophin-1, a nuclear protein with putative nuclear localizing signals. The mutation, due to an expansion of the triplet repeat results in an expanded polyglutamine tract, The expression of the mutant protein encoded by ATN1 results in a frequent formation of peri- and intranuclear aggregates with apoptotic cell death, suggesting that processed mutant proteins are more toxic to cells than full-length proteins (gain of function mutation).

The normal alleles of the DRPLA gene have 8–35 CAG repeats, while abnormal alleles have 49–93 repeats. The greater the number of repeats, the more severe the symptoms and the earlier the onset. The expansion also results in instability in the repeating sequence. Thus, in the transmission of mutant alleles from parent to child, the number of CAG repeats may increase particularly with paternal transmission. This can result in anticipation, meaning that affected offspring develop symptoms with an earlier onset in successive generations. This can be as much as 26–29 years earlier when the gene is inherited from affected fathers and 14–15 years earlier from affected mothers.

Clinical Features and Prognosis

The onset of DRPLA ranges from the first to seventh decade of life, with a mean onset of 30 years. The cardinal symptoms of DRPLA are cerebellar ataxia, myoclonic epilepsy, choreoathetosis, dystonia, and dementia. The clinical features can be diverse even within individuals in the same family. The age of onset and clinical features correlate well with the extent of the genetic abnormality (CAG repeat). For example, infantile DRPLA has been described with extreme expansion of CAG repeat.

Juvenile-onset disease (<20 years of age at onset) typically presents with symptoms consistent with progressive myoclonus epilepsy. Absence and atonic seizures are occasionally observed as well. Seizures and myoclonus are typical of the early adult-onset type (21–40 years of age), while cerebellar ataxia, choreoathetosis, and dementia are major features in the late adult-onset type (onset after the age of 40). Psychosis may sometimes be a presenting feature. Cervical dystonia was the presenting feature in one family. Corneal endothelial degeneration has been described.

In all cases, DRPLA is a slowly progressive condition. Individuals develop ataxia and/or movement disorders such as chorea, increasing difficulties with gait and balance, and cognitive dysfunction. While motor and cognitive problems are invariably present, emotional features, such as affective disorder and psychosis, are more variable. In juvenile-onset patients, epilepsy may become more severe over time and difficult to treat. Patients eventually become bedridden, with death resulting from complications such as infection.

Clinical Vignette

A 35-year-old Japanese-Canadian female presented with complex partial and generalized seizures at 17 years of age. This was followed by changes in personality and mild cognitive impairment associated with depression and behavioral changes. She later developed generalized choreiform movements and ataxia. Her seizures were reasonably controlled with valproic and carbamazepine; risperidone was given for abnormal movements. As she grew older, the choreiform movements decreased but cognitive and behavioral problems worsened. Quetiapine was substituted for respiridone for behavioral symptoms. She developed increasing difficulties with gait and ataxia, and eventually became anarthric and bedridden by 30 years of age. Genetic testing showed 17 repeat expansions on one allele and 65 repeats in another allele in the DRPLA gene.

Review of the family history revealed that her son also had developed problems with epilepsy at 5 years of age. Her father had developed gait ataxia and mild dementia at the age of 50. Both were shown to have expanded alleles consistent with DRPLA on genetic testing.

Differential Diagnosis

The diagnosis of DRPLA is based on characteristic clinical findings, positive family history, and confirmation by the detection of an expansion of a CAG/polyglutamine tract in the ATN1 (DRPLA) gene on genetic testing.

Clinically, DRPLA may be difficult to distinguish from Huntington's disease and the dominantly inherited spinocerebellar ataxias (SCA 2,3,17). A history of ataxia as an early symptom as well as atrophy of the cerebellum and brainstem (particularly pontine tegmentum) on imaging study can be helpful in differentiating Huntington's disease form DRPLA; presentation with chorea and atrophy of the caudate nucleus favors the diagnosis of Huntington's disease. DRPLA shares many clinical and pathological features with the spinoceberellar ataxias. Both ataxia and psychotic symptoms are common in both SCA17 and DRPLA and have been noted in some SCA7 cases. SCA 2 and 3 have clinical features such as chorea, dystonia, cerebellar ataxia, and pyramidal signs. Retinal degeneration is unique in SCA 7. Currently, molecular genetic testing is available to distinguish among these diagnostic considerations.

Wilson's disease or hepatolenticular degeneration is an autosomal recessive disease that can present in early to mid adulthood with symptoms of chorea, dystonia, and cognitive impairment. Elevated 24-h urine copper levels and decreased ceruloplasmin confirms the diagnosis of Wilson's disease. Genetic comfirmation is also available.

For onset of symptoms before the age of 20, other diagnositic considerations should include juvenile onset Parkinson's disease, drug-induced movement disorders, Lafora disease, Unverricht–Lundborg disease, neuronal ceroid-lipofuscinosis, MERRF, sialidosis, Gaucher disease, neuroaxonal dystrophy, pantothenate kinase associated neurodegeneration, familial essential myoclonus, postinfectious (Sydenham) chorea, neuroacanthocystosis, and Vitamin E deficiency.

Management

DRPLA is a slowly progressive disorder, with no known cure and no identified treatments that slow the rate of progression. Treatment is symptomatic and supportive, similar to other disorders such as Huntington's disease and the spinocerebellar ataxias. Seizures are treated with antiepileptic drugs in a standard manner. Psychiatric problems are addressed with appropriate psychotropic medications. If chorea is severe, dopamine-depleting or-blocking agents may be used. Gait and balance problems may benefit from intervention from physiotherapy, and dysphagia should be assessed by a speech pathologist. Eventually, patients will require institutional care. Support and counseling for family members should be considered. As with other similar disorders, care in an interdisciplinary movement disorders clinic would be recommended.

Genetic Counseling

As with all hereditary disorders, the diagnosis of DRPLA has implications on the whole family. When a positive family history is known, genetic counseling is strongly

recommended to inform all the family members of their risks of inheriting the gene. Presymptomatic genetic testing can be offered to those individuals wishing to know whether they have inherited the gene, through Medical Genetics clinics. If there is no known family history, or the diagnosis has not been made in the family previously, a full family history needs to be taken to determine whether any other family members may be affected. Early death of the parent before the onset of symptoms, misdiagnosis, adoption, or late onset of the disease may mask a positive family history. In these circumstances, genetic assessment and counseling are again important to determine whether there may be other family members at risk or affected.

See also: Ataxia; Chorea.

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Depression and Parkinsonism

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Glossary

Affective (mood) disorder – One of a group of psychiatric syndromes in which the primary and essential feature involves persistent and pervasive episodic disturbances of mood, either depression or elation, accompanied by emotional, cognitive, behavioral, psychomotor, somatic, vegetative, and functional changes. The most common affective disorders include major depression and bipolar disorder. Some definitions consider anxiety disorders a type of affective disorder. Affective disorders also include mood disorders that are induced by medications or illicit substances or that occur in the context of a general medical condition. Affective disorders may involve single or recurrent episodes of illness.

Antidepressant – Any number of medications used to treat major depressive disorders. Commonly used classes of antidepressants include tricyclic or heterocyclic antidepressants, serotonin reuptake inhibitors, and serotonin–norepinephrine reuptake inhibitors.

Antipsychotic medication – Can be used synonymously with the term *neuroleptic* medication. These include a group of medications used to treat psychotic symptoms in psychiatric disturbances, including mood disorders associated with psychotic features (hallucinations and delusions). Antipsychotic medications are sometimes used to augment the effects of an antidepressant for treatment refractory depressive disorders or as a mood stabilizer in patients with bipolar disorder or

recurrent major depression. Antipsychotics that block dopamine type II receptors are associated with drug-induced parkinsonism.

Bipolar affective disorder – A chronic affective illness characterized by fluctuations between depressive and manic episodes at different times. Clinical subtypes include depressive and hypomanic episodes or episodes of hypomania or mania induced by antidepressant medications.

Dysthymia (dysthymic disorder) – A term for a chronic mild depressive disturbance that is less severe than major depression. Treatment may involve antidepressants and/or psychotherapy.

Major depression – Refers to a unipolar mood disorder involving one or more depressive episodes in which a depressed mood and loss of interest and/or sense of enjoyment are associated with vegetative symptoms (appetite and sleep disturbances), loss of energy, problems with concentration and indecisiveness, and distressing emotional changes such as feeling of guilt, worthlessness, and suicidal ideation.

Minor depression – A term used to refer to a depressive disturbance of at least 2 weeks duration in which there is a presence of two to five of the DSM-IV-TR symptom criteria for major depression, including depressed mood, diminished interest, weight change, sleep disturbance, psychomotor changes, fatigue, feeling worthless, poor concentration, and recurrent thoughts of death.

Mood stabilizers – Any number of medications used to treat bipolar affective disorder or to prevent or limit mood instability in patients with recurrent unipolar depressive disorder. Can be associated with parkinsonism. Medications used as mood stabilizers include lithium, sodium valproate, carbamazepine, oxcarbazepine, and lamotrogine.

Definition and History

This article focuses on the clinical manifestations and management of depression in the context of parkinsonism. When parkinsonism and depression co-occur, the differential diagnosis includes a primary motor disorder, a psychiatric disorder, a medication side effect, or an interaction between these causes. Awareness of these relationships increases the likelihood of recognition, diagnosis, and treatment of both movement and mood disorders.

The term 'depression' refers to a mood state characterized by sad and gloomy emotions, but it is often used synonymously with the term 'depressive disorder.' Whereas frustration, embarrassment, sadness, grief, and demoralization are all potential emotions in an individual, depressive disorders are distinguished by their severity and impact or because they involve episodes of pervasive and persistent mood change accompanied by characteristic nonmood emotional, cognitive, and somatic signs and symptoms.

Parkinsonism refers to a group of motor symptoms and signs, including slowed movements (bradykinesia), resting tremor, and muscular rigidity. About 40% of patients with parkinsonism have idiopathic Parkinson's disease (PD), 20% have drug-induced parkinsonism (DIP), and 14% have Parkinson's-related neurodegenerative disorders (i.e., Parkinson's-plus syndromes). Importantly, DIP occurs in patients with or without preexisting movement disorders and can be mistaken for idiopathic PD. Alternatively, when there is underlying PD, DIP can present as new onset parkinsonism or exacerbate the existing motor signs. Parkinsonism is also associated with psychiatric disorders, age-related changes, environmental toxins, and infectious agents.

James Parkinson, in his 1817 *Essay on the Shaking Palsy*, asserted "the senses and intellect are uninjured" in the condition that eventually was to be called PD. Explicit associations between depression and PD were suggested by Pierre Janet in 1924, though he attributed mood changes to a psychological reaction. However, biological links between parkinsonism and depression were described in early medical writings. Parkinsonism, referred to as psychomotor retardation in the psychiatric literature, is a distinctive feature of depressive disturbances. Its similarities to PD stimulated research on basal ganglia abnormalities and its functional connections in major depression. For example, the slowed gait, limited gestures, hunched posture, expressionless face, and latent, quiet, and monotonous speech of major depression can be indistinguishable from the bradykinesia, hypokinesia, hypophonia, postural abnormalities, and hypomimia of nondepressed PD patients. Cognitive difficulties, fatigue, weight loss, and sleep disturbances also characterize both conditions.

Pathogenesis/Pathophysiology

Multiple lines of evidence suggest that depression in PD is related to the underlying disease, although psychological adjustment explains symptoms in some patients. Several studies show a higher lifetime prevalence of depression, with depression conferring a greater risk for developing PD. When evident before diagnosis of PD, depression occurs, on average, 4–6 years earlier. As early signs of PD can be overlooked when patients present with psychiatric complaints, such findings underscore the importance of initial and serial motor examinations for parkinsonism in adults with depression. After PD is diagnosed, occurrence of depression at all stages of PD

indicates that disability alone is not a cause of depression. Biological studies of PD-depression provide evidence for frontal–subcortical hypometabolism and disproportionate degeneration of ventral tegmental dopamine neurons and monoamine neurotransmitter systems (serotonin and norepinephrine). These findings form a basis for the treatment strategies.

Epidemiology/Risk factors

An estimated 40–50% of PD patients have depressive disturbances, although many are unrecognized or undertreated. About half of those affected have major depression and the remainder experience nonmajor forms of depression (minor depression, dysthymia, and subsyndromal depression, or major depressive episodes as a feature of bipolar disorder). There are no consistent disease-specific risk factors for depressive disturbances, other than PD itself. Greater cognitive impairment, female sex, and a personal history of depression before PD onset are associated with higher risk. Psychological factors may be relevant.

DIP is most commonly caused by dopamine-blocking antipsychotic agents, but all agents used to treat mood disorders are associated with DIP. In the general population, prevalence of DIP in response to antidepressants and other mood disorder treatments is unknown. In a series of PD patients, 4.5% had antidepressant-associated DIP, suggesting it as relatively uncommon. The likelihood of antidepressant-associated DIP is greatest with selective serotonin reuptake inhibitors (SSRIs), followed by imipramine-type medications, and then other antidepressants (e.g., the monoamine oxidase (MAO) inhibitor phenelzine, trazodone, and amoxapine). Valproate, a mood stabilizer, is underrecognized as a cause of DIP. Lithium also causes DIP. Antidepressants, lithium, and antipsychotics, can increase physiological tremor. Typically, improvement of depression is associated with a reduction in PD motor deficits and physical disability. Thus, motor and disability assessments before initiating psychiatric medications provide a baseline for identifying DIP, which may otherwise be difficult to identify in the context of preexisting and fluctuating motor deficits.

Research on psychopathology is limited, but depressive disturbances occur in all the Parkinson's-plus syndromes, that is, progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), multiple system atrophy (MSA), certain frontotemporal dementia (FTD) syndromes, and dementia with Lewy bodies (DLB).

Clinical Features and Diagnostic Criteria

Depressive disorders in PD resemble idiopathic depressive disorders; it is unclear whether PD-depression has a distinct symptom profile. Most commonly, and consistent with Diagnostic and Statistical Manual IV-Text Revision (DSM-IV-TR) criteria, depressive episodes involve a sad, blue or depressed mood, and anhedonia or withdrawal from one's usual interests. Not all patients experience sadness, leading some to contest they are 'not depressed.' Anhedonia, the experience of a reduced sense of pleasure in things or activities that ordinarily have that effect, is a core feature of depressive syndromes and frequently occurs in the absence of sadness. Other important emotions or ideational features include excessive and inappropriate feelings of guilt, feelings of failure, pessimism, beliefs of decreased self-worth, hopelessness, and helplessness. Anxiety and irritability are common, but have less specificity to depressive syndromes. Emotional blunting, or reduced emotional reactivity, is often observed. Several studies note high rates of anxiety and comorbid anxiety disorders.

Suicidal thoughts and behaviors were traditionally regarded as less common in PD relative to the general population. Recent reports refute this. Suicidal ideation or death ideation (the wish to die without intent to kill oneself) was present in up to 30% of patients in one series and associated with presence of major depression or more severe depressive symptoms. An international multicenter retrospective survey showed increased suicide risk associated with subthalamic nucleus deep-brain stimulation (DBS) in patients with PD as compared to the general population. Depression, being unmarried, and a history of impulse control disorders or dopaminergic medication abuse were independently associated with attempted suicides after DBS. Suicide attempts were also associated with younger age, younger age onset of PD, and a previous suicide attempt. Postoperative depression was the single factor associated with completed suicides.

In addition to mood changes, depressive syndromes involve persistent nonaffective changes that distinguish depressive episodes from nonpathological mood states. Among these are five of the nine DSM-IV-TR criteria for a major depressive episode (disturbances in sleep, appetite, energy or fatigue, psychomotor activity, or cognition). Because these symptoms occur in PD, mood disorders can be overlooked when symptoms are attributed to PD only and ideational features of depression are not elicited.

Overlapping clinical features account, in part, for nonrecognition of depression in PD patients or early PD in patients with depression, respectively. Occurrence of depression at all stages of PD suggests that depressive syndromes are not simply emotional reactions to the diagnosis or motor symptoms. Depressive disturbances also present as prodromal syndromes or early manifestations of PD, before its diagnosis is established and motor signs are subtle, if evident at all.

Drug-induced bradykinesia, rigidity, tremor, and hypomimia can be easily regarded as depressive signs. Thus, DIP is often unrecognized, though it is an important cause of imbalance, reduced dexterity, and embarrassment. This is especially the case for the elderly,

women, and individuals with central nervous system pathology or a family history of idiopathic PD. Important distinctions are that DIP is usually bilateral and tremor is less frequent (~35% vs. 80% in PD). Onset of DIP occurs acutely after drug exposure (within hours to days), subacutely (i.e., within weeks), or months to years after ongoing drug exposure. However, DIP usually resolves slowly, over several months, after withdrawal of the offending agent. Symptoms persist in patients with underlying PD.

Differential Diagnosis

Several mood disturbances in PD need to be distinguished from major and nonmajor depressive episodes. About 75% of patients with on–off motor fluctuations experience prominent mood fluctuations, usually depression or anxiety in the 'OFF' period. Hypomania or elation can also occur in the 'ON' state. Anxiety disorders, which often accompany depressive disorders, can be misdiagnosed as depressive disturbances. Emotional indifference and lack of initiative and curiosity define the presence of apathy in PD. Apathy is often a feature of depressive syndromes, but it can occur as an independent disorder. Cognitive impairment, whether mild or consistent with dementia, affects activity levels, and patients may appear apathetic. Up to 50% of patients have pathological crying that occurs as an independent symptom or as a feature of depressive disorders, delirium, or benzodiazepine use.

Depressive disturbances also occur in Parkinson-plus syndromes. In PSP, apathy and disinhibition are the most common psychiatric presentations in addition to depression, emotional lability with pathological laughter or crying (pseudobulbar affect), and irritability. Apathy in PSP is often mistaken for depression, which affects management. In CBD, depression is more common relative to its prevalence in PSP. Apathy, disinhibition, and delusions may co-occur with depression as separate syndromes. Psychiatric manifestations of MSA, a clinically heterogeneous group of Parkinson's-plus syndromes, have received limited attention. Affective disturbances occur, including early in the disease. Some series suggest that depression is less prevalent in MSA relative to PD. Clinically significant depressive symptoms, based on rating scale scores, are seen in up to 40% of patients, and impact quality of life.

FTD, a primary dementia syndrome characterized by behavioral changes and disinhibition, can involve parkinsonian signs. Apathy, disinhibition, euphoria, and behavioral changes are common. Depression and anxiety disorders occur less, although their rates may be higher in the primary progressive aphasia variant of FTD.

DLB, another primary dementia syndrome, is associated most commonly with parkinsonism and hallucinations, but other psychiatric disturbances can be present. Depression may be evident early in the course of DLB, and is now considered a supporting diagnostic criterion for DLB. In case series, prevalence of depression is greater in DLB as compared to Alzheimer's disease, but comparable to that in PD.

Diagnostic Work-Up/Tests

Evaluation of depression begins with a thorough history, diagnostic interview, and physical examination that also ascertains evidence of past psychiatric disturbances, even if untreated, and the role of medications, medication changes, surgery, or medical conditions in the clinical presentation. Even with nondemented patients, it is often useful to involve a caregiver or significant other as a source of collateral history about the patient's symptoms and changes in level of function from baseline. Assessment for current and past suicidal ideation or behavior is critical when depression is suspected. Diagnostic uncertainty, treatment-resistant depression, suicidal ideation, psychosis, and comorbid psychiatric conditions such as panic disorder or mania should prompt psychiatric referral. As a minimum, routine laboratory tests to rule out physical illnesses associated with mood changes include complete blood count (CBC), chemistry panel, thyroid profile, urinalysis, rapid plasma regain (RPR), and erythrocyte sedimentation rate (ESR). In nonpsychiatric practices, depression symptom screening tools can be used to facilitate depression detection and further inquiry into mood changes. No optimal instrument is identified; the Geriatric Depression Scale and Beck Depression Inventory are commonly used.

Management

Treatment for depressive disorders requires targeted and individualized approaches. Nonpharmacologic treatments include illness education, various forms of psychotherapy, rehabilitative strategies involving occupational, physical and speech therapies, and social support. The antiparkinsonian regimen should be optimized, especially if there are motor and mood fluctuations. Medical conditions or delirium should be addressed. Caregiver involvement enhances treatment compliance and provides additional perspectives on the patient's status and treatment response.

Psychiatric medications used to treat depression include the range of antidepressants. Evidence regarding pharmacological treatment of depressive disturbances in PD is still being gathered. Open-label studies of SSRIs suggest they are well-tolerated and efficacious, but methodologically limited placebo-controlled trials have failed to show their greater efficacy in PD. Recent well-designed

but brief (4–8 weeks duration) placebo-controlled trials in PD patients with major depression suggest that tricyclic antidepressants (nortriptyline and desipramine), which inhibit reuptake of serotonin and norepinephrine, were adequately tolerated and more effective than placebo in reducing depressive symptoms; SSRIs had delayed effectiveness (citalopram) or were no more efficacious than placebo (paroxetine). These findings contrast with usual clinical practice, which is to use SSRIs as first-line therapy because of the risk of cardiac conduction delays with tricyclic antidepressants. Trials of dual action nontricyclic antidepressants and SSRIs are underway and studies of other antidepressant classes are needed. For example, mirtazapine, a norepinephrine and serotonin antagonist, has side effects of increased appetite and sedation, and is often used when weight loss and insomnia are prominent symptoms.

Additional treatment strategies for geriatric depression have not been formally studied in PD. Electroconvulsive therapy, which improves parkinsonism, is used for severe depression with vegetative signs or psychosis. Mood stabilizers are used to treat bipolar disorder, augment antidepressants in treatment-refractory cases, or limit relapses in recurrent unipolar depression. Antianxiety medications, namely benzodiazepines, should be limited to short-term use, if at all. Atypical antipsychotics are used for troublesome hallucinations, delusions, or psychotic depression. Quetiapine is usually the first choice, and clozapine is the second option. Other antipsychotics are not well-tolerated in PD.

There are several important side effects and drug interactions with antidepressant treatment. First is the potential for hypertensive crisis or serotonin syndrome when antiparkinsonian monoamine oxidase inhibitors (selegeline and rasagaline) are used with antidepressants. However, clinical experience suggests that this effect is rare, consistent with the selective inhibition of MAO-B, not MAO-A, at antiparkinsonian doses, and that the combination is generally safe. Other common side effects include orthostasis, gastrointestinal upset, sedation, and the range of anticholinergic and benzodiazepine side effects, particularly confusion and increased fall risk. As discussed, parkinsonism can be aggravated by some antidepressants, lithium, sodium valproate, amoxapine, and antipsychotics.

Depression treatment in Parkinson-plus conditions involves similar strategies as for PD. Depression in PSP may be more treatment refractory, possibly because of the predominance of apathy. Antidepressants, though not always effective, and caregiver education are mainstays of treatment in CBD. Reported treatments in MSA include antidepressants and electroconvulsive therapy. Antidepressants are also used in DLB, but SSRIs, also used for behavioral disturbances, have variable effects on depression. Cholinesterase inhibitors may benefit apathy and anxiety in addition to cognition and psychosis.

Prognosis

Depression has a major influence on the clinical course of PD and related disorders. When unrecognized or incompletely treated, depression adversely affects motor deficits, function, cognition, quality of life, caregiver burden, and economic status as well as emotional well-being. In early PD, depression has greater influence than motor deficits as to when antiparkinsonian medications are started. Depression, along with cognitive impairment and psychosis, is more disabling than motor features as PD progresses. Adverse effects of depression are ameliorated by remission of the depressive episode, whether spontaneously or in response to adequate treatment.

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See also: Antidepressants and Movement Disorders; Bradykinesia; Bradyphrenia; Cognitive Assessments and Parkinson's Disease; Dementia, Movement Disorders; Depression and Parkinsonism; Drug-induced Movement Disorders; Executive Dysfunction; Hallucinations and Movement Disorders; Neuroleptics and Movement Disorders; Psychosis in Parkinsonism; Rating Scales in Movement Disorders; Serotonin Syndrome.

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Diffusion Tensor Imaging in Parkinson's Disease

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Glossary

Anisotropic diffusion – Diffusion that is directional in nature. High anisotropy equals high diffusion in one direction. Low anisotropy equal similar diffusion directions in all directions.
Fractional anisotropy – The degree to which diffusion is anisotropic. Fractional anisotropy of 1.0 represents planar diffusion in one direction, while fractional anisotropy of 0.0 represents completely random diffusion.
Mean diffusivity – The degree of diffusion irrespective of direction: translational diffusion.

Definition and History

Diffusion tensor imaging (DTI) is a magnetic resonance imaging (MRI) technique that measures the diffusion of hydrogen. This technique has been applied to studies of cardiac function and orthopedic integrity. However, its most common use is in the study of cerebral tissue integrity. In 1995, Peter Basser published his seminal article describing the principles of DTI. The technique is based on the fact that changes in cerebral integrity induce changes in brain water content. As MRI is based on excitation and relaxation of hydrogen atoms, this altered water content affects the MRI signal. DTI imaging makes it possible to examine alterations in the microstructure of cerebral tissue in vivo; in addition to volumetric changes, it can determine whether the remaining normal appearing cerebral matter is really normal.

Molecular Diffusion and DTI

DTI is based on sensitizing the MR signal to the movement of hydrogen on the order of several microns through the application of diffusion-weighted gradients in at least six noncollinear gradients simultaneously, and measuring the direction and magnitude of hydrogen movement. The application of six noncollinear gradients allows for the examination of diffusion characteristics irrespective of the head position. The three-dimensional geometry of the diffusion in a particular volume element (voxel) can be described by a mathematical construct called a 'tensor' that can be represented by a 3×3 matrix. From the diffusion tensor in each voxel, one can derive three eigenvalues defining the magnitude of the diffusion system and the three associated eigenvectors (λ_1, λ_2, and λ_3) that describe the direction of the diffusion system. The average of the three eigenvalues represents the mean molecular motion (mean diffusivity) that is affected by the barriers to diffusion, but does not provide information on the directionality of the diffusion. Based on the ratio of the three eigenvectors, the intravoxel direction of hydrogen diffusion can be determined. This scalar measure is termed fractional anisotropy (FA) and can range from 0 to 1, with 0 indicating completely random diffusion (isotropic diffusion) and 1 representing completely directional diffusion (anisotropic diffusion). CSF has extremely low FA values, because hydrogen is free to diffuse in any direction. Gray matter has low FA, because cellular structures (e.g., cell membrane, organelles) impede the free diffusion of hydrogen, but these structures do not promote organized, directional diffusion. Highly organized white matter tracts have high FA, because hydrogen diffusion is directionally constrained by the tract's cellular organization. Tractography is a technique that utilized the measures of intervoxel directional diffusion to develop models of cerebral white matter pathways.

The individual eigenvalues generated from the tensor model of diffusion may provide additional information about specific cellular structures. High FA is associated with a large primary eigenvalue (λ_1) and smaller secondary and tertiary eigenvalues (λ_2 and λ_3). Decreases in λ_1 are associated with axonal damage in nonhuman models, while increases in the average of λ_2 and λ_3 are associated with damage to the myelin sheath surrounding

axons. These difference in axial diffusion (λ_1) and radial diffusion (average of λ_2 and λ_3) may be applicable to humans, although no direct testing of this has been completed to date.

Interpretation of DTI in Neural Tissue

When the barriers to free diffusion of hydrogen degenerate, mean diffusivity increases. When that degeneration occurs in structurally organized tissue, such as white matter tracts, mean diffusivity increases and FA decreases because of a loss of the directionality of diffusion. When the damage occurs in white matter, the interpretation of DTI results is fairly clear: decreased FA represents a loss of organized structure. However, when the damage occurs in gray matter, the interpretation of changes in FA is not very straightforward. Damage to gray matter could result in increased gliosis, astrocytic alterations, and other necrotic changes. Such changes could result in a decreased FA because of the increased diffusion direction-potential in the three planes, or in increased FA because of increased structural uniformity.

DTI in Parkinson's Disease

Studies using DTI in Parkinson's disease (PD) have examined both white matter and gray matter, and have investigated motor, cognitive, and affective function as well as differential localization of brainstem nuclei. Most of the DTI studies are with patients, although a few have used nonhuman models of PD. For example, one study used a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) intoxication model in rodents to study changes is the substantia nigra. This study found that FA in the substantia nigra was significantly lower in the animals treated with MPTP compared with control animals.

Similar findings in humans have recently been reported. In one study, de novo (untreated) patients with PD were imaged using DTI, along with healthy controls. Regions-of-interest were drawn on the rostral, middle, and caudal substantia nigra, and DTI values of FA extracted from these regions. The study reported 100% sensitivity and specificity for differentiating PD from controls.

These studies applied DTI to the examination of the substantia nigra, a gray matter structure. A reason for a decrease of directional diffusion (e.g., decreased FA) in this gray matter structure is not immediately apparent, because there is little organized structure in healthy gray matter to be disrupted by PD. The decrease in FA may represent inclusion of both gray and white matter in the regions of investigation, with an associated decrease in the organization of the included white matter. Indeed, the average FA value in the human studies far exceeded the usual value reported in human gray matter. However, the studies demonstrated this change in FA with exposure of MPTP in the rodent and the presence of PD in humans, and therefore, this remains an active area of research.

DTI examinations of white matter integrity in PD have not presented a coherent picture. Some studies have found a decreased FA in selected regions along the nigral-striatal tract and supplemental motor area and anterior cingulum of the frontal lobes. However, another study found whole brain FA to be increased in patients with PD. The reasons for these conflicting finding are not known, but probably relate to the differences in PD samples, DTI scanning parameters, and methods of assessing FA (region of interest vs whole brain).

DTI in the Study of Nonmotor Symptoms of PD

An interesting application of DTI in patients with PD is the study of nonmotoric symptoms. DTI has been used to examine the relationship between regional diffusion and cognitive function in PD. One study found that parietal FA inversely correlated with performance on the Wisconsin Card Sorting test, a measure of concept formation and cognitive flexibility. The authors postulated that the decreased FA in parietal regions reflected impairments in the frontal/parietal network involved in executive function. A study of Parkinson's disease dementia (PDD) found that decreased FA in the posterior cingulum was associated with impaired cognitive status.

Another nonmotoric symptom in patients with PD is affective status. Diffusion differences between depressed and nondepressed patients with PD were examined in the orbital frontal, prefrontal, occipital, parietal, posterior cingulum, and anterior cingulum. The only region that demonstrated a significant difference was in the anterior cingulum. The authors suggest that the decreased FA in the anterior cingulum may reflect impaired functional status that could be responsible for the increased apathy in the depressed patients.

Conclusion

DTI is an evolving MRI technique that shows promise in the study of PD. Early results suggest that DTI may be used as a proxy measure of substantia nigra integrity, including the nigro-striatal tract. Additionally, decreased in organized diffusion, as measured by FA, may be related to the nonmotoric symptoms of PD, including cognitive dysfunction and depression. Advances in DTI technology, such as increased spatial resolution and advanced analytic methodologies, ought to provide additional applications for the study of PD.

See also: Neuroimaging, Parkinson's Disease; PET Imaging in Movement Disorders; SPECT Imaging in Movement Disorders.

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Direct Pathway

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Glossary

Basal ganglia – A group of interconnected subcortical nuclei, including the striatum, globus pallidus, subthalamic nucleus, and substantia nigra, that play a role in motor, limbic, and cognitive functions.

Chorea – Term derived from the Greek that means 'a kind of dance.' Involuntary movements characterized by irregular non-repetitive and non-rhythmic contractions of muscles. Primary motor deficit seen in patients with Huntington's disease.

Dopamine – A monoamine neurotransmitter produced mainly in the substantia nigra and ventral tegmental area, known to be important for motor control, reward, and learning; it stimulates two families of receptors: the excitatory D1 family and the inhibitory D2 family.

GABA – Gamma-aminobutyric acid; the main inhibitory neurotransmitter in the central nervous system.

Globus pallidus – Brain structure in the telencephalon part of the basal ganglia circuitry. Comprises an external and an internal segments, respectively called GPe and GPi. Use GABA as neurotransmitter. GPi is one of the two output structures of the basal ganglia to the thalamus and brainstem.

Huntington's disease – Genetic neurodegenerative disorder named after George Huntington who described the disease in 1872. Results from mutation in the gene that encodes for the protein Huntingtin. Characterized by severe loss of neurons in the striatum and the cerebral cortex. The main motor symptoms include uncoordinated involuntary jerky movements of different body parts (chorea) and cognitive deficits. Can be diagnosed by genetic testing.

Parkinson's disease – The second most common neurodegenerative disease, after Alzheimer's disease, characterized by severe, often idiopathic, degeneration of the nigrostriatal dopaminergic projection. Symptoms include bradykinesia, akinesia, muscle rigidity, resting tremor, cognitive impairment, and depression.

Putamen – Large core structure of the basal ganglia located in the telencephalon. With the caudate nucleus, it forms the dorsal striatum. Known as the main entry station for sensorimotor information to the basal ganglia circuitry.
Subthalamic nucleus – Almond-shaped brain nucleus located at the basis of the thalamus considered as a key structure in the basal ganglia circuitry. Neurons use glutamate as transmitter. Lesion of this nucleus alleviates Parkinson's disease motor symptoms.

Definition and History

The direct pathway is one of the two major tracts of the basal ganglia circuitry. It received its name because it consists of a single 'direct' projection from the striatum, known as the main basal ganglia input nucleus, to the internal globus pallidus (GPi) and substantia nigra pars reticulata (SNr), the two basal ganglia output nuclei. This system runs in parallel with the 'indirect pathway,' which conveys information from the striatum to the output nuclei, indirectly via the external globus pallidus (GPe) and the subthalamic nucleus (STN).

Striatal Direct Pathway Neurons

The striatum contains one main type of projection neurons which comprises ~90% of the total striatal neuronal population: the GABAergic medium spiny neurons (MSN). The dendrites of these neurons are covered with spines targeted by glutamatergic afferents from the cerebral cortex and thalamus. Dopaminergic inputs from the substantia nigra pars compacta (SNc), serotonergic afferents from the dorsal raphe, as well as GABAergic and cholinergic inputs from interneurons and MSN axon collaterals represent the bulk of other inputs that impinge upon striatal MSNs. The corticostriatal projection is by far the main source of information to striatal MSNs. This projection is topographically organized such that inputs from sensorimotor cortices terminate in the posterior putamen, projections from associative cortical areas innervate predominantly the caudate nucleus and the anterior putamen, and limbic information is conveyed to the ventral striatum.

Regardless of their location within the striatum, MSNs can be divided equally into two groups based on their distinct chemical phenotype and projection targets. Direct pathway (GPi/SNr-projecting) MSNs preferentially express D1 dopamine receptors and the neuropeptides substance P and dynorphin, whereas indirect pathway (GPe-projecting) MSNs preferentially express D2 dopamine receptors, adenosine A_{2A} receptors, and the neuropeptide enkephalin. Other subtle, though functionally important, differences exist in the physiology and morphology of direct and indirect pathway MSNs. Indirect pathway MSNs seem to be more responsive to cortical inputs than direct pathway MSNs, as shown by their immediate-early gene expression following microstimulation or pharmacological disinhibition of the motor cortex. Another difference is that striatal cholinergic interneurons often receive axon collaterals from direct, but not indirect pathway MSNs.

Segregation of Direct vs. Indirect Pathway Neurons

Despite clear phenotypic and hodologic differences, the degree of segregation between the two groups of striatal MSNs may not be as clear-cut as originally thought. The axonal projections of many direct pathway MSNs that arborize extensively in the GPi and SNr send axon collaterals to the GPe. The reverse also holds, that is, some indirect pathway MSNs that project preferentially to the GPe send axon collaterals to the GPi and SNr. The complete segregation of D1 and D2 dopamine receptors between direct and indirect pathway MSNs remains a subject of debate because a certain percentage of striatal projection neurons express mRNA for both receptor subtypes. Direct and indirect pathway MSNs communicate with each other via local axon collaterals in the striatum; the connections from D2- to D1-containing MSNs being more common than connections from D1- to D2-positive neurons.

Imbalanced Activity of Direct and Indirect Pathways in Parkinson's Disease

The concept of direct and indirect pathways has been the basis for significant development in our understanding of basal ganglia pathophysiology and the revival of surgical therapies for Parkinson's disease in the early 1990s. In patients with PD, there is a progressive degeneration of the dopaminergic projection from the SNc to the striatum. Because of the differential expression of dopamine receptors between direct and indirect pathway neurons, the loss of dopamine has an opposite functional effect on the activity of direct or indirect pathway neurons, creating an imbalance in the basal ganglia circuitry. Direct pathway MSN activity is decreased, while indirect pathway MSN activity is increased following striatal dopamine depletion. Together, these changes result in decreased GABAergic inhibition from the striatum and increased glutamatergic drive from the STN upon basal ganglia output nuclei. These changes increase the GABAergic tone from the GPi/SNr upon thalamocortical neurons and brainstem nuclei, known as the main recipient regions

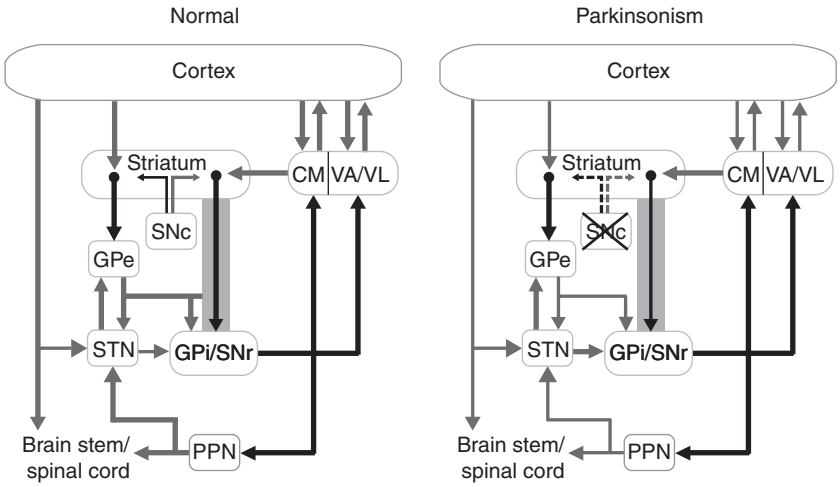

Figure 1 Schematic diagram of the basal ganglia under normal and parkinsonian conditions. Black arrows represent inhibitory projections, and gray arrows represent excitatory projections. In the parkinsonian condition, the weight of the arrows represents the level of neuronal activity relative to the normal state. The inhibitory striatofugal connection that makes up the direct pathway is shaded in gray. CM, centromedian thalamic nucleus; GPe, external globus pallidus; GPi, internal globus pallidus; PPN, pedunculopontine nucleus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; VA/VL, ventral anterior/ventral lateral thalamic nuclei. Adapted from Wichmann and DeLong (2003) Pathophysiology of Parkinson's disease: The MPTP primate model of the human disorder. *Annals of the New York Academy of Sciences* 991:199.

of basal ganglia outflow. The resulting decreased thalamocortical activity likely contributes to the cardinal motor symptoms of parkinsonism (**Figure 1**).

Morphological changes in direct and indirect pathway MSNs may also contribute to their pathological activity in parkinsonism. In human parkinsonians and animal models of PD, the depletion of striatal dopamine is accompanied by a significant loss of striatal spines, the main recipient of glutamatergic and dopaminergic inputs in the striatum. Although some authors have suggested that this loss of spines is selective for D2-containing neurons in rodents, these observations have not been confirmed in the nonhuman primate model of parkinsonism or patients with PD.

Direct Pathway Neurons and L-DOPA-induced Dyskinesia

The current pharmacological treatment for PD is based on dopamine replacement therapy using either dopamine precursors like levodopa or direct dopamine receptor agonists. However, such chronic therapy often results in the progressive development of involuntary movements known as dyskinesias. The supersensitivity of the D1 dopamine receptors and the aberrant activation of downstream ERK1/2 MAP kinase in direct pathway MSNs is considered as a potential substrate for the development of L-DOPA-induced dyskinesias. Another, less-studied receptor likely to be involved in the development of dyskinesia is the dopamine D3 receptor, which is co-expressed with D1 in direct pathway MSNs. Although it is expressed at low levels in animal models of parkinsonism, its expression is greatly increased in individuals with levodopa-induced dyskinesias. Not only does this receptor's expression mirror the development of dyskinesias, but D3 antagonists or partial agonists attenuate dyskinesias, further implicating the direct pathway in this neuropathic phenomenon.

Pathology of Direct and Indirect Pathway Neurons in Huntington's Disease

Huntington's disease (HD) is a genetic disorder in which a polyglutamine repeat is expanded in the N-terminal region of the huntingtin protein. This mutation causes protein aggregation and death of striatal MSNs (as well as cortical neurons), resulting in chorea, psychiatric disorders, cognitive decline, and eventually death. As is the case with Lewy bodies in Parkinson's disease; it is not clear whether the protein aggregation in HD actually causes neuronal death, or if it is a protective mechanism to prevent cell death. Although the cellular mechanisms underlying neuronal degeneration in HD are not well understood, different studies suggest a differential susceptibility of direct and indirect pathway MSNs.

Postmortem studies from HD brains showed that direct pathway neurons are less sensitive to degeneration than indirect pathway neurons. This preferential loss of the striatopallidal projection could create a situation opposite to that in PD, that is, an increased activity of the direct pathway relative to a decreased transmission

along the indirect pathway, which could possibly underlie the choreic and unwanted movements seen in HD. These findings corroborate recent data showing that dopamine can enhance activation of the proapoptotic JNK/c-Jun pathway and potentiate huntingtin aggregation in cultured striatal MSNs transfected with pathogenic huntingtin; an effect that can be blocked by D2, but not D1, dopamine receptor antagonists. On the other hand, dopamine and glutamate act synergistically to cause aberrant elevations in intracellular calcium levels, and thus, apoptosis in striatal MSNs; an effect blocked by D1, but not D2, receptor antagonists. Both mechanisms may contribute to striatal cell death in HD.

See also: Basal Ganglia; Basal Ganglia, Functional Organization; Chorea; Dopamine; Dopamine Receptors; Dopamine Transporter: Aging and Parkinson's Disease; GABA and Movement Disorders; Huntington's Disease; Indirect Pathway; Parkinson's Disease: Definition, Diagnosis, and Management; Substantia Nigra; Subthalamic Nucleus.

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Dopa-decarboxylase Inhibitors

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Glossary

Area under the curve – An indirect but standard measure of how long an active drug remains in serum or plasma after dosing. It is the area underneath a plot of concentration (*y* axis) versus time (*x* axis).

Biotransformation – Pharmacological term used to describe the metabolic and spontaneous conversion of a drug from its administered state, usually to an inactive state.

C_{max} – The highest concentration achieved in serum or plasma.

Formulation – All the components (drugs, inert filler, and active filler that may regulate the rate of release of a drug) that are used to make a pill.

$t_{1/2}$ or half life – The time it takes for one half of the drug to be eliminated from serum or plasma.

The advent of levodopa for the treatment of Parkinson's disease (PD) represented a significant step in the management of neurological disease. Its effect produced miraculous therapeutic results in many patients. Unfortunately, levodopa therapy was fraught with side effects and involved oral delivery of gram quantities of drug, making administration difficult for many PD patients. The primary side effects were nausea, vomiting, and epigastric distress as well as cardiovascular disturbances, including hypertension, orthostatic hypotension, and dysrhythmias (sinus tachycardia and atrial and ventricular extrasystoles). These side effects were primarily a result of peripheral conversion of administered levodopa to dopamine (DA). Because of the prevalence and severity of these side effects, levodopa was titrated up slowly delaying the effective therapeutic efficacy. However, even when therapeutic benefit was realized, gastrointestinal and cardiac side effects were often present, but tolerated.

Udenfriend and colleagues (1966) were the first to demonstrate that α-methyldopahydrazine (an aromatic amino acid decarboxylase (AAAD) inhibitor (AAADI)) increased catecholamine content in the brains of animals following levodopa treatment. The following year, Birkmayer is credited with the first coadministration of benserazide and levodopa to patients demonstrating increased efficacy and reduced side effects. Bartholini et al. is generally credited with the concept that AAADs worked because they predominantly inhibited AAAD in the periphery thereby making levodopa more available to brain. The reduction in peripheral side effects, the ease with which dosage could be escalated, and the enhancement of levodopa potency produced by the peripheral AAADIs led to a rapid adoption of their use in the management of PD, and today, levodopa is not prescribed in the absence of an AAADI.

Carbidopa and Benserazide

The two AAADIs in use today are carbidopa (L-α-hydrazino-α-methyl-β (3,4 dihydroxybenzene) propionic acid; MW 244.25) and benserazide (2′-(2,3,4-Trihydroxybenzyl)-DL-serinohydrazide; MW 293.71; **Figure 1**). Carbidopa was first formulated with levodopa as Sinemet by Merk Sharpe and Dohme, while benserazide with levodopa was called Modopar (Roche). The two AAADIs are structurally somewhat similar, although benserazide used clinically contains both the levo- and dextrorotary form, whereas carbidopa is exclusively levorotary. The utility of these drugs is in their peripheral inhibition of AAAD when combined with levodopa. Both the drugs are potent competitive inhibitors of AAAD in both the periphery and brain. However, carbidopa does not cross the blood brain barrier (BBB) under normal circumstances, whereas benserazide can be detected in brain following high-administered doses. At what dosages benserazide begins to enter brain is unknown. However, recent studies from my laboratory suggest that the BBB may not be intact in PD patients and therefore, even carbidopa may enter brain.

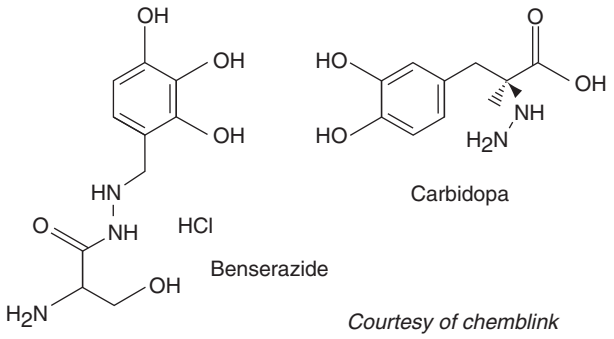

Figure 1 Structures of the two aromatic amino acid decarboxylase inhibitors used clinically.

Distribution of AAAD

Aromatic-L-amino acid decarboxylase (EC 4.1.1.28) is ubiquitously distributed throughout the body and brain where it decarboxylates aromatic amino acids for use in metabolism and protein synthesis. Several aromatic amino acids, including phenylalanine, histidine, tryptophan, and tyrosine, are taken in through the diet and subsequently biotransformed by enzymes, including AAAD, to substances needed by the body. AAAD is essential, although not normally rate limiting, for the conversion of DOPA to dopamine (DA; and also norepinephrine and epinephrine given their common anabolic pathways), 5-hydroxytryptamine (5HTP) to serotonin (5HT), and several trace amines (e.g., octopamine and phenylethylamine) in both the periphery and brain. The activity of AAAD is under transcriptional and posttranscriptional regulation and is upregulated by DA antagonists and downregulated by DA agonists and chronic levodopa. Splice variants exist for AAAD and may explain differential responses by some patients to AAADI treatment. Pyridoxyl-5-phosphate, the active form of pyridoxine (one of the vitamin B6 group), is a cofactor for AAAD.

AAAD is found in the cells lining the GI tract, the liver, pancreas, kidney, heart, and peripheral nerves. It is also found in the endothelial cells of blood vessels and in neurons and astrocytes within the CNS. Since AAAD is present in the GI wall, liver, and endothelial cells, the oral administration of levodopa is subject to a significant first pass effect. The presence of AAAD in endothelial cells that compose the BBB is particularly important, given levodopa's need to enter the brain for its anti-Parkinson's effect. The highest concentrations of AAAD are found in the kidney, followed by the liver and heart.

Tritiated distribution studies reveal that 40–70% of carbidopa and 66–74% of benserazide are absorbed from the gut. Both cross into placenta and breast milk. Both the AAADs undergo spontaneous biotransformation to substituted quinones in the GI tract. Peak plasma levels are generally realized within one hour for both inhibitors, although this is highly variable. Metabolic biotransformation involves side-chain degradation as well as glucuronide conjugation. The half-life for carbidopa is 2–3 h and somewhat less for benserazide (1.5–2.5 h). Approximately 30% of both carbidopa and benserazide are excreted unchanged primarily leaving only metabolites present in the urine after 6 h. Fecal excretion is more prevalent for carbidopa and its

metabolites than benserazide, although both are highly variable. Thirty-six percent of carbidopa is bound to serum proteins.

Efficacy of AAADIs

The coadministration of AAADIs together with levodopa produces greater absorption, reduced first-pass effect, and increased entry into brain. Central efficacy of levodopa is generally increased 4–5-fold in the presence of AAADIs. Although levodopa is absorbed from the gut via the large neutral amino acid facilitative transporter (LAT1), its availability for transport is dependent upon decarboxylation that occurs in the GI tract. By inhibiting AAAD, the AAADIs increase LAT1 substrate availability. Similarly, inhibition of AAAD in liver and the rest of the body increases the amount of levodopa available for transport across the BBB by LAT1 found in endothelial cells in the BBB. As a result, a significantly larger fraction of levodopa is available for entry into the brain in the presence of AAADIs. Since AAADIs at administered doses used clinically do not enter the brain in the presence of an intact BBB, levodopa is transported into brain where it can be decarboxylated to DA by AAAD present in neurons and astrocytes.

The AAADIs competitively inhibit AAAD in a dose-dependent fashion. Prior to the advent of AAADIs, inhibition of AAAD was achieved somewhat by depleting pyridoxine in the patient's diet, although the clinical benefit was always controversial. This approach is not needed if AAADIs are coadministered with levodopa. Both the AAADIs have longer plasma half-lives than levodopa, and as a result, accumulate over the day under the multiple daily dosing regimens generally used clinically. Initial administration of low doses of the combination formulation can result in inadequate AAAD inhibition resulting in peripheral side effects. This problem can be averted by prescribing a higher ratio of AAADI/levodopa in the combination formulation. Carbidopa is available as a monotherapy to supplement decarboxylase inhibition when patients exhibit peripheral side effects following combination therapy.

Toxicology

At dosages used clinically, AAADIs have no observable pharmacological actions in humans. Similarly, acute challenges in animals are extremely safe with no discernable changes in cardiovascular, renal, GI, or CNS function. Moreover, very few alterations are observed acutely even with extremely high doses (greater that 1000 mg/kg). Chronically, at extremely high doses, carbidopa reduces locomotor function slightly and can produce weight gain, while benserazide at chronic high doses was associated with fatty degeneration of the liver and skeletal changes. However, it is important to appreciate that the doses used in these studies were more than 100-fold higher than those used clinically.

Clinical Effects of AAADI on Levodopa

The primary objective for the use of AAADIs in combination with levodopa is to reduce peripheral side effects and increase central efficacy. This has been clearly and repeatedly demonstrated. Introduction of the combination formulation led to a significant reduction in the amounts of levodopa needed to produce anti-Parkinsonian effects (~4–5-fold reduction), providing significant benefit to patients whose swallowing capability was compromised by disease. Animal studies revealed that concomitant AAADI administration led to a ten-fold increase in brain DA, likely reflecting the significant reductions in first-pass effect, reduced biotransformation outside of the portal system, and inhibition of AAAD in the BBB. The reduced peripheral conversion of levodopa to DA in the periphery is also associated with significant reductions in nausea, vomiting, and epigastric distress. However, the addition of an AAADI to the treatment regimen must still be cautiously titrated since nausea and vomiting are still produced, albeit dose escalation can be achieved much more quickly because of the AAADI. Most importantly, AAADIs significantly attenuated the cardiovascular side effects associated with levodopa monotherapy, including tachycardia, hypertension, and arrhythmias. Interestingly, chronic treatment with levodopa monotherapy was well known to produce hypotension following an initial hypertensive phase that lasted for up to an hour. The addition of AAADIs dramatically attenuated the hypertensive effects, but had little effect on hypotension, suggesting that the later was centrally mediated.

When levodopa is combined with carbidopa or benserazide, the optimal ratios for therapeutic benefit (i.e., levodopa/AAADI) are 10:1 and 4:1, respectively. There will always be patients who require AAADI supplementation in which case carbidopa (Lodosyn) can be added to the regimen. Problems with inadequate AAADI are more prevalent early in therapy when lower doses of levodopa are required. Several studies have shown that daily levels of carbidopa greater than 75–160 mg failed to produce further AAAD inhibition (100 mg daily is the general rule of thumb). When only low levels of levodopa are required as part of the therapeutic regimen, the levels of AAADI may not be adequate for effective AAAD inhibition. As the disease progresses, however, the higher administered doses of levodopa are associated with larger daily dosages of carbidopa, and because of its longer half-life, the 100 mg daily target is more readily achieved. However, this is not necessarily true of benserazide, because it crosses the BBB as plasma levels get higher. The level at which this occurs

has not been firmly established, but doses as high as 400 mg daily have been used without untoward CNS effects.

Carbidopa's effect on the peripheral kinetics of levodopa have been highly studied. C_{max} for levodopa is increased and achieved more quickly translating into a larger area under the curve. In addition, the half-life for levodopa is increased significantly when carbidopa is coadministered. Similar findings have been observed with benserazide, although there is controversy as to whether the half-life is significantly extended. Regardless, both the AAADIs smooth the levodopa dose–response curve and reduce individual variation.

Extended Release Formulations

The advent of extended release formulations of levodopa/AAADIs has reduced dosage intervals, further improved the smoothing of the plasma curves, and extended the duration for which levodopa levels remain within the therapeutic window. The efficacy of the AAADIs within these formulations, as is true of all extended/delayed release formulations, is dependent upon dissolution rates within the GI tract, and individual patient variation can always contribute to poor patient response.

Combination Therapies with Catechol-O-methyl Transferase Inhibitors

The most recent addition to the levodopa formulation has been the addition of the catechol-*O*-methyl transferase (COMT) inhibitor entacapone to the levodopa/carbidopa formulation (Stalevo). When levodopa is administered with benserazide, entacapone can be added on as an adjunctive agent. In the presence of an AAADI, levodopa is driven through an otherwise trace metabolic pathway involving COMT. Because AAAD is ubiquitously distributed and has high activity for levodopa, most levodopa is biotransformed to DA. However, when an AAADI is coadministered, levodopa biotransformation to DA is inhibited leaving more levodopa substrate available for COMT, which converts levodopa to 3-*O*-methyldopa (3OMD). Numerous studies demonstrated that 3OMD accumulation can compete with levodopa for access to brain via competitive inhibition for the large neutral amino acid transporter although the therapeutic implications within the context of the number of large neutral amino acids taken in by diet are controversial. Regardless, the addition of a COMT inhibitor to the therapeutic regimen is well documented to further increase the availability of levodopa to the brain and to enhance C_{max} of levodopa, while smoothing plasma levels even more so than that seen with only the addition of an AAADI.

See also: Dopamine; Levodopa.

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Dopamine

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Glossary

Catechol-*O*-methyl transferase (COMT) – One of several enzymes that degrade catecholamines such as dopamine, epinephrine, and norepinephrine.
Monoamine-oxidase inhibitor (MAO) – Enzymes that catalyze the oxidation of monoamines, found bound to the outer membrane of mitochondria in most cell types in the body.
Neurotransmitter – Chemicals that relay, amplify, and modulate signals between a neuron and another cell. Neurotransmitters are packaged into synaptic vesicles that cluster beneath the membrane on the

presynaptic side of a synapse and are released into the synaptic cleft, where they bind to receptors in the membrane on the postsynaptic side of the synapse.
Parkinson's disease – Neurodegenerative disease of the brain characterized by degeneration of the nigrostriatal system, resulting in tremor, bradykinesia, rigidity, and postural reflex abnormalities.

Dopamine (DA) is a member of the small molecule neurotransmitter class of biogenic amines found primarily in the CNS, but also in the periphery. It is the most studied neurotransmitter (based on the number of Pubmed citations) reflecting its role in numerous CNS diseases and disorders. Thus, DA function is centrally involved in Parkinson's disease (PD), schizophrenia, attention deficit/hyperactivity disorder (AD/HD), Gilles de la Tourette's syndrome, Huntington's disease, prolactin secretion, emesis, the sense of smell, and drug dependence. Central DA likely also plays somewhat of a role in depression, obsessive/compulsive disorders, and learning. In the periphery, DA regulates pyloric sphincter tone and gastric motility, light–dark adaptation in the retina, vascular flow to the kidney, hypoxic drive in the carotid body, and autonomic and cardiac function. Dopamine is a highly conserved neurotransmitter and is found in numerous phyla, including worms, fruit flies, and snails.

DA Pathways

There are four major dopaminergic systems in the human brain (**Table 1**). The nigrostriatal pathway is by far the largest and accounts for 80% of the brain's DA. Thus, dopaminergic fibers course primarily from the substantia nigra pars compacta, and to a significantly lesser extent from the substantia nigra (SN) reticulata, via the medial forebrain bundle to the striatum (caudate and putamen). Lesser projections in this pathway innervate the globus pallidus. This pathway predominantly regulates motor activity. The mesolimbic pathway contains dopaminergic fibers coursing from DA cell bodies in the ventral tegmental area (VTA; located medial to the SN), and to a lesser extent from medial regions of the SN and retrorubral area, to the nucleus accumbens, anterior cingulate cortex, septum, hippocampus, amygdala, nucleus of the diagonal band, and anterior olfactory nucleus. These target structures are primarily limbic in nature and thus point to dopamine's involvement in limbic function. The third pathway is the mesocortical. It projects predominantly from the VTA to the anteromedial frontal, orbitofrontal, suprarhinal, and other cortical areas. This pathway regulates cognitive processing. The final pathway is the tuberoinfundibular/incertohypothalamic tract. Dopaminergic fibers from the periventricular and arcuate nuclei of the hypothalamus project into the median eminence of the hypothalamus where they release DA into the perivascular space, which then circulates to the lactotrophs in the anterior pituitary in a paracrine fashion to inhibit their secretion of prolactin. DA is thus prolactin inhibitory factor (PIF). Other fibers in the hypothalamus project to the anterior and periventricular hypothalamus as well as the septum and medial preoptic area where they may participate in the regulation of gonadotropin releasing hormone and corticotropin releasing hormone. Given that drugs affecting DA receptors currently lack regional/target specificity, pharmacotherapy designed to affect one system generally affects all of these systems, leading to unwanted effects.

DA Function

Dopamine is said to perform a 'gating' function. As is true of the other biogenic amines as well as acetylcholine, fibers

Table 1 Primary dopaminergic pathways in the brain

Pathway	*Area of origin*	*Target structures*	*Primary function*
Nigrostriatal	Substantia nigra in midbrain	Caudate and putamen (striatum)	Motor control
Mesolimbic	Ventral tegmental area, medial nigra and retro-rubral area	Nucleus accumbens, anterior cingulate cortex, septum, hippocampus, amygdala, nucleus of the diagonal band and anterior olfactory nucleus	Limbic regulation
Mesocortical	Ventral tegmental areas	Anteromedial frontal, orbitofrontal, suprarhinal and other cortical areas	Cognitive processing
Tuberoinfundibular/ incertohypothalamic tract	Periventricular and arcuate nuclei of the hypothalamus	Median eminence, the anterior and periventricular hypothalamus as well as the septum and medial preoptic area	Prolactin inhibitory factor and regulation of gonadotropin releasing hormone and corticotropin-releasing hormone (CRH)

from the bed nuclei for these small molecule neurotransmitters mostly bypass thalamic circuitry to affect the passage of electrical activity through their target structures. Thus, in the striatum DA probably affects the flow of electrical activity emanating from the glutaminergic corticostriate pathway to the globus pallidus, thalamus, and eventually the frontal cortex. This somatotopically highly organized parallel pathway is likely designed to progressively focus the excitation of upper motor neurons (corticospinal track) to facilitate only those motor units needed for an intended movement. I have always viewed dopamine as playing a center-surround function in the striatum enabling the selected group of glutaminergic pathways needed for an intended movement while inhibiting surrounding nonnecessary fibers to ensure appropriate movement; thus a gating function. Too little DA, as occurs in PD, precludes glutaminergic output, leading to hypokinesia; too much DA does not provide adequate center surround function, leading to the involvement of additional, unneeded nearby motor circuits in the movement, resulting in dyskinesias. A similar function may be assumed in the mesocortical pathway where too little DA leads to bradyphrenia while excess DA activity, as is thought to occur in schizophrenia, leads to disjointed thinking.

DA Biochemistry

First identified by Arvid Carlsson in 1952, DA is the end-product of synthesis from tyrosine (**Figure 1**). Tyrosine is a nonessential amino acid that is either taken up into the DA neuron from the diet or synthesized intraneuronally from the essential amino acid phenylalanine. The fact that tyrosine is synthesized from the large neutral amino acid phenylalanine is interesting, given that the use of levodopa in the management of PD utilizes the large neutral amino acid pump (LAT1) to gain access to circulation from the gut and to gain access to the brain from the vasculature. Thus, levodopa treatment, although it bypasses the tyrosine synthetic step, may inhibit the uptake of phenylalanine and thereby deprive dopaminergic and noradrenergic neurons of necessary amino acid precursor. Tyrosine is converted into dihydroxyphenylalanine (DOPA) by the rate-limiting enzyme tyrosine hydroxylase (TH) in the presence of the cofactor tetrahydrobiopterin, which is also required in the production of tyrosine from phenylalanine, as well as in the synthesis of serotonin and nitric oxide.

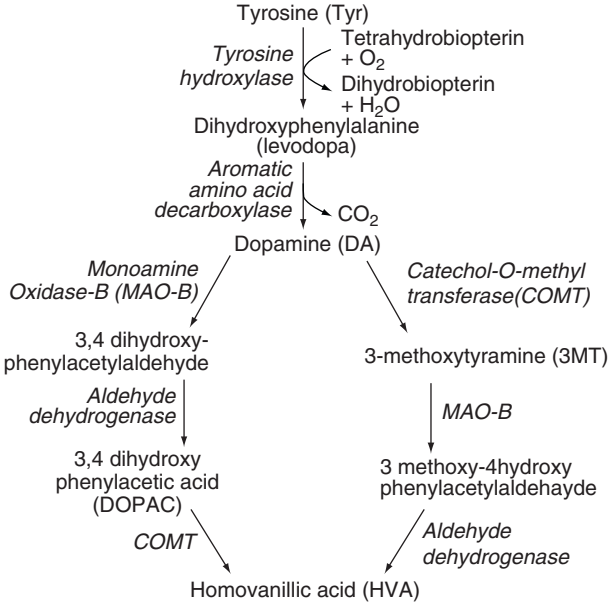

Figure 1 Dopamine synthesis and degradation pathways.

TH is a highly regulated enzyme. It is subject to classical end-product inhibition perhaps through competition between DA and tetrahydrobiopterin (BH_4) or another noncompetitive site. Thus, when free DA levels are high inside the DA neuron (the cytoplasmic or so-called mobile pool), synthesis is reduced. Since BH_4 is obligatory for TH activity, reduced availability of this cofactor can also reduce synthesis. BH_4 is the product of a three-step synthetic pathway in which GTP cyclohydrolase I is the rate-limiting enzyme. BH_4 subsequently binds to TH to increase its activity and BH_4's binding affinity (low or high) is affected by the phosphorylation status of TH. Increased neuronal firing leads to a reduced end-product inhibition by altering the phosphorylation status of TH, thus increasing the rate of hydroxylation (conversion of TH from a low to high affinity state for BH_4) and effectively enhancing the supply of DA for highly active neurons. The alterations in TH phosphorylation status are regulated through four sites on the enzyme that are activated by PKA, PKC, and Ca^{2+}-calmodulin-dependent kinase with the latter thought to be more active than PKA or PKC. Neuronal activity affects these phosphorylation reactions thereby affecting synthetic rate. Also, released DA acting through its presynaptic autoreceptor reduces TH through regulation of phosphorylation. These posttranscriptional mechanisms appear to be the primary regulators of TH activity and it is currently unknown whether transcriptional increases in mRNA for TH occur as they do in other catecholaminergic neurons. Several polymorphic forms of TH are known to exist leading to further variations in synthetic rate and phosphorylation capacity. Finally, it is widely believed and likely true that tyrosine availability to TH is rate limiting and near saturation under normal conditions. However, excessive or prolonged periods of DA neuron firing can lead to reduced levels of tyrosine such that the availability of this precursor then becomes rate limiting. Whether or not this is relevant to DA neurodegenerative diseases such as PD is unclear.

Once formed, DOPA is subsequently converted into DA by aromatic amino acid decarboxylase (AAAD), which is a ubiquitous enzyme found throughout the body and brain.

Because of the abundance of this enzyme in the stomach, GI track, liver, and vascular beds throughout the body, administered levodopa is extensively metabolized (first pass effect) dramatically reducing the amount of levodopa available to brain. AAAD requires pyridoxine (vitamin B6) as a cofactor. Prior to the advent of AAAD inhibitors, including carbidopa and benserazide, peripheral metabolism of levodopa could be reduced by depleting B6 (avoiding B6 rich foods and multivitamins), a therapeutic strategy that is no longer required. AAAD is far from being saturated under normal conditions and levels of DOPA are generally undetectable in the brain. This formulated the basis for the effectiveness of the so-called 'precursor load strategy,' where DA levels are effectively increased in the brain by administering its immediate precursor, levodopa. Although it is widely assumed that AAAD is not rate limiting in the production of DA, it does become rate limiting when high levels of levodopa are administered. Thus, levodopa's efficacy may exhibit a ceiling effect following very high doses or in the late stages of disease when significant losses of DA neurons reduce the pool of AAAD in the targeted DA neurons. Since polymorphism is known to occur in AAAD as well, the point at which there is a ceiling effect for levodopa conversion to DA will differ from one patient to another. Indeed, at one time saturation of AAAD was thought to contribute to the well known on–off effect observed in many later-stage PD patients.

DA is synthesized in the varicosities and end terminals of DA neurons as well as in the cell bodies (**Figure 2**). Since synthesis occurs in terminals, released DA and other neurotransmitters working through auto and hetero-receptors respectively, can influence the phosphorylation status of TH and the local synthetic rate of DA. Regardless, once synthesized, DA eventually collides, via Brownian motion, with the vesicular monoamine transporter (VMAT2) sites on synaptic vesicles and is transported into vesicles forming the so-called vesicular pool of DA. VMAT2 is a H^+-dependent antiporter and a member of the toxin extruding antiporter (TEXAN) gene family that confers antibiotic resistance in many bacteria. The acidic pH inside of vesicles is created by a V-type ATPase H^+ transporter creating an electrochemical gradient out of the vesicle that drives VMAT2. DA in exchange for two H^+ ions is transported into the vesicle where it binds to unknown sites inside of the vesicles sequestering it in the vesicular pool and effectively lowering its concentrations in the mobile pool. The latter point is critical to DA neuron function, since it has been proposed that high levels of mobile pool DA lead to overwhelming concentrations of reactive oxygen species (ROS) that affect the integrity of the DA neuron. Indeed, methamphetamine toxicity and α-synuclein mutations appear to affect vesicular transport function and lead to cell death. Additionally, DA has a pK_a of 8.45 at 37 °C that effectively ion traps DA inside of the vesicles. The result of this ion trapping, together with the binding of DA to proteins inside the vesicle, creates extremely high concentrations in the vesicular pool (10 000-fold relative to the mobile pool). Subsequent vesicular release of DA into the synaptic cleft (the so-called synaptic pool) is mediated by traditional Ca^{2+}-dependent release through exocytosis. Once released, DA is then free to interact with receptors on its target structures via bulk diffusion.

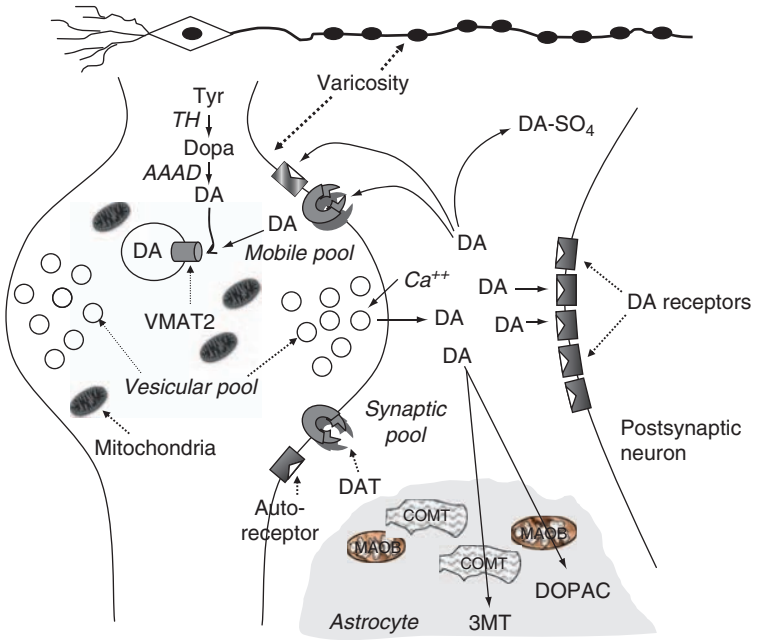

Figure 2 Depiction of the fates of dopamine (DA) as it is synthesized and distributed throughout the synaptic release phase.

Fate of Released DA

Once released into the synaptic pool, DA is free to diffuse and it will collide with postsynaptic DA receptors to produce is effects. Concentrations needed to meet the affinity needs of the target receptors are in the high-nanomolar and low-micromolar range; concentrations readily achieved in the synaptic pool as part of Ca^{2+}-dependent release. The vast majority of released DA (85–95%) is taken back up into the DA neuron via the dopamine transporter (DAT). DAT is located away from the synaptic zone consistent with the notion that only the DA diffusing away from the receptor fields is subject to reuptake.

DAT is a symporter carrying two molecules of Na^+ and one molecule of Cl^- into the neuron together with two molecules of DA. Once bound, DAT is translocated to the cytoplasmic side of the membrane releasing its DA into the mobile pool. Once back inside, the transporter releases its two molecules of DA where it can recollide with the DA binding sites on the DAT and can be transported back into the synaptic pool. This process continues until extracellular concentrations of DA are depleted effectively trapping the DAT on the external surface of the DA neuron membrane in preparation for the next synaptic volley. Psychostimulant drugs that have affinity for DAT and behave as ligands such as amphetamine and methylphenidate take advantage of this shuttling ability of the DAT. Thus, they bind to the DAT (have affinity) and are transported to the cytosolic side of the membrane (they are ligands), where mobile pool DA can then bind and can be transported back into the synaptic pool, producing the so-called Ca^{2+}-independent release. Psychostimulants like cocaine appear to bind to a regulatory site on the DAT and alter the affinity of DAT for DA effectively reducing reuptake. The gene for DAT has a variable number of tandem repeats (VNTR) associated with various basal levels of expression. In addition, both MAPK and PKC modulate the rate at which DA is transported.

Once DA is back in the mobile pool, it can bind to TH and produce feedback inhibition. Alternatively, it can collide with VMAT2 and can be resequestered into the vesicular pool effectively recycling DA. It is often believed that mobile pool DA is catabolized by monoamine oxidase type B (MAOB) located in the mitochondria of DA neurons. This is likely untrue. Although some DA cell bodies in the SN have been shown to contain MAOB, it is generally assumed that MAOA is primarily located in DA neurons. Thus, MAO primarily functions as a scavenging enzyme in terminals effectively catabolizing serotonin, norepinephrine, and other bioactive amines that may be inadvertently taken up by the terminal because they have some affinity and behave as ligands for the DAT. This scavenger function reduces the likelihood that false neurotransmitters will be taken into DA vesicles. This does not mean that DA is not catabolized. It simply means that the vast majority of its catabolism occurs outside the DA neuron.

Although the vast majority of DA is taken back up, DA is catabolized by catechol-O-methyl transferase (COMT) and MAOB. It is widely believed that COMT is expressed on target neurons and as such can catabolize DA directly at the target site in a fashion similar to that known to occur when acetylcholinesterase catabolizes ACh. Several studies have also observed soluble COMT in the brain. However, these two forms of COMT have a low affinity for DA. High-affinity COMT is found primarily in astrocytes and perhaps microglia. There are Na^+-dependent and Na^+-independent transport sites for biogenic amines on astrocytes. These apparently unsaturable uptake sites deliver DA into the cytosol of astrocytes, effectively sequestering it from the synaptic pool. Once inside, COMT transfers a methyl group from *S*-adenosyl-L-methionine to the catechol substrate in the presence of magnesium producing 3-methoxytyramine (3MT). COMT activity is genetically polymorphic, and individuals with the low-activity genotype have a thermolabile COMT protein that affects the efficacy of the COMT inhibitors tolcapone and entacapone. This genotype is less common in Asians than in Caucasians.

Once sequestered in astrocytes, DA can also be catabolized by MAOB located on the outer membrane of mitchondria in the cytoplasm of these cells. MAOB requires a flavin cofactor, flavin adenine dinucleotide (FAD), which binds to the cysteine residue of a pentapeptide sequence (Ser-Gly-Gly-Cys-Tyr). Monoamine oxidase catalyzes the oxidative deamination of DA. Oxygen is used to remove the amine group from DA resulting in the corresponding aldehyde 3,4-dihydroxyacetylaldehyde and ammonia. The resulting aldehyde is acted on by aldehyde dehydrogenase to produce DOPAC and then by COMT to produce homovanillic acid (HVA). Similarly, 3MT, the product of COMT acting on DA, is similarly acted on by MAOB and then aldehyde dehydrogenase to produce HVA. GT repeat sequences exist within MAOB, suggesting variations in its activity, although differences in the length of these repeats are not associated with the PD phenotype.

Since DA is catabolized outside of the DA neuron, the ratio of its metabolites to the parent neurotransmitter is widely used as an index of release. Referred to broadly as DA activity, the ratio of DOPAC/DA or HVA/DA has been widely shown to be associated with DA release status. Thus, increases in either of these two ratios are usually associated with loss of DA neurons. The term DA activity should not be confused, as it often is, with the term turnover, which more accurately reflects the ratio of tyrosine/DA and therefore reflects synthetic rate.

In addition to enzymatic degradation by COMT and MAOB, released DA can also be conjugated with sulfate or act on autoreceptors. DA sulfates have been isolated in low quantities from CSF. The sites of these conjugation reactions are unknown, although they probably occur ubiquitously as is true in the periphery. DA that is not taken up by astrocytes or the DAT can also bind to DA autoreceptors. These autoreceptors are, like the DAT, located well away from the active synaptic area, probably farther away from the active zones than the DAT field. This physical location ensures that only when synaptic pool DA concentration is excessive, will it diffuse to and bind to the autoreceptor. Binding to the autoreceptor not only will affect kinases to reduce TH activity, but also will reduce future DA release by interfering with Ca^{++}-dependent release mechanisms.

See also: Basal Ganglia; Basal Ganglia, Functional Organization; Direct Pathway; Dopa-decarboxylase Inhibitors; Dopamine Depletors and Movement Disorders; Dopamine Dysregulation Syndrome; Dopamine Receptors; Dopamine Transporter: Aging and Parkinson's Disease; Dopaminergic Agonists in Parkinson's Disease; Indirect Pathway; Levodopa; Substantia Nigra.

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Dopamine Depletors and Movement Disorders

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Glossary

Alpha-methyl-para-tyrosine – Inhibitor of tyrosine hydroxylase; a dopamine depletor not in clinical use but used extensively in research.
Dopamine depletor – A pharmacologic agent that decreases the amount of dopamine available for synaptic release by one of the two mechanisms: blocking of vesicular monoamine transporters or inhibition of production by tyrosine hydroxylase; sometimes used to treat extreme hypertension or hyperkinetic movement disorders.
Monoaminergic neurotransmitters – Neurotransmitters derived from amino acids; include norepinephrine, epinephrine, histamine, serotonin, and dopamine.
Reserpine – The prototype for the dopamine depletor class of drugs; a vesicular monoamine transporter inhibitor.
Tetrabenazine – A reversible vesicular monoamine transporter inhibitor; approved for use in Huntington's chorea.

Dopamine depletors are a class of pharmacologic agents that decrease the amount of dopamine available for synaptic release. Although commonly known to reduce dopamine availability in the synapse, these agents reduce other catecholamine levels as well, contributing in large part to their clinical indications. Dopamine depletors have been used for treatment of hyperkinetic movement disorders such as chorea, tardive dyskinesia, and Tourette syndrome, as well as for hyperadrenergic states such as severe hypertension and pheochromocytoma. They frequently have been used in experimental animal model studies on mechanisms of dopamine release, parkinsonism, and depression.

In dopamine-producing cells, two pools of intracellular dopamine can be identified. The cytosolic pool contains newly synthesized dopamine, while the vesicular pool contains stored dopamine. The two best known dopamine depleters are reserpine and tetrabenazine, both of which work by depleting the vesicular pool of dopamine. The mechanism of action of reserpine and tetrabenazine is to inhibit monoaminergic neurotransmitter storage by blocking vesicular monoamine transporters (VMAT) that normally store histamine, norepinephrine, serotonin, and dopamine in storage vesicles. Effects of tetrabenazine are largely confined to the central nervous system, while reserpine has effects on peripheral (VMAT1) and central (VMAT2) nerve terminals. Reserpine is also likely to be an irreversible inhibitor of VMAT. Because of numerous side effects associated with reserpine such as bradycardia, hypotension, and depression, its use in this area of clinical practice has been limited.

Reserpine, considered the prototype for this class of drugs, was isolated from the root of *Rauwolfia serpentina*,

also known as Indian snakeroot, a plant that was used for medicinal effects dating back to the sixteenth century. Its use in nervous system disorders was first reported in 1933 by Chopra for treating insomnia and hypochondriasis in India. In the 1950s, after its introduction to the western hemisphere, it was used for hypertension, psychosis, chorea related to Huntington's disease (HD), and later for tardive dyskinesia. It came into more widespread use in the western hemisphere after its isolation, identification, and synthesis, but significant side effects were noted including hypotension, depression, and weight gain. Importantly, though clinical use of reserpine diminished with time, the discovery of reserpine enabled several different lines of scientific inquiry, including the mechanisms of central nervous system dopamine storage and release and in generating animal models of parkinsonism.

Tetrabenazine was synthesized in 1956 in an effort to find a similar agent with a more tolerable side effect profile. In 1969, Dalby reported on tetrabenazine's benefit in a variety of hyperkinetic disorders including chorea, hemiballismus, dystonia, parkinsonian tremor, and intention tremor. Tetrabenazine's usefulness for hyperkinetic movement disorders was recognized by many, especially in light of the poor tolerability of reserpine. Though not available in the United States until 2008, it has been in widespread use for tardive dyskinesia, Tourette syndrome, and chorea.

Tetrabenazine, the most important of the dopamine depletors, is a selective and reversible VMAT2 inhibitor, which also exhibits preferential depletion of dopamine over other monoaminergic transmitters. It also has weak D2 receptor antagonist activity, which is thought to play only a minor role in producing its clinical benefits. Although much less commonly used chronically than antipsychotic drugs, tardive dyskinesia has not been reported after use of tetrabenazine, thereby making it a more attractive option than neuroleptics for treatment of hyperkinetic disorders. Tetrabenazine is a mainstay of treatment of persistent tardive dyskinesia after removal of neuroleptics as well as in Huntington's chorea. In a Huntington Study Group multicenter randomized controlled trial involving over 80 HD patients, tetrabenazine was shown to be safe and effective with only five reported adverse events (suicide by drowning, a complicated fall, restlessness/suicidal ideation, and breast cancer). Side effects of tetrabenazine include sedation, depression, akathisia, and parkinsonism that require close monitoring. Incidence of postural hypotension is probably lesser than that in reserpine. Patients with preexisting depression are more likely to experience worsening depression on this drug than patients without preexisting depression. However, 10–15% of patients may experience de novo depression while taking tetrabenazine. Effective doses of tetrabenazine range from 25 to 150 mg daily with recommended starting dose of 12.5 mg twice to three times daily. Tetrabenazine is extensively metabolized in the liver to intermediate compounds which also are similarly active in producing monoamine depletion.

In contrast to the mechanisms of action of reserpine and tetrabenazine, alpha-methyl-para-tyrosine (AMPT), also known as metyrosine, reduces the cytosolic pool by directly inhibiting tyrosine hydroxylase, which is the rate-limiting step in the conversion of tyrosine to levodopa and norepinephrine. Its discovery in the mid-1960s led to its use in treating pheochromocytoma, but its use in movement disorders was limited for unclear reasons. Several reports surfaced in the early 1980s regarding its benefit in chorea and tardive dyskinesia, especially as a potentiator of the action of other dopamine depleters such as reserpine and tetrabenazine. Rare cases of neuroleptic malignant syndrome were reported in conjunction with tetrabenazine, but by and large, severe adverse reactions were not seen with AMPT. Currently, it is only approved for use in pheochromocytoma by the US FDA, and its clinical use in neurological disorders is minimal to nonexistent.

Dopamine depletors have been used extensively in research. Because cocaine stimulates dopamine release, reserpine and AMPT have been tried unsuccessfully as potential therapeutic agents for cocaine dependence. AMPT has been used in neuroimaging and clinical studies of major depression. In patients with depression in remission, AMPT can cause return of depressive symptoms particularly in those patients chronically taking serotonergic and noradrenergic reuptake inhibitors. AMPT has also been used in conjunction with reserpine as a means for producing nearly complete dopamine depletion in functional imaging studies that evaluated dopaminergic radioligands. Tetrabenazine and its metabolites, methoxytetrabenazine and dihydrotetrabenazine, have also been used as investigational positron emission tomography radiotracer ligands. Because these agents bind to VMAT2, which is located on dopaminergic terminals in the striatum, it may serve as a biomarker of dopaminergic neuronal loss in PD.

See also: Alien Limb; Dopamine; Gait Disturbances in Parkinsonism; Huntington's Disease; Kinesia Paradoxica; Parkinson's Disease: Genetics; Tardive Syndromes.

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Dopamine Dysregulation Syndrome

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Glossary

Akathisia – A syndrome characterized by unpleasant sensations of 'inner' restlessness that manifests itself by an inability to sit still or remain motionless. It can be a side effect of medications, mainly neuroleptic antipsychotics.
Anhedonia – An inability to experience pleasure.
Compulsive behavior – Behavior resulting from an irresistible urge to perform a certain act, regardless of the rationality of this act.
Dysphoria – A state of feeling unwell or unhappy; a feeling of emotional and mental discomfort and suffering from restlessness, malaise, depression, or anxiety.
Hedonistic homeostatic dysregulation syndrome – A neuropsychological behavioral disorder associated with substance misuse and addiction.
Hypersexuality – Excessive interest or involvement in sexual activity.
Pathological gambling – An urge to gamble despite harmful negative consequences or a desire to stop.
Punding – Activity characterized by a compulsive fascination with and performance of repetitive, mechanical tasks, such as assembling and disassembling, collecting, or sorting common household objects.
Substance abuse – Overindulgence in and dependence on a drug or other chemical leading to effects that are detrimental to the individual's physical and mental health, or the welfare of others.
Suicide – The intentional taking of one's own life.

Definition and History

Dopamine dysregulation syndrome (DDS) is a neuropsychological disorder in patients with Parkinson's disease (PD) associated with compulsive misuse of and addiction to dopamine replacement therapy (DRT). The model of maladaptive use of addictive medications, called hedonic homeostatic dysregulation (HHD), was first described in association with psychostimulant abuse, specifically cocaine. It was later recognized that similar behavioral problems can occur in patients with PD as a consequence of DRT. Although the name HHD was used in the first reports of this phenomenon in PD patients, recently the term DDS in relationship to compulsive and maladaptive use of DRT is more accepted.

Pathophysiology

Dopamine plays a key role in the mesocorticolimbic system connecting the basal ganglia, ventral striatum, nucleus accumbens, ventral tegmental area (VTA), and basal forebrain. This system controls many aspects of normal human behavior, such as feeding, motivation, and reward processing, as well as pathological behaviors such as substance abuse, gambling, overeating, hypersexuality, and other addictions and compulsions. Changes in dopamine neurotransmission within this system are responsible for positive reinforcement of substance abuse in the 'reward pathways.' Facilitation of dopamine transmission in this pathway is critical for acute reinforcing actions of cocaine, amphetamine, and nicotine. Multiple dopamine receptors, including D1, D2, and D3, have been implicated in this reinforcement. Recent pathological studies revealed an intriguing link between mechanisms of neurodegeneration in PD and in chronic cocaine abusers. α-Synuclein, a major component of Lewy bodies and possible pathological agent in PD, was found in increased levels in the midbrain and nigral dopamine neurons of cocaine abusers. It was postulated that overexpression of α-synuclein occurs as a protective response to increased dopamine turnover and oxidative stress caused by chronic cocaine use. There are also striking similarities in clinical effects of psychostimulant use and DRT. Cocaine can cause hyperkinetic movements, such as reversible chorea

and stereotypies; behavioral alterations, such as mood swings, paranoia, panic attacks, and psychosis; and withdrawal symptoms of depression and anxiety. All of these are well-known, dose-dependent side effects from DRT in PD patients. It was concluded that both neurobiological and clinical effects of psychostimulants are similar to those of dopamine, and therefore, the mechanism of dependence on DRT is analogous to that of stimulant dependence. In fact, PD patients with DDS fulfill the DSM-IV clinical criteria of American Psychiatric Association (APA) for substance abuse and dependence that include 'overwhelming involvement with the use of a drug' (compulsive use), loss of control over drug intake, and drug seeking. These patients demonstrate the classic 'spiraling distress–addiction cycle' with stages of binge intoxication (emotional well-being on DRT), preoccupation–anticipation (feeling of need for the next dose of DRT in anticipation of the upcoming emotional wearing off), negative effect of withdrawal (anxiety and depression described as 'non-motor mental off'), and back to binge intoxication that provides positive reinforcement. This cycle increases in amplitude with repeated experience leading to addiction. However, as most drug users do not become drug abusers, most of PD patients treated with DRT do not develop DDS. A number of social, psychiatric, psychological, and neurochemical factors can be involved in the failure of the self-regulation of the appropriate use of DRT.

Epidemiology and Risk Factors

DDS has been reported in ~4% of all PD patients. This number, however, is likely biased, because it is based on the reports from the subspecialty movement disorders clinics. Milder forms of DDS are under recognized and under reported in general practice. There is also some evidence that PD patients with DDS are over represented in certain PD populations. For example, among potential surgical candidates for deep brain stimulation (DBS), the incidence can be as high as 18%. About 80% of PD patients affected by DDS are men. Younger patients have a much higher risk of DDS than older patients. The average age of the disease onset for PD patients with DDS is about 43. It is yet to be determined whether the age of the disease onset or the age of the exposure to the DRT determines the susceptibility to DDS. On the one hand, patients with young-onset PD (YOPD) represent a different spectrum of the disease, often determined by genetic mutations, and might already have genetic predispositions for the development of DDS. For example, clinical features of PARK-7-linked autosomal recessive Parkinsonism, characterized by psychiatric, emotional disturbances, and obsessive-compulsive behavior, are similar to those of PD patients with DDS. On the other hand, age critically mediates vulnerability to addiction in general. Adolescents have much higher novelty seeking and risk acceptance personality traits that make them more likely to experiment with alcohol and drugs. Younger age of exposure to addictive drugs influences subsequent severity of substance abuse. It had been shown that younger age of the exposure to DRT independently increased the risk of development of DDS in PD patients.

There are certain personality traits that can predispose PD patients to the development of DDS. Novelty seeking is most strongly associated with DDS. PD patients with DDS scored much higher on impulsive sensation seeking rating than those without DDS. Significantly more PD patients with DDS have a past history of experimental drug use, compared with PD patients without DDS. History of alcohol abuse and dependence, as well as current level of alcohol intake is predictive for the development of DDS. Depression is another important predictor of DDS in PD. Although depression is a common symptom of PD, it is also a common comorbidity in drug abusers. PD patients with DDS report more severe off-period dysphoria, apathy, and anxiety. That prompts them to take more frequent and higher doses of DRT, often in excess of what is needed for their motor control, to avoid those unpleasant withdrawal symptoms. This, in turn, reinforces the positive emotional effect in the vicious cycle. As a result, the daily doses of DRT in PD patient with DDS are usually much higher than in patients in a similar stage of the disease without DDS.

To conclude, the typical-case scenario for DDS is a depressed male with YOPD and a history of alcohol and substance abuse or at least experimentation in the past, on very high doses of DRT.

Clinical Picture

Core clinical criterion of DDS is a pattern of pathological use of DRT in excess of what is required to alleviate motor impairments of PD despite disabling dyskinesias resulting in euphoric effect and behavioral disturbances affecting social and occupational functioning for more than 6 months in duration.

The term 'pathological use' of DRT in PD is difficult to define, because the patients need DRT for the improvement of motor symptoms. However, if the medications are taken to achieve emotional, not only motor, 'on' state despite severe complications with disabling dyskinesias, it should be considered pathological. The emotional and behavioral effects of medications in this situation can range from simple relief of withdrawal symptoms of anxiety, dysphoria, depression, irritability, apathy, and fatigue, perceived as 'mental off state,' to symptoms of intoxication with hypomania, mania, paranoia, and compulsive behaviors. These patients have an altered perception of 'on' state, which usually includes wild dyskinesias and emotional 'on.'

The preoccupation and anticipation involved in taking medication for this purpose negatively affects the patients' social and family life. Aggression, irritability, and an unwillingness to decrease doses despite severe consequences are typical of this condition. The decreasing of doses can indeed be very difficult because of severe negative withdrawal effects, and the attempts to do so have been proved to be unsuccessful on most occasions. Instead, due to the development of tolerance, the typical phenomenon of addiction, the patients tend to increase the doses over time on their own despite physician's advice. Medication hoarding becomes the major task. Unfortunately, because the symptoms of DDS are difficult to recognize immediately and because DRT is widely prescribed for controlling motor symptoms in PD, usually these patients do not have trouble to stock massive doses of levodopa. Any dopaminergic medications could potentially cause DDS. Rapid acting medications with shorter half life present much higher risks likely because of their pulsatile nonphysiological stimulation of dopamine receptors. Among them are rapid-release carbidopa/levodopa and apomorphine. The latter gives patients a subjective 'kick' or 'rush,' which some patients describe as being high, resembling the similar effect of psychostimulants. Therefore, subcutaneous infusions of apomorphine in high doses can potentially provoke this condition.

Behavioral disturbances escalate with escalating doses of medications. The patients become irritable, agitated, intolerant to critique, demanding, and hyperexcitable. Their thoughts become disorganized, they display poor judgment and frequent mood swings. Paranoia and frank psychosis can occur. Pathological compulsive behaviors are common, including, but not limited to, punding, hypersexuality, walkabouts, pathological shopping, gambling, overeating, excessive preoccupation with hobbies, and other activities. The consequences of these behaviors can be devastating. Many patients find themselves in financial crises more then once due to overspending on shopping and gambling. Many patients destroy their family relationships due to inappropriate sexual behavior, ranging from increased libido to prostitution, exhibitionism, and others. Some develop restlessness and akathisia that make them wander long distances without realizing it. Food cravings can become severe and uncontrollable. All of these, combined with physical limitations caused by dyskinesias, result in loss of families, friends, absence from work, social isolation, and subsequent worsening of depressive symptoms.

Management

Management of DDS is extremely difficult. Psychological help with psychotherapy is essential. Since this syndrome is a variant of substance abuse, a formal evaluation and treatment with psychiatrist are warranted. The goal should be to restrict DRT and dispense medications only under strict supervision of the physician and/or pharmacist in the amount needed only to control motor symptoms of PD. This task, however, is proven to be difficult, because dopaminergic medications are not considered to be drugs of abuse, and as a result, it is easy to get a prescription from another physician. Therefore, in severe cases, the medication reduction should be attempted in the hospital under strict supervision of both a neurologist and a psychiatrist. Severe manic and psychotic episodes should be treated with antipsychotics, such as clozapine, olanzapine, or quetiapine. After a decrease in doses of DRT, psychotic features can be rapidly replaced by the equally dangerous depressive state, often with suicidal ideations. During that period, the patient should be closely supervised by a psychiatrist. Antidepressants are usually needed for a longer period of time even after clinical resolution of depressive state.

Prognosis and Prevention

Prognosis of DDS is poor. Even appropriately treated DDS has a tendency to relapse. Unlike other substances of abuse, it is impossible to avoid DRT completely in PD patients, because they still need it to alleviate their motor impairments. Sooner or later, they tend to fall back into the vicious cycle of 'reward reinforcement' and lose control over their dopaminergic medication use.

To prevent relapse, the lowest doses of DRT needed for control of motor problems should be used, preferentially in the form of slow-release medication. Rapid-release medications, doses given 'as needed,' and specifically, boluses of subcutaneous apomorphine should be avoided. Ongoing psychotherapy should use positive reinforcement of appropriate behavior. Education of family and caregivers about the nature of this problem is important, as they are willing to provide more social support when they understand the medication-related nature of their loved one's problems.

In recent years, there has been more evidence that bilateral subthalamic nucleus deep brain stimulation (STN DBS) can improve or completely abolish the addiction to DRT. The mechanism of this effect is still controversial but likely consists of two parts. First, dramatic improvement of motor symptoms by STN DBS allows significant decrease and sometimes complete discontinuation of DRT in PD patients. This eliminates the nonphysiological pulsatile stimulation of dopamine receptors that is a major strategy in the treatment and prevention of DDS. Second, the direct effect of high-frequency STN stimulation on the dopaminergic reward-seeking pathways inhibits the neurochemical circuitry of positive

reinforcement in the mesocorticolimbic system. Animal data have shown that STN DBS reduces the rewarding effect of cocaine. That can explain why PD patients with DDS can tolerate rapid medication decrease and withdrawal after STN DBS without typical dysphoric symptoms or craving of dopamine. They no longer need that emotional 'kick' that they were getting from medication prior to surgery. This data, however, are still controversial, because STN DBS was shown to cause a variety of different effects on emotional state and behavior in PD. Some patients can develop depression, dysphoria with suicidal ideation in the postoperative state, while other patients exhibit quite opposite symptoms of hypomania and paranoia. Therefore, until we better understand the behavioral effects of DBS, the perioperative psychiatric and psychological care for patients with DDS should be very vigilant. A slow medication taper in the postoperative period helps to avoid anhedonia and depression and to decrease the risks of suicide. Antidepressants could be used during this period if needed. Nevertheless, STN DBS can be potentially curative for DDS and should be strongly considered early in the course of the disease for PD patients suffering from DDS and for those at risk of this disabling behavioral disorder with an otherwise-poor prognosis.

See also: Deep Brain stimulation; Depression and Parkinsonism; Dopamine; Dopamine Receptors; Dopaminergic Agonists in Parkinson's Disease; Obsessive-Compulsive Disorder; Punding (PD).

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Dopamine Receptors

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Glossary

G protein – Cell membrane protein involved in the cellular signal transduction pathway.

Neurotransmitter – A chemical substance carrying signals or messages from one nerve cell to another nerve cell.

Nigrostriatal pathway – Dopaminergic pathway connecting substantia nigra to striatum.

Substantia nigra – An area located in the midbrain containing dopamine-producing neurons that project to striatum.

Transmembrane receptors – Integral membrane proteins spanning the entire thickness of the membrane.

Introduction

Dopamine is a neurotransmitter, which is synthesized from amino acid tyrosine and has a significant role in regulating a variety of physiological functions. It exerts its actions by binding to different dopamine receptors located throughout the peripheral and central nervous systems (CNS).

Classification and Structure

Dopamine receptors are the pharmacological targets of many drugs in treating several neurological, psychiatric, and cardiovascular disorders. Currently, five distinct dopamine receptors are known. These receptors have seven transmembrane domains connected by three intracellular and three extracellular loops, and belong to the

G-protein-coupled receptor superfamily. Based on their biochemical and structural properties, dopamine receptors are divided into two main groups. The D_1-like group includes the D_1 and D_5 receptors, whereas the D_2-like group consists of the D_2, D_3, and D_4 receptors. There are significant sequence similarities in the transmembrane domains between members of each group. D_1 and D_5 receptors share an overall homology of 80%, but are only 31% identical to the D_2-like receptors. Similarly, D_2 and D_3 receptors share a 75% homology, and, to a lesser degree, D_3 and D_4 receptors share a 54% homology in their transmembrane domains. All dopamine receptor subtypes have similar numbers of amino acids in their extracellular NH_2-terminal stretch and the three extracellular loops and a variable number of *N*-glycosylation sites. Dopamine receptors also have two cysteine residues in the second and third extracellular loops, which form a disulfide bridge stabilizing the receptor structure.

There are some differences between the D_1 and D_2 families. Unlike the D_2-like group, the D_1-like receptors have a much larger c-terminal tail extending into the cytoplasmic compartment which is rich in serine and threonine and has a cysteine residue anchoring the cytoplasmic tail to the membrane; they also have a shorter third cytoplasmic loop between transmembrane helices 5 and 6. The third cytoplasmic loop is responsible for the G-protein coupling, signal transmission, and activating different signaling pathways.

It is important to note that the D_2 receptor has two main isoforms, the long isoform, D_{2L}, and the short isoform, D_{2S}. The D_{2L} is different from D_{2S} by a 29 amino acid stretch in the third cytoplasmic loop, which does not affect ligand recognition but affects G-protein coupling and signal transmission.

The D_5 receptor has two related pseudogenes that code for incomplete, nonfunctional forms of the receptor. D_4 receptor has many variants that differ in the number of repeat amino acid units in the third cytoplasmic loop. $D_{4,4}$, $D_{4,7}$, and $D_{4,11}$ have 4, 7, and 11 repeats, respectively. The $D_{4,4}$ is the most common variant. In addition, several nonfunctional variants of D_3 receptor have been identified.

The binding site of dopamine and other agonists is predicted to be between transmembrane helices 3, 4, 5, and 6 with tight binding between helices 3 and 5, whereas the binding of the antagonists involves helices 2, 3, 4, 6, and 7 with tight binding between helices 3 and 6 and minimal contact with transmembrane helix 5.

Transduction Pathways

Activation of dopamine receptors modulates adenylyl cyclase activity. Stimulation of D_1-like receptors is excitatory. The short third cytoplasmic loop interacts with G-stimulatory (Gs) subunits of the G proteins, activating adenylyl cyclase. This results in an increase in intracellular concentration of the second messenger, cyclic AMP. On the contrary, D_2-like receptors interact with G-inhibitory (Gi) subunits and their stimulation inhibits the activity of adenylyl cyclase decreasing the formation of cAMP.

Cyclic AMP is an activator of protein kinase A (PKA) and stimulation or inhibition of cAMP results in modulation of PKA, which through phosphorylation of cytoplasmic, nuclear and membrane proteins can significantly affect the cellular regulation and physiology.

Other important transduction pathways and effector systems modulated by dopamine receptor activation include phospholipases, arachidonic acid, activity of the K^+ and Ca^{2+} ion channels, mitogen-activated protein (MAP) kinases, Na^+/H^+ exchanges, and Na^+–K^+-ATPase. Coupling to potassium and calcium channels is one of the signaling pathways by which dopamine receptors can affect cell excitability. With regards to K^+ channels, activation of D_1 receptor reduces K^+ conductance causing depolarization and enhancing excitability and cell firing. Conversely, D_2 receptor activation results in hyperpolarization of the membrane and reduction of firing rate. Similarly, modulation of Ca^{2+} channels via activation of D_1 receptor enhances excitability, while the activation of D_2 receptor reduces Ca^{2+} current and has the opposite effect.

Binding Affinities

The D_1 and D_2-like receptors show pharmacological differences based on variable affinity of certain agonists and antagonists. Dopamine binds the five receptors and, although no pharmacological differences have been identified between the D_1-like receptors, dopamine has 10 times higher affinity for the D_5 than the D_1 receptor. The affinity of other agonists for these two receptors is identical, while antagonists bind the D_1 receptor with a slightly higher affinity. Among the D_2-like receptors, no compound has been able to distinguish between the D_{2L} and D_{2S} isoforms. Although D_3 and D_4 receptors bind D_2 receptor ligands with high affinity, they can be distinguished by some agonists or antagonists based on their pharmacological characteristics. As an example, dopamine has 20 times higher affinity for the D_3 compared with the D_2 receptor and ropinirole binds D_3 receptor with higher affinity compared with D_2 and D_4 receptors. With respect to antagonists, haloperidol shows 10–20 times higher affinity for the D_2 receptor. The D_4 receptor is distinguished from the other two by its higher affinity for clozapine.

CNS Distribution

Dopamine receptors are widely distributed throughout the CNS, mediating the effects of dopamine on locomotion motivation, emotion, cognition, and endocrine system. The dopamine receptors are mainly located in the striatum, the limbic system, the brain cortex, and the infundibulum which form the three main dopaminergic pathways, the nigrostriatal, the mesocorticolimbic, and the tuberinfundibular.

The D_1 receptor is the most widespread receptor and its mRNA has been found in striatum, nucleus accumbens, and the olfactory tubercle. In addition, D_1 receptors have been detected in the limbic system, thalamus, and hypothalamus. The D_5 receptor expressed less compared with D_1, and its mRNA has been found in the cerebral cortex, lateral thalamus, striatum, hippocampus, and to a lesser degree in the substantia nigra, and medial thalamus.

The D_2 receptor has mainly been located in the striatum, nucleus accumbens, and olfactory tubercle. D_2 receptor mRNA is also present in the prefrontal cortex, amygdala, hypothalamus, hippocampus, and substantia nigra. The D_3 receptor has been found in the nucleus accumbens and the olfactory tubercle, and is poorly expressed in the dorsal striatum. In comparison to D_2 receptor, minimal expression of D_3 receptor has been detected in the substantia nigra, hippocampus, and ventral tegmental area. The D_4 receptor is highly expressed in frontal cortex, amygdala, hippocampus, hypothalamus, and mesencephalon.

Physiological Properties

Movement

Disturbances in the dopaminergic systems result in several neurological and neuropsychiatric disorders. Dopamine in the nigrostriatal pathway serves to generate voluntary movement. Destruction of the dopaminergic neurons of the substantia nigra is the pathological hallmark of Parkinson's disease, causing bradykinesia, akinesia, and muscular rigidity. The degree of forward movement is mainly controlled by the activation of D_1, D_2, and D_3 receptors in the ventral striatum. Activation of D_2 autoreceptors causes a decrease in dopamine release and decreases locomotion; on the other hand, activation of postsynaptic D_2 receptors slightly increases locomotion. It has now been confirmed that the simultaneous activation and synergistic interaction between the D_1 and D_2 receptors are essential for a D_2 agonist to exert its maximal effect on locomotion. As a result, the blockade of D_2 receptors by antipsychotic drugs can manifest motor dysfunctions similar to those in Parkinson's disease.

It is also important to note that activation of postsynaptic D_3 receptors in the nucleus accumbens can have an inhibitory effect on movement. Activation of these receptors by an agonist inhibits motor activity, whereas activation by an antagonist has the opposite effect.

The symptoms of restless leg syndrome (RLS) are more severe at night when dopamine level falls and is at its lowest amount. In addition, RLS symptoms improve with dopamine agonists, ropinirol, and premipaxole and worsen with dopamine antagonist such as neuroleptics. These observations indicate a relationship between dopaminergic system and RLS. In fact, positron emission tomography (PET) studies have suggested a reduction in D_2 receptor binding in the striatum of patients with RLS.

Reward, Motivation, and Cognition

The mesolimbocortical pathway is involved in cognition, reward, reinforcement, motivation, and emotional stability. An increase or decrease in dopamine activity in the mesolimbic pathway has been associated with different symptoms of schizophrenia. The increase in dopaminergic transmission causes a state of psychosis, resembling the positive symptoms of schizophrenia. D_2 receptor antagonists (i.e., neuroleptic drugs) treat these symptoms very effectively with little effect on the negative symptoms of the disease. A number of the patients treated with neuroleptics suffer from movement disorders or extrapyramidal side (EPS) effects. It is thought that the antipsychotic properties of neuroleptics derive from their action on the dopamine receptors in the mesolimbic system, while their EPS are from blocking the D_2 receptors in striatum.

The dopaminergic activity in the mesolimbic system also plays a significant role in reward and reinforcement. Drugs of abuse increase dopamine release in the mesolimbic system, whereas their withdrawal reduces dopaminergic transmission. Studies have shown that both D_1 and D_2 receptors are involved. Receptor antagonists attenuate this behavior while agonists enhance the reinforcement effects of these drugs.

Learning and Memory

The effect of dopamine on learning and memory has been studied extensively. Studies have reported a relationship between the activation of the D_1 receptor in the prefrontal cortex (PFC) and optimization of working memory. One study indicated that too much or too little stimulation of D_1 receptors in PFC impaired the working memory. A similar relationship between D_2 receptors in PFC and working memory has not been established. However, there is some evidence that stimulation of D_2 receptors in the hippocampus can improve memory functions and performance. Studies have also shown that the activation of hippocampal D_1 receptors may improve acquisition and retention of memory. The high expression of D5 receptors

in hippocampus indicates their potential role in mediating the effect of dopamine and other agonists in learning and memory; however, their role has not been shown to be as significant as D_2 receptors. Based on these findings, both D_1 receptors in the PFC and D_2 receptors in hippocampus can be considered pharmacological targets for cognitive impairments that are associated with debilitating disorders like Parkinson's disease and Alzheimer's disease. Unfortunately, currently, there are no medications available to target these receptors in these specific areas. Clinically, all available dopamine agonists tend to worsen the cognitive function in patients with Parkinson's disease and memory impairment.

Pituitary Gland and Prolactin

Tuberoinfundibular pathway is one of the major dopamine pathways in the brain originating from hypothalamus. The release of dopamine in this pathway regulates prolactin secretion by the pituitary gland. D_2 receptor and its isoforms, D_{2L} and $D_{2S,}$ are expressed in the anterior and intermediate lobes of the pituitary gland with D_{2L} isoform being more prominent. In addition, D_4 receptor and in particular, $D_{4,4}$ variant, has been found in the anterior pituitary. The major role of the D_2 receptor in the pituitary gland is to inhibit the synthesis and secretion of prolactin, while the physiological role of the $D_{4,4}$ variant in the pituitary gland is not known. Some antipsychotic drugs block dopamine receptors in this pathway causing hyperprolactinemia, while D_2 receptor agonists, such as bromocriptine, are shown to be very effective in normalizing elevated prolactin levels. Several studies also suggest that dopamine may play a role in regulating the release of thyroid stimulating hormone, follicle stimulating hormone, and luteinizing hormone from the anterior pituitary gland.

Migraine

The role of D_2 receptors in the treatment of migraine has been studied and reported. It has been hypothesized that migraine sufferers have a lower threshold for dopamine receptor activation. This is consistent with typical features of a migraine attack. Studies have shown that administration of a dopamine agonist such as apomorphine can induce a statistically significant higher rate of dopaminergic symptoms such as nausea and vomiting in migraine patients. It has been suggested that this is due to a chronic deficiency of dopamine release by the presynaptic neurons making the postsynaptic dopamine receptors hypersensitivite in these individuals. D_2 receptor antagonists, such as prochlorperazine and metoclopramide, have shown to acutely relieve several symptoms of a migraine attack.

See also: Dopamine; Dopamine Depletors and Movement Disorders; Dopaminergic Agonists in Parkinson's Disease; *Drosophila* Models of Parkinson's Disease; Parkinson's Disease: Definition, Diagnosis, and Management; Restless Legs Syndrome.

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Dopamine Transporter: Aging and Parkinson's Disease

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Glossary

Cholinergic – Acetylcholine-based neurotransmission of neural impulses.
Dopamine (DA) – A monoamine catecholamine neurotransmitter and hormone.
Dopamine transporter (DAT) – A 12 transmembrane symporter protein that transports DA out of the synaptic cleft and into the presynaptic terminal.
1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) – A neurotoxin selective for substantia nigra DA neurons.
Single positron emission computerized tomography (SPECT) – 3-dimensional tomographic imaging system using gamma waves and radionucleotides.

Definition and History

Dopamine Transporter

Dopamine transporter (aka. dopamine active transporter; DAT) was first described by Iversen and colleagues in 1971 and cloned 20 years later by Giros and coworkers.

DAT, a 12 transmembrane-spanning protein, is a symporter coupled to Na^+/Cl^- encoded on chromosome 5 (5p15.3) and is ~64 kbp long containing 15 coding exons. The neurotransmitter DA is transported out of the synapse and into the neuron by DAT (**Figure 1**), which is found in the perisynaptic area of dopaminergic neurons. Select neuronal populations within the brain express DAT including the striatum (caudate and putamen), nucleus accumbens, globus pallidus, cingulate cortex, olfactory tubercle, amygdala, and the midbrain subgroups of the substantia nigra and ventral tegmental area.

Dopamine

Dopamine (DA), a monoamine catecholamine belonging to a class of compounds that function as both a neurotransmitter and a hormone (**Figure 2**), was first synthesized by George Barger and James Ewens in 1910 in the Wellcome laboratories in London.

The enzyme which converts levodopa (L-dopa) to DA, termed dopa decarboxylase, was discovered by Peter Holtz in 1938. Sir Henry Dale evaluated the biological actions of DA and found them to be similar to adrenaline and in 1952 suggested the name, DA, to replace the full chemical name 3,4-dihydroxyphenylethylamine. In 1957, scientists at the Hans Weil–Malherb's laboratory first demonstrated DA in the brain. Two years later, DA was localized in the striatum. DA is a neurotransmitter for several neural pathways including the nigrostriatal, mesolimbic (including the tegmental area, nucleus accumbens, ventral striatum, and amygdala) and mesocortical (ventral tegmental area to the medial prefrontal, cingulate, and entorhinal cortex) pathways. DA is also found in the tuberoinfundibular pathway coursing from the arcuate and periventricular nuclei of the hypothalamus to the pituitary and median eminence.

Pathogenesis/Pathophysiology

DAT and Parkinson-Like Syndrome

Although the biological action of DAT is to selectively transport DA into the presynaptic neuron, it can transport structural analogues of DA such as the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP; **Figure 2**), which induces a Parkinson-like syndrome in humans, some nonhuman primates, and mice. MPTP selectively degenerates dopaminergic neurons in the substantia nigra *pars compacta* by metabolizing monoamine oxidase type B followed by spontaneous oxidation to 1-methyl-4-phenylpyridium (MPP^+), which is structurally similar to DA. DAT transports MPP^+ (**Figure 2**) into neurons at rates similar to DA uptake leading to DA cell toxicity.

Other DAT Transported Compounds

In addition to MPTP/MPP^+, two pyridine derivatives, 2-methyl-MPP^+ and *p*-amino-MPP^+, are also intraneuronally symported by DAT, although with less toxicity and selectivity than MPP^+. Environmental factors such as isoquinoline (**Figure 2**) and its derivatives are considered as dopaminergic neurotoxins, and play a role in the pathogenesis of a Parkinsonian-like syndrome. These compounds have a lower affinity and uptake velocity than MPP^+, which may limit toxicity in dopaminergic cells. β-Carbolines, heterocyclic molecules structurally related to MPTP/MPP^+ (**Figure 2**), use DAT to enter nondopaminergic

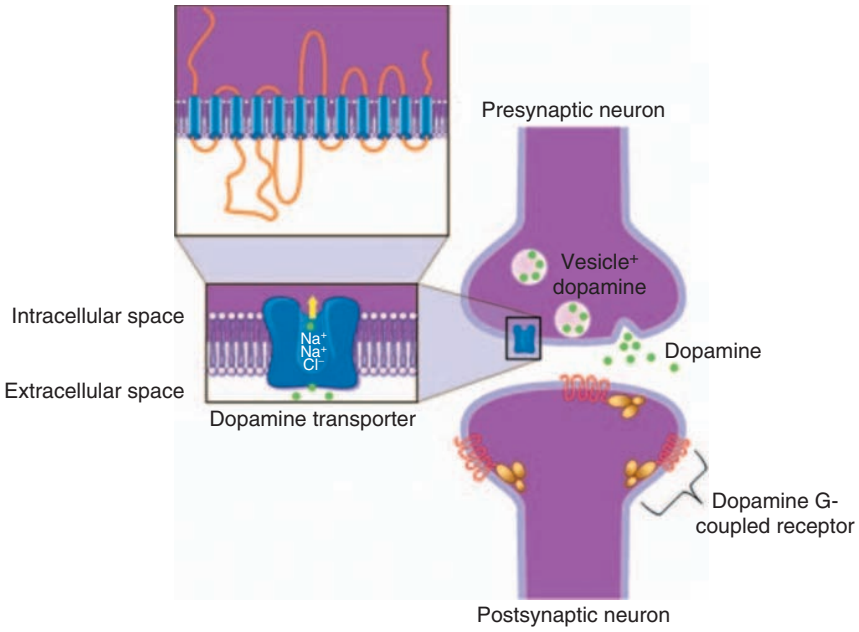

Figure 1 Structural diagram of DAT.

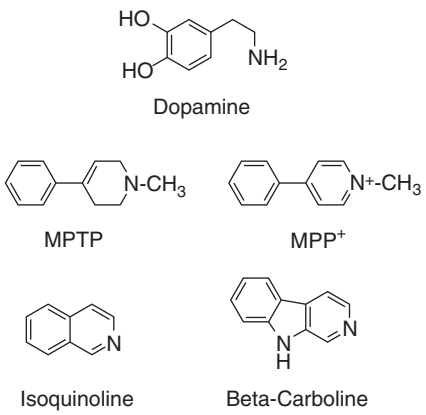

Figure 2 DAT transported compounds.

neurons such as cholinergic perikarya. The functional consequences of these molecules are poorly understood as is their involvement in Parkinson's disease (PD) and other movement disorders.

Epidemiology/Risk Factors

DAT Levels

The epidemiologic risk factors that affect the biochemistry of DAT remain ill defined. However, there is evidence suggesting that high levels of DAT play an important role in the selective vulnerability of substantia nigra dopaminergic neurons. On the other hand, a corresponding loss in DAT is associated with reduced transport of DA neurotoxins such as MPTP/MPP^+, resulting in less dopaminergic neuron loss over time. In this regard, animal models of DA cell death indicate that high levels of DAT lead to increased MPTP vulnerability whereas low DAT levels correlate with less MPTP toxicity.

Age

Age is a major risk factor for several neurological diseases including PD. Clinical pathological studies have reported a reduction in the number of neurons containing the protein and genetic signature for DAT within the substantia nigra beginning around the fifth decade of life. The structural and functional consequences of the reduction in DAT during normal aging are unknown. Since ~40% of human dopaminergic cells in the substantia nigra may be lost by 60 years of age, the remaining dopaminergic cells may attempt to maintain synaptic dopamine levels by decreasing DAT expression. Age-related reductions in neuronal DAT may be a protective mechanism aimed at slowing the detrimental effects of dopaminergic dysfunction.

Clinical Features and Diagnostic Criteria

Although it is well established that there is a threshold loss of ~70–80% of nigral DA neurons which correlates with the onset of the classic motor symptoms seen in patients with PD, the normal age-related loss of DAT containing nigral neurons does not result in a similar sequela of symptoms. Alterations in DAT activity

determined by single positron emission computerized tomography (SPECT) imaging are used as a diagnostic tool to differentiate PD from essential tremor and other overlapping syndromes. For example, a progressive loss in DAT striatal ligand uptake corresponding with PD severity is distinguished from essential tremor where there is normal striatal uptake.

Diagnostic Work-up/Tests

Parkinson's Disease

The clinical diagnosis for PD is generally straightforward; however, when incomplete or overlapping syndromes are presented, DAT imaging can improve diagnostic accuracy. Alzheimer's disease, essential tremor, vascular Parkinsonism and drug-induced Parkinsonism are examples of inconclusive parkinsonian features. SPECT–DAT allows imaging of striatal DA activity using different SPECT ligands ([^{99m}Tc]TRODAT, [^{123}I]β-CIT, [^{123}I]IPT, or [^{123}I] FP-CIT) that bind to the DAT. SPECT–DAT assists in differentiating between patients with frank PD and other movement disorders depending on differential DAT imaging. Positron emission tomography (PET) using radioligands is also used to evaluate DAT density in the striatum of humans. In fact, dopa-decarboxylase PET labeling was the gold standard for evaluating DA neurons in the substantia nigra prior to the advent of DAT tracers. Although PET has a higher resolution and provides better quantitative capacity than SPECT, the shorter half-life for the radiotracers and the higher cost per scan are caveats associated with the use of PET.

See also: Dopamine; Dopamine Dysregulation Syndrome; Dopamine Receptors; Parkinson's Disease: Definition, Diagnosis, and Management.

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Dopaminergic Agonists in Parkinson's Disease

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Glossary

Agonist – A neurochemical entity that acts at a receptor to stimulate a physiological response.

Dopamine – A naturally-occurring catecholamine active throughout the body in various neuronal and neuroendocrine roles. Dopamine is a neurotransmitter whose major deficiency in the striatum confers the symptomatology of Parkinson's disease.

Dopamine receptor – The structural and functional element of a neuron in a dopaminergic pathway at which dopamine acts. The dopamine receptor, which has several sub-types, is also subject to the influence of synthetic compounds that can act as either an agonists or antagonist.

Dopaminergic agonist – A compound with the neurochemical property of stimulating one or more classes of dopamine receptor.

Definition and History

Drugs that stimulate dopamine receptors in the striatum (putamen and caudate nucleus) have been a major direction of drug development for PD. Following the success of levodopa, an amino acid precursor of dopamine, researchers sought small molecules that could duplicate and, possibly, improve upon the effectiveness of levodopa at reversing parkinsonian signs and symptoms. Although these efforts yielded major advances in PD therapeutics, this class of drugs – *dopaminergic agonists* – has not replaced levodopa as the major therapy. Today, there is worldwide marketing of 12 dopaminergic agonists (DAs) with pharmacological actions resembling those of dopamine. DAs are extensively used for treating patients affected at all stages of PD. Their effectiveness as a primary management strategy for another movement disorder, restless leg syndrome (RLS), introduced them to an even larger group of patients.

The initial roles for DAs were as a substitute or as a means to augment the effectiveness of levodopa in PD. However, there has been evidence that their long-term use from the start can lower the risk of a PD patient to develop dyskinesias or motor fluctuations in association with levodopa. Furthermore, there is also an indication that DAs might be neuroprotective against PD progression. The consensus of most clinicians is that each of the available orally-administered DAs is quite similar in clinical effectiveness for PD and RLS. The major differences are found in their delivery and side-effect profiles. Despite more than two dozen prototypes of DAs that underwent clinical trials, major pharmacological improvements to either their potency or their selectivity of action (particularly to avoid adverse effects) have not been accomplished.

Table 1 The 29 dopaminergic agonists that are currently marketed or else have undergone clinical trials for Parkinson's disease

- ABT-431
- Aplindore (DAB-452)[a]
- Apomorphine[b]
- Bromocriptine [Parlodel][b,c]
- Cabergoline [Cabaser, Dostinex][b,c]
- CF 35–397[c]
- Ciladopa (AY27,110)
- CI 201–678[c]
- CQA 206–291 (and CQ 32–084)[c]
- CQP 201–403[c]
- CV 205–502[c]
- CY 208–243[c]
- α-Dihydroergocryptine [Almirid][b,c]
- FCE 23884[c]
- Lergotrile[c]
- Lisuride [Dopergin][b,c]
- Mesulergine (CU 32–085)[c]
- Naxagolide (PHNO; MK-458)
- Pardoprunox (SLV-308)[a]
- *N*-Propyl-aporphine
- Pergolide [Permax][c]
- Piribedil[b]
- Pramipexole [Mirapex, Mirapexin, Sifrol][b]
- Rotigotine TDS [Neupro][b]
- Ropinirole [Requip, Ropark][b]
- SK&F 38393-A
- Sumanirole (P&U 95666)
- Talipexole [Domin][b]
- Terguride[c]

[a]Currently undergoing clinical trial.
[b]Currently marketed in one or more countries.
[c]Compounds with an ergot or ergolene structure.
Marketing brand names are listed in square brackets.

Dopaminergic Agonists for Parkinson's Disease

Listed in **Table 1** are all of the DAs that have undergone clinical trials for PD since 1974. Of these, 10 are currently marketed. Structures of some of the marketed DAs are shown in **Figure 1**. Currently, two DAs are engaged in clinical investigation (aplindore and pardoprunox). Of the DAs that were discontinued from development, the major issues have been inefficacy, side-effects or toxicity, or the lack of clear advantage over other drugs.

Besides levodopa, the first drug administered for PD with dopaminergic properties was apomorphine. In 1951, a small clinical trial was published showing that transient reversal of parkinsonian features was accomplished with subcutaneous injections of this drug. The prominent nausea and hypotension acutely caused by apomorphine limited any practical application as a therapy. Furthermore, there was no understanding at this time that nigrostriatal dopamine deficiency was the key pathophysiology in PD. Hence, apomorphine was ignored from further development as a PD therapy for almost 3 decades. The subsequent rediscovery of this drug capitalized on its requirement for subcutaneous administration, in order to achieve rapid and reliable reversal of PD symptomatology. Apomorphine is now used for "rescue" from immobile states. It also can be infused continuously in the subcutaneous space by means of a portable pump, thereby maintaining constancy in anti-parkinsonian actions. However, despite its anti-parkinsonian potency, the inconvenience and discomforts of subcutaneous injection have relegated apomorphine to a rarely-utilized therapeutic niche as compared to the orally-active DAs.

Bromocriptine: The First Oral Dopaminergic Agonist for Parkinson's Disease

Introduced in 1974, bromocriptine was the first oral DA used to treat PD. Bromocriptine is synthetically modified from a naturally-occurring ergot structure and shares a structural homology with the molecular structure of dopamine,

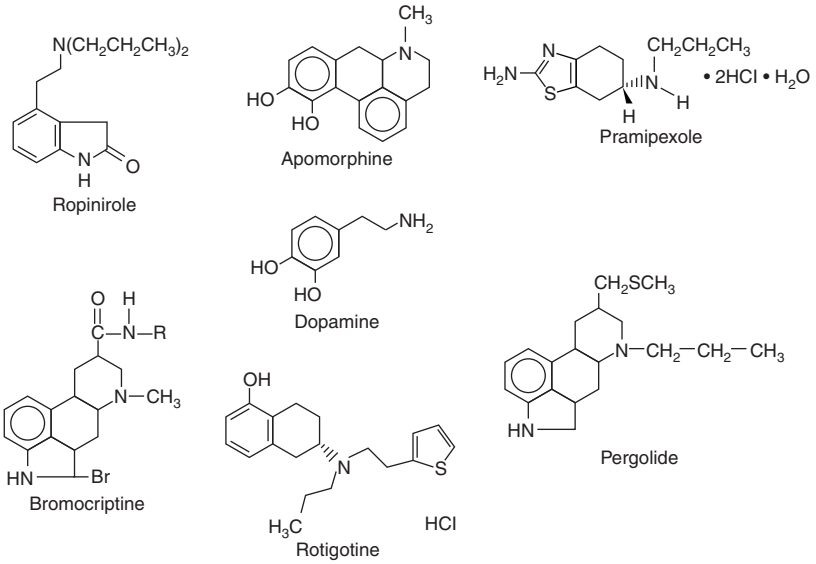

Figure 1 Dopaminergic agonists for Parkinson's disease.

as do virtually all of the marketed DAs (**Figure 1**). Bromocriptine was chosen for treating PD based on its dopaminergic properties that are also enacted on hypothalamic endocrine systems. Following initial clinical trials with bromocriptine, clinicians realized that this compound provided a possible substitute for levodopa that was not subject to its capricious absorption and metabolic pathways. In addition, many studies in PD subjects showed that the problems of advanced PD could be helped with this DA. Treating motor fluctuations and the opportunity for the lowering of LD dose (to lessen dyskinesias) were some of the clinical applications that bromocriptine offered to the patient with advanced PD. These properties are largely shared by the other marketed DAs, whose clinical differences are largely due to their side-effect profiles. Bromocriptine is still available but only infrequently used today.

Further Development in Dopaminergic Agonists: Dopamine Receptor Activity

In developing new DAs, the "ideal" receptor stimulation profile has not been definitively created. Early on, the predominant dopamine receptor population in the striatum was recognized to be a G-protein receptor not linked to adenylate cyclase. As additional classes of dopamine receptors were discovered, DAs in clinical use were found also to be quite potent at other dopamine receptors, termed D-3 and D-4. Relationships between the stimulation of these receptors and clinical outcomes (anti-parkinsonian effect and adverse effects) have not been clearly defined. Among marketed DAs, each differs in affinities at D-2, D-3, and D-4 receptors. The properties most closely linked to anti-bradykinetic effect in animal model studies were those of D-2 and D-3 agonism. However, these pharmacological differences do not seem to translate into altered profiles of clinical effectiveness.

One possible anti-parkinsonian target that has puzzled researchers is the adenylate cyclase-linked D-1 dopamine receptor. Experiments with animal models of Parkinsonism might suggest that stimulating the D-1 receptor should be avoided, since the mechanism for LD-induced dyskinesias seems to be mediated through this system. Among DAs used to treat PD, pergolide confers D-1 agonism while bromocriptine was a weak antagonist of the D-1 receptor. The relative similarity in clinical outcomes from these two drugs might suggest that the D-1 receptor played no role in anti-parkinsonian effects. However, one topic of interest has been whether a selective D-1 agonist might be effective for parkinsonian features without causing hallucinations or other undesired effects common with drugs acting at other classes of receptor. Two DAs, CY 208–243 and ABT-431, underwent limited testing in clinical trials and indicated that an anti-parkinsonian action could be achieved in the absence of stimulating D-2 receptors. (These drugs were not characterized with respect to the higher-order dopamine receptors such as D-3 and D-4). The limited clinical experience with each of these compounds did not allow answering the critical question of whether selective D-1 agonism would result in a better side-effect profile. Both D-1 agonists were discontinued after limited clinical trials because of their adverse effects.

Pharmacological Challenges with Dopaminergic Agonists: Adverse Effects

Managing side-effects of DAs is a major challenge for their use, especially at their initiation. Their adverse effects

can include nausea and vomiting, hypotension, sedation, confusion, hallucinations, and exacerbation of levodopa-induced dyskinesias). Fortunately, there are several medication strategies that can help to manage many of the adverse effects of DAs, including concomitant use of the anti-nausea compounds trimethobenzamide, domperidone, and clozapine, and other drugs that can counteract orthostatic hypotension. In addition, the principles of gradual introduction of these drugs and the development of tolerance permit DAs to be used successfully. Even regular use of apomorphine, a potent emetic, can be well tolerated with prior use of a DA.

The side-effect profile of DAs includes adverse reactions also encountered with the use of LD. At initiation of therapy, DAs are best titrated upward over several weeks in small steps to avoid problems. Dopaminergic side-effects previously experienced with LD, such as dyskinesias, can be exacerbated. A unique category of behavioral adverse reactions has been recognized with DAs. Termed *impulse control disorders*, these problems can develop in association with conventional DA dosage in PD (and RLS) patients with no prior propensity for uncontrolled gambling, hypersexuality, excessive participation in hobby activities, compulsive shopping or eating, or any of a number of similar behavioral alterations.

Another category of problems occurring with DAs was the discovery that they were associated with rare instances of fibrotic disorders. This was a known property of certain drugs with ergot structures like the anti-migraine drug methysergide, which had long been recognized to have the risk of causing retroperitoneal fibrosis. The first of the fibrotic disorders recognized to occur with bromocriptine was pleural thickening, intraparenchymal fibrosis, and effusion. This disorder led to severe pulmonary compromise in some instances, but appeared to remit gradually after discontinuation of the drug. Similar problems were recognized to occur after the introduction of pergolide. The ergot-related structure of these compounds and of others to follow was linked to this rare and seemingly idiosyncratic problem. The latest fibrosis-related problem to be recognized was that of cardiac valve thickening, sometimes requiring surgical treatment. Several reports linking this problem appeared in analysis of cases involving pergolide and cabergoline treatment. Though rare, these serious consequences have led to a reappraisal of the role for ergot-derivative DAs in PD therapy, especially since DAs without an ergot structure (like pramipexole and ropinirole) appeared to be equally effective as the ergot compounds. In the United States, pergolide has been withdrawn from the market because of its toxicity. Cabergoline has never been marketed in the United States for PD. In other countries, these compounds continue to be used, and so regular monitoring for the occurrence of pulmonary and cardiac valve fibrosis continues to be necessary.

Pharmacological Experience with Dopaminergic Agonists: Symptomatic Benefits

The initial experience with bromocriptine led to recognition of how effective DAs can be to enact major improvements in the various motor features of parkinsonism. Among several dozen studies, clinical observations indicated that tremor, rigidity, slowed movement, gait disorder, and postural disturbance could be helped, much as was accomplished by levodopa. In addition, the advanced PD patient often could be helped for problems not readily responsive to further increases of the levodopa regimen. The problem of regular wearing-off in the actions of levodopa can be helped by combining it with a longer-acting DA. Other clinical experience has shown PD patients with unpredictable "off" states and freezing of gait can be improved after addition of a DA regimen. Although the combination of DA with levodopa can lead to an increase of adverse effects, especially dyskinesias, it appears that DAs do not seem to exacerbate the problem as much as would an increased intake of levodopa. In fact, one strategy for managing patients with marked levodopa-induced dyskinesias was to substitute a DA against the prior regimen of levodopa.

As shown by the initial experience with bromocriptine and found subsequently with other DAs, one important application has been the treatment included early morning dystonia, especially if the drug was taken at bedtime. Adjunctive DA therapy also seems to lessen dystonic symptoms at other times of day as well. Combination of a DA with levodopa can be used as initial therapy to some advantage in avoiding various undesired outcomes occurring with levodopa alone. In several clinical trials carried out with bromocriptine, ropinirole, and pramipexole, initial treatment with a DA (even if combined at some point with levodopa) fared better than levodopa in risk for developing dyskinesias or motor fluctuations.

Several other parkinsonian disorders besides PD also have a dopaminergic deficiency, including progressive supranuclear palsy and multiple system atrophy (previously termed olivopontocerebellar atrophy, Shy–Drager syndrome, and striatonigral degeneration). Clinical trials investigating the possible effectiveness of DAs in these disorders did not find, in general, that DAs offered any relief of their parkinsonian features (as has been the experience with levodopa treatment). In typical PD, problems usually unresponsive to levodopa such as retropulsive imbalance and forward-flexed posture are also unlikely to improve with a DA. One study with pramipexole found that patients with resting tremor persisting during levodopa therapy did lessen after this DA was added.

Besides the ergot-derivative pergolide, the major DAs currently marketed on a worldwide basis are pramipexole and ropinirole. Both of these compounds with nonergot structures enact potent stimulation at D-2 and D-3

dopamine receptors but lack D-1 agonism. Each underwent extensive preclinical testing in animal models of parkinsonism that found they could act independently of levodopa in treating PD. This property was tested with each drug in a number of clinical trials. In addition to demonstration of their symptomatic efficacy as monotherapy and as adjunctive treatment with levodopa, other clinical trials investigated long-term outcomes of DA monotherapy and combined with levodopa, as compared to levodopa alone. Both ropinirole and pramipexole share with levodopa a similar profile of anti-parkinsonian actions. Added to levodopa in advanced PD with motor fluctuations and suboptimal response, various response measures have also demonstrated improvements and better quality of life from the DA, as compared to placebo treatment. The results of these studies have not, in general emphasized the improved features of one DA over another, although there haven't been randomized clinical trials comparing pramipexole to ropinirole. Earlier crossover studies comparing the anti-parkinsonian effectiveness of the DAs lisuride and pergolide to bromocriptine concluded that there was no overall difference.

Pharmacological Experience with Dopaminergic Agonists: Protective Benefits

As described above, DAs can be regarded as a therapeutic alternative to levodopa. Their increased expense and incidence of side-effects, as well as somewhat less symptomatic effectiveness, might seem to be reasons not to make use of DAs in early stages of PD. However, the demonstration of protective roles for various DAs has prompted consideration of their use in additional contexts.

Clinical trials exploring the risk for developing dyskinesias and motor fluctuations have been influential in charting an important role for DA therapy in PD. This role has arisen from hypotheses that the longer duration of action of DAs (based on their pharmacokinetic profiles) offers more continuous dopaminergic stimulation and, hence, less provocation of dyskinesias and motor fluctuations than shorter-acting levodopa preparations. This notion has been tested in two large scale studies involving randomizations between optimized regimens of levodopa and the DAs pramipexole and ropinirole (the CALM-PD and Ropinirole 056 studies, respectively). Both studies were carried out for several years and permitted a comparison between outcomes with levodopa alone and the DA (either as a monotherapy or with some supplemental levodopa, as needed). Subjects were followed with respect to clinical outcomes such as relief of Parkinsonism and the development of dyskinesias (and, in the case of the CALM-PD study with pramipexole, also for development of motor fluctuations). In both studies, monotherapy with the DAs was associated with less incidence of dyskinesia, even if levodopa needed to augment to the previous DA monotherapy regimen. After a few years of treatment, most subjects needed to supplement DA regimens with levodopa for optimal effect. Although the supplemental levodopa clearly increased the incidence of dyskinesias or motor fluctuations, risks for developing these chronic levodopa-related outcomes were diminished by the early use of the DA. These studies also provided the chance to compare symptomatic control of parkinsonism by the two randomized treatment options; benefits of the DAs appeared to be less than achieved by levodopa. Combining a DA with levodopa does permit a smaller daily dose of levodopa to be used, but this levodopa sparing effect may not be the entire story for improved outcomes. It is also possible that the more continuous dopaminergic stimulation with the combination regimens was the basis for the better results with respect to dyskinesias and motor fluctuations, although this question clearly needs further exploration.

Another protective dimension of DAs has to do with their possible actions as disease-modifying drugs. Neuroprotective actions of both ropinirole and pramipexole have been demonstrated in various in vitro models of neuronal degeneration induced by toxins or other experimental interventions. These results have been extrapolated to hypotheses that doses of DAs used in PD therapeutics might offer a PD patient not only symptomatic benefit but, possibly, slowing of disease progression. The two studies investigating this question compared regimens of pramipexole (a subset of patients enrolled in the CALM-PD study) or ropinirole (a trial termed REAL-PET) versus randomization to levodopa. In each instance, a surrogate marker of disease progression was the basis for interring neuroprotection. For the pramipexole study, it was change from baseline in presynaptic dopamine transport binding in the stratum with a single-photon emission computerized tomography ligand, beta-CIT (whose binding is proportional to the extent of nigrostriatal dopaminergic projections). The ropinirole trial used positron emission tomography scans of the striatum using ^{18}F-fluorodopa (a levodopa analogue), also providing a view of whether the continuing degeneration of dopaminergic nigrostriatal neuronal projections differed between the levodopa and DA regimens. In each instance, these surrogate markers of neuronal degeneration suggested that the DAs slowed disease progression compared to levodopa.

Although alternative views might be that levodopa might have accelerated disease progression (as judged by loss of dopaminergic presynaptic innervation in the striatum), or that the neuroimaging studies were merely artefactual, many neuroscientists have viewed these trials as confirmation of preclinical animal model data with the DAs. Further investigation of these intriguing findings is needed before firm conclusions are warranted as to a disease-modifying neuroprotective role of DAs in PD.

Furthermore, the question remains whether the apparent benefits of these drugs are linked to their DA properties or other pharmacological actions.

Delivery of Dopaminergic Agonists

The continuity of dopaminergic action appears to be critical for avoiding long-term and irreversible complications of LD treatment in PD. There is evidence from animal models of parkinsonism that intermittent pulsatile receptor stimulation with a DA can generate dyskinesias (much as short-acting LD does). In these experiments, the same drug administered in a more continuous manner avoids this outcome. These observations are in support of a therapeutic strategy for long-acting dopaminergic stimulation. The available oral drugs have plasma elimination half-lives in excess of that for a LD. It may be for this reason that DAs produce better results than LD on a long-term basis. However, other evidence from animal studies suggests that LD confers increased risk for dyskinesias independently of its short plasma elimination half-life.

The three major marketed DAs (ropinirole, pramipexole, and cabergoline) offer pharmacokinetic profiles useful for managing different problems in this disorder. In recent years, a transdermal DA was introduced with a 24-h effect. Rotigotine, a novel nonergot compound with a short clearance half-life, was formulated for maintaining constant dopaminergic stimulation. The product can be especially helpful for patients needing PD medication effect throughout the night or upon awakening. Otherwise, the effects of rotigotine are quite comparable to the other marketed DAs. A controlled-release preparation of ropinirole, introduced in 2008, also offers also a 24-h continuity of effect.

On the other side of the pharmacokinetic spectrum, injection of apomorphine provides a rapid dopaminergic effect. With the onset of the anti-parkinsonian effect typically occurring within 5 min after subcutaneous injection, apomorphine can rapidly and reliably rescue a PD patient from immobility associated with irregular effects of oral medications. Apomorphine is a potent DA with both D-1 and D-2 dopamine receptor effects. It has also been used for continuous subcutaneous infusion as a substitute for all other PD treatment. Continuous apomorphine delivery can be titrated to a dose that maintains an "on" state without triggering dyskinesias.

Dopaminergic Agonists: Role in Therapy

DAs have achieved a major role in the treatment armamentarium for PD, especially as a means for boosting the effectiveness of anti-parkinsonian control when levodopa effect is maximal. Their extended plasma clearance half-life is another factor contributing to their utility. As shown by a large number of studies, these drugs can provide sustained benefit for advanced PD. They may also help to avoid problems associated with long-term LD use and, possibly, progression of the disease itself. DAs are far from an ideal therapy: they are expensive and have a number of adverse effects associated with them, especially the relatively uncommon though potentially disabling behavioral disorders discussed above. Younger PD patients seem to be good candidates for the initial use of DAs, since LD exposure poses the risk for developing dyskinesias and motor fluctuations. Some clinicians are concerned that older PD patients are not likely to tolerate this class of medications at usual therapeutic doses, although there are many examples of elderly patients well managed on DAs. The still-unconfirmed findings of apparent neuroprotective actions are a reminder that drugs sometimes have additional actions beyond initial intentions that guided their development.

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Drosophila Models of Parkinson's Disease

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Glossary

Drosophila – *Drosophila melanogaster*, a common fruit fly.
GAL4/UAS – A widely used bipartite system that uses the induced expression of yeast transcription activator GAL4 to drive expression of a transgene adjacent to upstream activator sequences (UAS).
Mutagenesis – The process of inducing changes in the DNA, usually by chemicals or mobile DNA elements, to attenuate the function of a gene.
Parkinson disease (PD) – A neurodegenerative disorder leading to loss of motor skills, caused by the loss of dopaminergic neurons in the central nervous system.
RNAi – RNA interference, a mechanism by which endogenous gene transcripts are degraded following exposure to short, complementary sequences of double stranded RNA.

Definition and History

Drosophila melanogaster, commonly referred to as fruit flies reflecting their natural habitat on rotting fruit, belongs to the family *Drosophilidae*, which derives its name from the Greek *drosos* = dew and *philos* = loving. *Drosophila* is a widely used laboratory model organism, particularly in the fields of genetics and developmental biology. Recently, *Drosophila* has been used to study human disease mechanisms. The first *Drosophila* model of Parkinson disease (PD) was reported in 2000 with the generation of transgenic flies expressing normal and dominant mutant forms of α-synuclein. The first model of recessive forms of PD was reported in 2003 with the generation of loss-of-function mutations in the *Drosophila* homolog of *parkin*.

Why Use *Drosophila* Models?

Drosophila present a number of technical advantages over other common laboratory organisms. These include a short life cycle and generation time, taking only 10 days from fertilized egg to mature adult, a myriad of powerful molecular and genetic tools available, and a diverse and freely accessible public resource centers. One of the most powerful tools used in *Drosophila* is the GAL4/UAS system, which exploits the potent yeast transcription activator GAL4 to selectively drive the expression of a designated sequence adjacent to the upstream activator sequence (UAS). This system has been widely used in the investigation of gene function in vivo, since it offers a high degree of temporal and spatial controllability. Typically used to overexpress a gene of choice, this system has recently been adapted to induce gene-specific RNAi knockdown in vivo. To complement this, a wide array of classic genetic approaches is available to mutate the genome for gene-specific or random mutagenesis. It is relatively straightforward, rapid, and extremely cost-effective to generate 'knock out' models of a gene of interest by targeted mutagenesis.

Perhaps the most widely lauded advantage of *Drosophila* research is the ability to conduct large-scale genetic screens capable of identifying novel genes regulating a biological process of interest. This approach allows the identification of other genes that interact with a gene of interest through modification of a loss-of-function or overexpression phenotype. These flies are then mated to a mutagenized strain and the progeny screened for mutations that either suppress or enhance the phenotype. Identifying the genes that modify the mutant phenotype is an extremely powerful method for uncovering the biological basis of the pathology. It is largely for this reason that in recent years *Drosophila* has received significant attention as a powerful model organism with which to dissect the pathogenic mechanisms of human disease and even as a tool in the drug discovery pipeline.

The specific clinical and pathological details concerning idiopathic PD and other forms of Parkinsonism are elaborated in other articles of this Encyclopedia; however, we shall briefly iterate the salient points relevant to the context of modeling PD in *Drosophila* and its contribution to our understanding of the disorder. Briefly, the cardinal features of PD include degeneration of dopaminergic (DA) neurons, progressive locomotor deficits, and in many cases the presence of Lewy body inclusions. All of these features can be analyzed experimentally in *Drosophila*.

Much insight into the pathogenic mechanisms contributing to PD has been provided by the analysis of genes linked to relatively rare heritable forms. Mutations in a growing list of genes can give rise to dominant and recessive Parkinsonism, indicating aberrant toxic gain-of-function or loss-of-function, respectively, of those inherited cases. It is thought that similar pathogenic mechanisms may contribute to the more common sporadic form of PD. The genetic aberrations that cause heritable Parkinsonism can be mirrored using standard genetic approaches in *Drosophila*. For example, dominantly acting mutations in

Table 1 Major characteristics of the current *Drosophila* models of PD

Gene/ protein	*Mode of inheritance*	*Model type*	*DA neuron loss*	*Locomotor deficits*	*Other*	*Putative function*
SNCA/α-synuclein	Dominant	Transgenic	±	±	Lewy body-like aggregates	Synaptic plasticity?
Parkin	Recessive	Mutation	+	+	Mitochondrial dysfunction	E3 ubiquitin-protein ligase
DJ-1	Recessive	Mutation	− (+)	−	Oxidative stress sensitive	Oxidative stress sensor, chaperone
PINK1	Recessive	Mutation	−	+	Mitochondrial dysfunction	Mitochondrial kinase
Dardarin/ LRRK2	Dominant	Transgenic, mutation	±	++		Kinase
HtrA2/Omi	?	Mutation	−	+	Oxidative stress sensitive	Protease

α-synuclein and LRRK2 have been successfully modeled by generating transgenic lines that can express wild-type and pathogenic forms in a spatially and temporally controlled manner. Similarly, loss-of-function mutagenesis has been used to target the conserved genes for recessively inherited Parkinsonism *parkin*, *PINK1*, and *DJ-1*. The major characteristics of the various current models are summarized in **Table 1** and provided in further detail in the following section.

Summary of Model Characteristics

Although the *Drosophila* genome does not encode members of the synuclein family, models to study the pathogenic mechanisms of α-synuclein have been established. A number of independent transgenic lines expressing wild-type or pathogenic human α-synuclein have been shown to cause degeneration of DA neurons and locomotor deficits have been reported. It should be noted that not all experimenters have observed robust DA neuron degeneration but instead have reported a decreased DA neuron integrity. Protein aggregates with Lewy body-like characteristics have also been reported in this model, further strengthening the popular hypothesis that aberrant protein aggregation/degradation underlies α-synuclein pathogenesis. Consistent with these ideas, it has been reported that transgenic or chemical induction of molecular chaperones, such as heat shock proteins, is able to prevent some aspects of α-synuclein pathology in *Drosophila*.

Studies in other systems suggested that the toxicity of α-synuclein may be affected by posttranslational modifications such as phosphorylation. Compelling evidence using transgenic lines expressing phospho-mimic and phospho-defective forms of α-synuclein has demonstrated that phosphorylated α-synuclein may promote aggregation and toxicity.

Loss-of-function mutations in *parkin* cause age-related degeneration of DA neuron loss and locomotor deficits. They also show widespread mitochondrial disruption accompanying the degeneration of flight muscles and defects in spermatogenesis. Parkin mutants are also sensitive to chemicals that elevate oxidative stress or disrupt mitochondrial function. These observations support the view that a primary role of Parkin is to maintain mitochondrial integrity and protect against oxidative stress. Remarkably, these phenotypes are exactly recapitulated in loss-of-function *PINK1* mutants. In a ground-breaking study, a number of groups demonstrated using classic genetic analysis in *Drosophila* that parkin and PINK1 likely act in a common pathway, and epistasis analyses showed that parkin acts downstream of PINK1. This work in *Drosophila* was the first evidence that two genes linked to PD function in a common biological pathway. Another breakthrough came with the discovery that PINK1 and parkin genetically interact with components of the mitochondrial fission and fusion pathway. A number of studies in *Drosophila* models have now shown that the PINK1/parkin pathway likely regulates mitochondrial fission events, which have since been corroborated in mammalian systems. These findings provide a compelling lead toward the function of the PINK1/parkin pathway and its role in PD pathogenesis.

In contrast to the distinct overt phenotypes of *parkin* and *PINK1* mutants, mutations in *DJ-1* do not cause morphological or behavioral defects. Drosophila encodes two genes highly homologous to DJ-1, although the expression of one (DJ-1a) appears to be restricted to the male germline. Surprisingly, *DJ-1a/b* null mutations display no observable external abnormality and no degeneration of DA neurons; however, it has been shown that *DJ-1* mutants are strikingly sensitive to oxidative stress agents such as paraquat and rotenone. Indeed, a combination of biochemical and transgenic techniques has shown that posttranslational modification of DJ-1 upon oxidative stress is critical to DJ-1's protective role.

The most recent new *Drosophila* model of PD has been created using the common human $LRRK2^{G2019S}$ mutation.

This model recapitulates the cardinal features of progressive DA neurodegeneration and locomotor deficits; however, currently little more is known about the mechanism of LRRK2-mediated pathology. One intriguing recent report studying the sole *Drosophila* homolog has shown that one target of its kinase activity may be to 4E-BP, regulating protein translation and the induction of stress response programs.

Oxidative stress is a central theory in the pathogenesis of PD. *Drosophila* models have contributed to this idea by demonstrating that transgenic or pharmacological induction of antioxidant mechanisms is capable of mitigating toxic effects in nearly all models analyzed to date, including α-synuclein, parkin, PINK1, and DJ-1. Further work using these models to identify additional protective pathways will provide valuable insight into the pathogenic mechanisms of PD and highlight putative therapeutic avenues.

See also: Alpha-synuclein; Mitochondrial Dysfunction; PARK1, Alpha Synuclein; PARK2, parkin; *PARK6, PINK1*; PARK7, DJ1; Parkinson's Disease: Definition, Diagnosis, and Management; Parkinson's Disease: Animal Models; Parkinson's Disease: Genetics.

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Drug-induced Movement Disorders

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As drugs that affect central nervous system chemistry have only been in widespread use for the last 50–60 years, drug-induced movement disorders have not been long recognized. Akathisia, which is not a movement disorder but an inner feeling of restlessness and inability to sit still, was first described, in 1947, as a drug-induced state in association with the use of promethazine. The introduction of typical neuroleptics, which have a common dopamine receptor antagonism, made the clinical phenomenon of drug-induced akathisia apparent. Atypical antipsychotics have expanded the spectrum of drugs that induce akathisia.

Drug-induced parkinsonism was first described with the use of reserpine, a dopamine depleting agent. When traditional antipsychotics were introduced, drug-induced parkinsonism became a common clinical phenomenon. In the late 1950s and early 1960s, the first understanding of parkinsonism as it related to dopamine deficiency or dopamine blockade led to the momentous discovery that levodopa could alleviate the motor symptoms of Parkinson's disease. The successful introduction of large dosages of levodopa to treat Parkinson's disease in 1967 also included the description that athetoid movements were induced by levodopa in some of the patients. In 1969, additional reports about the early usage of levodopa in Parkinson's disease described that as many as 50% of the patients receiving levodopa developed dyskinesia. Levodopa became the treatment of choice for Parkinson's disease, and in subsequent years, many types of dyskinesia associated with the administration of levodopa have been described including wearing off dyskinesia, peak-dose dyskinesias, diphasic dyskinesias, and off-period dystonia. Most of the abnormal movements associated with the administration of levodopa are choreodystonic.

Tardive dyskinesia encompasses all of the delayed onset movement disorders associated with the use of dopamine receptor blocking agents. The movements seen in tardive dyskinesia can be choreoform or dystonic. Tardive dyskinesia was probably first described in 1957, 5 years after the introduction of chlorpromazine when a number of patients were reported who had been exposed to the drug for 2–8 weeks. These patients were elderly women who developed a lip-smacking dyskinetic movement. In subsequent years, isolated reports of choreodystonic movements and lingual facial buccal dyskinesia developing after the use of dopamine receptor blocking agents were published. Initially, the psychiatric community was reluctant to accept the notion that these movement disorders were secondary to the administration of neuroleptic agents. It was only in the late 1960s, when large-scale epidemiologic studies that demonstrated that these movements were associated with long-term neuroleptic treatment appeared, that the concept of tardive dyskinesia was accepted.

Pathophysiology

Most drug-induced movement disorders involve alterations in dopaminergic transmission. Drugs that are dopamine receptor antagonists such as the traditional neuroleptics – chlorpromazine and haloperidol – and the atypical neuroleptics – olanzapine, resperidone, and clozaril – as well as the antiemetic metaclopramide can all induce akathisia, acute dystonia, drug-induced parkinsonism, and tardive dyskinesia. The simplest and most long-standing theory of the pathophysiologic basis of these movements is that, dopamine receptor blockade induces supersensitivity of the dopamine receptors, which leads to abnormal movements. This concept was first published in 1970, based on the similarity between levodopa-induced dyskinesia in parkinsonism and tardive dyskinesia. The suggestion was made that chronic neuroleptic treatment produced supersensitivity of striatal dopamine receptors analogous to denervation-induced cholinergic supersensitivity seen in peripheral muscles. This concept has remained an important central construct in thinking about managing drug-induced movement disorders secondary to dopamine receptor blockade. However, there has been much criticism of this theory, and several important inconsistencies have been noted. In animal models of dopamine receptor antagonism-induced supersensitivity, the supersensitivity and the behavioral response occur quickly whereas tardive dyskinesia, in patients, usually takes months or years to develop. In addition, the movements of tardive dyskinesia can persist for years and sometimes be permanent whereas in the animal model, supersensitivity tends to dissipate quickly. It is also apparent that supersensitivity can be readily induced in the animal model whereas only a subset of patients develop a 'supersensitive' response, resulting in tardive dyskinesia. The supersensitivity dopamine receptor model is attractive and simple, but probably not the entire explanation.

Types of Drug-Induced Movement Disorders

The following drug-induced movement disorders will be described: acute dystonia, akathisia, drug-induced parkinsonism, and tardive dyskinesia. Drug-induced movement disorders can be divided into those movement disorders that are related to drugs which block or interfere with dopaminergic mechanisms and those which are dopaminergic agonists. Drug-induced movement disorders related to dopamine receptor antagonists occur in a temporal sequence from the earliest administration of the drug to more prolonged administration of the drug. The earliest drug-induced movement disorder is acute dystonia followed by akathisia, drug-induced parkinsonism, and, finally, tardive dyskinesia. Drugs which act as dopaminergic agonists or promote dopaminergic mechanisms including levodopa, methyphenidate, amphetamine, and cocaine induce choreo dystonic movement disorder after its prolonged use. However, cocaine and amphetamine can induce acute choreo dystonic disorders, but the most common agonist-induced movement disorder is levodopa-induced dyskinesia following months to years of dopaminergic administration for Parkinson's disease.

Drug-Induced Movement Disorders Related to Dopamine Receptor Antagonists

Akathisia

Akathisia is not a movement disorder but a subjective complaint of restlessness, often associated with the inability to keep still. Patients may complain of tension or abnormal limb sensations such as pulling or drawing feelings. The subjective inner sensation of restlessness often results in the patient performing a variety of motor movements in an attempt to relieve this sensation. Mildly affected patients may demonstrate little movement or can be seen physically tapping their toes or shifting in their chair. They may also move from one foot to another while standing and feel that they have to keep walking. Patients who are more severely affected may pace, run, rock, and, quite simply, be unable to sit still or even lie still for any period of time. The important point is that akathisia is not associated with any particular involuntary movement.

Differential diagnosis

The differential diagnosis of akathisia is not large. Other diagnoses to be considered in patients with this subjective sensation include agitation seen with psychiatric disorders, drug withdrawal states, and restless leg syndrome (RLS). Differentiating akathisia from agitation in a very disturbed patient can be difficult and may rely on a trial of increasing the neuroleptic dose. If an increase in the neuroleptic dose improves the psychosis and the restlessness, then it is probably more related to the psychiatric state. However, if increasing the neuroleptic increases the restlessness then the patient has akathisia. Opiate withdrawal can also result in restless, painful sensations in the legs and this is obviously diagnosed with the history of opiate ingestion. RLS can be difficult to distinguish, but in RLS, the abnormal sensation is usually limited to the legs and is particularly prominent at rest and often more so at night. It is quite useful that in RLS, movement alleviates the abnormal sensation.

Management

The most reliable therapy for akathisia includes neuroleptic dosage reduction or withdrawal if this is possible from a psychiatric standpoint. If this is not possible, a less potent neuroleptic or atypical neuroleptic could be

substituted, but this may not be possible from a psychiatric standpoint. There are reports that anticholinergics, antihistamines, and amantadine may improve restlessness. Benzodiazapines, β-blockers, and clonidine may be useful in treating akathisia.

Epidemiology

Akathisia can develop extremely rapidly after the initiation of neuroleptic treatment or it can develop after neurolpetic dosage is increased or a change is made from an atypical to a more potent traditional neuroleptic. The prevalence of akathisia varies widely in the literature depending on the potency and dosage of the drug examined. Prevalence estimates range from as low as 5% to as high as 75% with potent traditional neuroleptics such as haloperidol.

Pathophysiology

The underlying pathophysiology of akathisia is not known. It is known that akathisia seems to be related to reduced dopaminergic function either by receptor blockade or by dopamine depletion. There has been speculation that mesocortical dopaminergic mechanisms are involved.

Drug-Induced Acute Dystonia

Acute dystonic reactions, along with akathisia, are early drug-induced movement problems. Fifty percent of acute dystonic reactions occur within 48 h of beginning treatment with a neuroleptic, and 90% of acute dystonic reactions occur within 5 days of beginning the treatment. Acute dystonic reactions are associated not only with all antipsychotic drugs, but also with metaclopramide.

Epidemiology

The risk of acute drug-induced dystonia varies considerably depending on the age of the population studied, the potency and dosage of the drug administered, the route of administration, and any previous history of dystonic reactions. This movement disorder is much more likely to occur in younger individuals and is almost never seen after the age of 40. There does not seem to be a gender predilection for this reaction and there has been some discussion whether previous cocaine use is a risk factor. Patients who experienced a previous dystonic reaction seem to be at more risk.

Pathophysiology

The pathophysiology of acute dystonic reactions is obscure. It is related to dopaminergic mechanisms since this type of dramatic reaction is only seen with drugs that interfere with dopaminergic mechanisms. However, very little is known about why one patient develops an acute dystonic reaction and another does not when both are exposed to the same potent drug.

Clinical features

Acute dystonic reactions consist of a wide variety of prolonged or short-lived muscle spasms that result in typical dystonic abnormal postures and movements. Involvement of the eyes, face, throat, and neck are the most frequent manifestations. Oculogyric crisis in which the eyes are forced upward and lateral can be associated with head and neck dystonic postures. Acute dystonic reactions may encompass blepharospasm, grimacing, forceful jaw opening, tongue protrusion, and glossopharyngeal contractions. Torticollis, scoliosis, and trunk flexion are also possible. If the movement and postures are severe enough, there may be considerable pain. Younger children tend to have more generalized dystonic posturing particularly of the extremities and trunk.

Management and treatment

If the offending drug is withheld, the movement disorder will resolve spontaneously. However, the movements are distressing and can be disabling and acute treatment is warranted despite the self-limited nature of the condition. Almost all acute dystonic reactions will respond rapidly to parenteral injection of an anticholinergic or antihistaminic drug such as benztropine, procyclidine, or diphenhydramine. A single intramuscular dose of benztropine 1–2 mg or diphenhydramine 25–50 mg will usually resolve the episode within 15–20 min, but must be followed by an oral anticholinergic for at least a few days. Parenteral diazepam may be equally effective in relieving the movements; however, parenteral diazepam will usually sedate the patient and possibly cause respiratory depression. Acute laryngeal spasm, which is potentially a life-threatening condition, should be treated with intravenous benzodiazepam or benztropine. If no response is obtained within 30 min, the dosage of medication can be repeated.

After the resolution of the acute dystonic episode, most movement disorder experts will continue to administer benztropine or trihexyphenidyl in low dose for 4–7 days. This is done to prevent the reoccurrence of acute dystonia.

Drug-Induced Parkinsonism

Epidemiology

Drug-induced parkinsonism is a clinically distinct syndrome consisting of resting tremor, cogwheel rigidity, bradykinesia, and gait impairment. It is not clinically distinguishable from Parkinson's disease. There are some caveats with regard to the previous statement, which will be discussed in 'clinical course.' Risk factors for the development of drug-induced parkinsonism are uncertain and the literature has many contradictory reports. These risk factors have variously been listed in the past as including female gender, being elderly, administration of high potency and high dosages of neuroleptics. Other risk factors that have been examined include prior brain

damage, hereditary factors such as a family history of Parkinson's disease, and cognitive impairment. The most commonly accepted risk factors for the development of drug-induced parkinsonism remain female gender and the potency and dosage of the drug administered. Even with these risk factors, however, many patients taking high-dose potent neuroleptics do not develop drug-induced parkinsonism. Further, the time course for the development of drug-induced parkinsonism can vary considerably. Occasionally, patients develop severe parkinsonism after only a few days of a small-to-moderate dose of a neuroleptic administration and on other occasions, it may take months for the parkinsonism to develop. It is important to follow patients with drug-induced parkinsonism even after neuroleptics or dopamine depleting drugs are stopped, because reports exist demonstrating the evolution of Parkinson's disease, both clinically and pathologically, years after the development of transient and reversible drug induced parkinsonism. This observation suggests that patients who develop drug-induced parkinsonism may have subclinical Parkinson's disease and the drug exposure has served as a 'drug challenge' to unveil a disorder that may only develop spontaneously years later.

Pathophysiology

The pathophysiology of drug-induced parkinsonism when precipitated by typical or atypical neuroleptics seems straight forward with dopamine receptor antagonism resulting in parkinsonism. However, many patients receiving traditional or atypical neuroleptics at high dosage do not develop drug-induced parkinsonism. Obviously, more than simple dopamine receptor antagonism is involved. However, interference with dopaminergic mechanisms is the best explanation for this phenomenon. It is also consistent with the observation that drugs that deplete central nervous system dopamine, such as reserpine, also induce parkinsonism.

Parkinsonism can also be induced by medications which are not traditional or atypical neuroleptics; for example, Lithium. Lithium, more commonly, causes a symmetric postural and kinetic tremor. However, it has been reported to induce hypokinesia, akathisia, rigidity, and a resting tremor. Another nonneuroleptic which induces parkinsonism through mechanisms unknown is valproic acid, which is a standard anticonvulsant. Valproic acid does not affect dopamine receptors. Certain calcium channel blockers, particularly cinnarizine and flunaraizine, not available in the United States, also induce parkinsonism. However, these particular calcium channel blockers may influence calcium-mediated neurotransmitter release, and thus might decrease the amount of dopamine available. It has been reported that SSRIs (selective serotonin reuptake inhibitors) can induce parkinsonism. However, in my experience, this is a very rare phenomenon. More often than not, these cases involve misdiagnosis.

Clinical features

Parkinsonism induced by neuroleptic drugs can mimic all of the features seen in Parkinson's disease. Bradykinesia is particularly common in a drug-induced state with a paucity of tremor. Since the basic clinical features of drug-induced parkinsonism can appear exactly the same as Parkinson's disease, it is important to recognize certain historical and additional clinical features that can be helpful in differentiating drug-induced parkinsonism from Parkinson's disease. Historically, drug-induced parkinsonism is seen in persons taking one of the medications known to cause this problem. In addition, the onset from normal motor behavior to moderate parkinsonism is usually of a subacute nature occurring over weeks to months instead of the slow insidious progression over years seen in Parkinson's disease. In addition, drug-induced parkinsonism is almost always symmetric in presentation whereas Parkinson's disease almost invariably starts in a unilateral fashion, and over a period of years spreads to the opposite side.

Management and treatment

The management and treatment of drug-induced parkinsonism involves understanding the reason the patient is taking the causative drug. The ideal approach from a neurological standpoint is to discontinue the agent inducing parkinsonism. Even if this is possible, it may take weeks to months for the parkinsonism to resolve. In the event that the patient's psychiatric state requires continued administration of a neuroleptic, changing the dose to a less potent neuroleptic might prove beneficial, in terms of the motor phenomenon, to the patient. However, this can result in an increase in the psychiatric problem. Depending on the clinical manifestations of the parkinsonism, anticholinergics, amantadine, and levodopa can be employed to treat drug-induced parkinsonism with varying degrees of success.

Drug-induced parkinsonism requires pharmacological treatment only when the patient is markedly symptomatic from the parkinsonism. Treatment should be continually reevaluated since it will not be needed for long periods.

Tardive Dyskinesia

Epidemiology

The epidemiology of tardive dyskinesia has been both controversial and confusing. Tardive dyskinesia is defined as any delayed onset movement disorder induced by a dopamine receptor antagonist (neuroleptics and antiemetics). The definition of what constitutes tardive dyskinesia has been made difficult because many of the abnormal movements recognized as part of the tardive dyskinesia spectrum were described in schizophrenic patients long before the introduction of neuroleptic agents. A wide variety of stereotyped mannerisms,

agitated behaviors, and other motor disorders have been seen in psychotic patients. It is true that the mannerisms seen in psychosis that resemble tardive dyskinesia are usually more complex, highly ritualistic, and may have symbolic significance to the patient. When formal epidemiologic studies were first reported to study tardive dyskinesia there were methodological problems, including a paucity of proper prospective studies using matched untreated controls, clinical definitions were not often given, accepted rating scales were not employed, and documentation of treatment schedules were not recorded. Nonetheless, despite all of these initial problems, it became clear that the administration of certain categories of medications, particularly the dopamine receptor antagonists, can result in a wide range of abnormal choreodystonic movements. Estimates of the prevalence of tardive dyskinesia range from 1% to 60% of patients. Standard neuroleptic therapy results in tardive dyskinesia in ~20% of patients. The average yearly rate of developing tardive dyskinesia is ~5% per year for the first several years with accumulative 5-year incidence of 20–25%. A wide variety of risk factors have been identified including age, psychiatric diagnoses, gender, pre-existing organic brain damage, diabetes, potency and dosage of neuroleptics administered, and the question of whether medication-free periods also enhance the risk of developing tardive dyskinesia. However, many of the risk factors have been controversial or at least inconsistently reported. Patients who were psychiatrically normal can develop tardive dyskinesia. The most consistent risk factors seem to be age and type of medication administered. There has been increased interest in the use of the so called atypical neuroleptics as a way of reducing the risk and incidence of tardive dyskinesia. There have been multiple studies indicating that atypical neuroleptics seem to have a lower risk of inducing tardive dyskinesia, but the caveat is that this lower risk has led to the more wide spread use of the atypical neuroleptics and the end result may be that more patients develop tardive dyskinesia because more are exposed.

Pathophysiology

Dopaminergic mechanisms seem to be heavily involved in the development of tardive dyskinesia. It has been proposed that the chronic administration of neuroleptics results in a chronic blockade of striatal dopamine receptor sites and that this chronic blockade ultimately induces alterations in the sensitivity and numbers of dopamine receptors. Clinical data that support this notion include the exacerbation of tardive dyskinesia with dopaminergic medications, suppression of tardive dyskinesia with dopaminergic antagonist, and enhancement of the movements with anticholinergics. In addition, the study of atypical antipsychotics has demonstrated that those with the lowest risk for extrapyramidal side effects are those atypical neuroleptics that do not chronically bind to dopamine receptors. Clozapine is an example of such an atypical neuroleptic. The dopaminergic supersensitivity model remains essential when thinking about tardive dyskinesia; however, it is probably simplistic and not the only mechanism. Other neuro transmitters have been investigated regarding their role in tardive dyskinesia. The role of GABA has been investigated and it has been proposed that release of GABA from the external globus pallidus neurons innervating the subthalamic nucleus could result in decreased outflow from the globus pallidus and result in abnormal movements. Finally, there has been some discussion that an additional pathophysiologic mechanism might be direct neurotoxicity of neuroleptic medications. It has been hypothesized that the blockade of dopamine receptors results in increased dopamine turnover which results in the formation of increased free radicals, which damage those neurons.

Clinical features

Choreodystonic movements which characterize tardive dyskinesia are usually seen in the context of a chronically administered neuroleptic without a change in dosage. The most common clinical setting in which the movement disorder emerges is after the dosage is lowered or discontinued entirely. The movements may also emerge when a more potent neuroleptic is substituted with a less potent neuroleptic. Involuntary movements usually begin after as little as 3 months of neuroleptic exposure although, more often than not, exposure has been much more prolonged. In very rare instances, tardive dyskinesia may begin with a shorter course of neuroleptic therapy.

The most common movement, buccolingual facial dyskinesia can look like chewing or biting movements, teeth clenching, or lateral side-to-side movements of the jaw. Lip involvement can result in pouting, pursing, or sucking movements which often times have an audible component. If the movements are severe enough, it may ulcerate the tongue or grind down the teeth. Excessive eye blinking, blephrospasm, and grimacing of the lower jaw may also be seen. Neck, trunk, and axial muscles can be involved resulting in locking or thrusting movements. The diaphragm can be involved resulting in respiratory dyskinesias which often are experienced by the patient as a feeling of shortness of breath. Limb movements in this clinical setting may be choreoform, athetotic, or ballistic, and are often more stereotypic than those seen in other choreoform disorders such as Huntington's disease. The intensity of the movement is mild to quite severe with resulting disability.

Management and treatment

The movements of tardive dyskinesia often remit and dissipate entirely with time. However, it may take years for the movements to disappear entirely and some portion of patients with tardive dyskinesia develops a permanent

movement disorder. Since tardive dyskinesia is an iatrogenic disorder, prevention is better than treatment. There are some straight forward management steps that help to prevent the development of tardive dyskinesia. Most importantly, the number of subjects at risk should be limited and this implies that typical and atypical neuroleptics as well as antiemetics should be administered only with definite therapeutic goals in mind and in appropriate clinical situations. The neuroleptics are for the treatment of severe psychiatric disorders including psychosis and severe bipolar problems and are not for the treatment of mild anxiety, restlessness, insomnia, and other minor psychiatric disturbances. Neuroleptic dosage should be limited and guided by therapeutic response. In patients who have developed tardive dyskinesia, the best possible course of therapy is to discontinue the offending agent if that is possible from a medical and psychiatric standpoint. If that is not possible from a psychiatric standpoint, then switching to a less potent atypical neuroleptic might prove useful. Drugs which deplete the brain of dopamine such as reserpine or tetrabenazine can also used to reduce the choreodystonic movements seen in tardive dyskinesia. Typical potent neuroleptics can be administered to reduce the movements in tardive dyskinesia, but this places the treating physician in the position of using the etiologic agent to treat the complications of that agent. This is obviously not a smart move unless movements are so severe that they are causing severe disability or are life-threatening.

Additional therapeutic attempts to treat tardive dyskinesia have included use of dopamine agonists such as levodopa or dopamine receptor agonists such as bromocriptine with the idea of 'downregulating' dopaminergic hypersensitivity. There is not much support in the literature for this approach. A variety of GABA agonist drugs including valproic acid, diazepam, clonazepam, and baclofen have been used, but all have been disappointing. There are reports in the literature of high dosage Vitamin E being effective, but this is not thought to be a very useful approach.

Drug-Induced Movement Disorders Related to Dopamine Receptor Agonists

Levodopa-Induced Dyskinesias

In contrast to drug-induced disorders that are seen with dopamine receptor antagonists or dopamine depleting agents, levodopa or dopamine agonist-induced dyskinesias develop in Parkinson's disease patient treated with drugs that augment dopaminergic pharmacology. These dyskinesias are abnormal involuntary movements usually of a choreo dystonic nature. Extremities, lingual facial buccal regions, neck, trunk, and, occasionally, thoracic and abdominal musculature may be involved. Although these movements occur with dopamine agonists as well as levodopa, they are classically referred to as 'levodopa-induced dyskinesias' because they were originally described with this drug and are more frequently encountered with levodopa therapy than dopamine agonist treatment.

Epidemiology

Levodopa-induced dyskinesias only occur in the context of the treatment of Parkinson's disease or other neurodegenerative disorders involving the dopaminergic system. The chronic administration of levodopa in high dosage in patients with a normal central nervous system will not induce abnormal movements. Levodopa-induced dyskinesias begin after 2–3 years of levodopa treatment and become progressive and more prevalent until ~50% of patients exhibit some form of levodopa-induced dyskinesias after treatment for 5 years. Levodopa-induced dyskinesias can range from very mild adventicial movements, which are of no concern to the patient or family, to more severe choreo dystonic movements, which can interfere with the activities of daily living including dressing, eating, and walking. Most patients with Parkinson's disease prefer to have a degree of levodopa-induced dyskinesias rather than being more parkinsonian. Balance between inducing dyskinesias or alleviating the motor symptomotology of Parkinson's disease is the art of pharmacologic therapy for these patients. The interplay between dyskinesias and the alleviation of motor symptoms has also been at the heart of controversy regarding whether to begin therapy with levodopa or dopamine receptor agonists in the initial treatment of Parkinson's disease. Another potential risk factor for the development of levodopa-induced dyskinesias includes young age of onset of Parkinson's disease. There is a widely held perception from clinical practice and the literature that, younger patients seem to be more prone to the development of levodopa-induced dyskinesias. It is also true that patients with more long-standing and severe parkinsonism who have not been treated with levodopa are more likely to develop levodopa-induced dyskinesias in a shorter period of time.

Pathophysiology

The pathophysiology of levodopa-induced dyskinesia is not entirely understood. The most simplistic approach to explain these movements is that dopamine receptors become supersensitive because of the loss of the dopaminergic input from the substantia nigra which occurs in Parkinson's disease. However, levodopa-induced dyskinesias rarely, if ever, occur with the initial dose of levodopa. Chronic administration of levodopa is required to bring out the dyskinesias, thus it cannot simply be that the receptors are supersensitive. Other potential mechanisms

to explain dyskinesia is a shift in dose response to levodopa, alterations in dopamine receptor subtypes, and the possible influence of the temporal pattern of drug administration. A number of other neurotransmitter systems may also be involved in the pathophysiology of dyskinesias, including drugs that affect the glutamate receptors, serotonergic system or the opiate system, and the GABA system.

Clinical features

In addition to the abnormal movements of a choreo dystonic nature, levodopa-induced dyskinesias can include myoclonus, dystonia, ballism, and stereotyped movements. There are different temporal patterns of levodopa-induced dyskinesia with the most common being 'peak-dose' dyskinesia which occurs when the beneficial effects of levodopa on the motor symptoms of Parkinson's disease are most apparent. Diphasic dyskinesia occurs just as levodopa begins to take effect and as it is wearing off. Off-period dystonia is the occurrence of dystonic postures when the patient is off and the levodopa antiparkinsonian effect is at its lowest efficacy. A new type of dyskinesia was described recently as a result of clinical research trials involving embryonic mid-brain fetal transplants into Parkinson's patients. This type of dyskinesia has been called 'run away dyskinesia.' This is a typical choreo dystonic movement which is unrelated to the dosing cycle. In some patients who developed run away dyskinesia, levodopa was discontinued and the dyskinesia persisted.

Management and treatment

Although it is important to determine the pattern of dyskinesia to plan effective management, the best overall strategy is simply to understand that levodopa-induced dyskinesias are more properly referred to as dopaminergic-induced dyskinesias. All of the drugs used to alleviate the motor symptoms of Parkinson's disease have a positive and promoting effect on the dopaminergic system in one way or another, and in order to alleviate levodopa-induced dyskinesias, antiparkinsonian drug dosage must be slowly decreased until the patient reaches a point of improvement in the dyskinesias to a manageable level or when the motor stigmata of Parkinson's disease begins to be a burden. When that point is reached, other pharmacologic therapy directed specifically at the dyskinesia, such as amantadine, may be introduced. The best plan in terms of reducing antiparkinsonian medications in a patient with troublesome dyskinesias is to slowly decrease and eliminate drugs which are having the least beneficial effect in terms of the management of the Parkinson's disease. Typically, this means decreasing and stopping drugs in more or less the following order, anticholinergics, MAO (monoamine oxide inhibitors), COMT (catechol-*O*-methyl transferase inhibitors) dopamine agonists, and, finally, levodopa. Patients can always be assured that dyskinesia can be controlled; however, the problem in controlling the dykinesia is that the parkinsonism will worsen. It is also true that if pharmacologic therapy fails, or the dyskinesias are severe enough, deep brain stimulation surgery with the target being either the STN (subthalamic nucleus) or GPI (globus pallidus interna) is quite effective in alleviating dyskinesias.

Miscellaneous Drugs Which Can Induce Movement Disorders

Anticonvulsant medication has been reported to induce various movement disorders. In fact, if one considers cerebellar syndromes as a 'movement disorder' then phenytoin, phenobarbital, primodone, and carbamazepine can cause a kinetic tremor as well as asterixis and myoclonic jerks. Valproic acid can induce a postural and kinetic tremor. This tremor has even been reported at rest. The severity of the tremor is usually mild, but can be severe. Valproic-induced tremors are often quite amenable to treatment with β-blockers.

A less often, anticonvulsant-induced movement disorders are phenytoin-and, more rarely, carbamazepine-induced choreo dystonic movements. The majority of patients with these types of dyskinesias usually demonstrate other evidence of toxicity such as cerebellar features or elevated plasma drug level. However, there is some evidence that pre-existing cerebral pathology predisposes patients to the development of phenytoin-induced or carbamazepine-induced dyskinesias.

Phenytoin has also been reported to induce parkinsonism; however, valproic acid has emerged as the most common anticonvulsant to induce parkinsonism. In the clinical setting of the subacute onset of symmetric parkinsonism, a careful search of the patient's history for the administration of anticonvulsants is always important.

Occasionally, anticholinergic, antihistaminic, antianxiety, oral contraceptive, antihypertensive, and cardiac drugs have been reported to be associated with tremor, myoclonus and parkinsonism, and chorea. In addition, stimulants such as amphetamine and cocaine have also been reported to induce choreo dystonic movements on rare occasions.

See also: Dystonia, Drug-induced (Acute); Myoclonus; Tremor: Drug-induced.

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Dysarthria

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Glossary

Altered Auditory Feedback (AAF) – A collective term for delayed auditory feedback (DAF), frequency-altered feedback (FAF), and masking noise, or a combination of the three.
Dysarthria – A group of speech disorders that are due to lesions in either the peripheral or central nervous system.
Festinating speech – A type of speech characterized by increasingly fast and accelerated speaking rate with diminished volume and significantly reduced speech intelligibility. It is commonly observed in patients with advanced PD and Parkinsonism such as PSP or MSA. Patients with festinating speech often experience festinating gait and freezing of gait.
Lee Silverman Voice Treatment (LSVT/LOUD) – An evidence-based treatment method for hypophonia and hypokinetic dysarthria experienced by 89% of patients with IPD. Its single treatment target is loudness with high intensity in its delivery mode and sensory retraining.
Speech intelligibility – The amount of speech that can be understood by listeners who speak the same language.

Definition and History

Speech problems experienced by persons with Parkinson's disease (PD) were first described in a case in 1817 by James Parkinson in his famous book '*An Essay on the Shaking Palsy*'. The patient, the Count de Lordat, who suffered from a fall three and half years earlier prior to the visit, was still able to walk alone with a cane with great difficulty but had limited range of motion of his upper limbs. He could not control his saliva, drooling continuously. He had great trouble swallowing liquids and could no longer swallow solids. Although his mind was sound and he was able to attend and understand conversations, 'What words he still could utter were monosyllables, and these came out, after much struggle, in a violent expiration, and with such a low voice and indistinct articulation, as hardly to be understood but by those who were constantly with him.' Speech impairments such as this were termed as dysarthria. It comes from the Greek prefix dys and the Greek root arthroun, while 'dys' means 'bad or abnormal' and 'arthroun' means 'to speak clearly.'

In their influential studies of the dysarthrias published in 1969, Darley, Aronson and Brown used correlation matrices to demonstrate for the first time that cooccurrence of deviant speech dimensions observed could be delineated into different types of dysarthria. They further defined that 'Dysarthria is a collective name for a group of speech disorders resulting from disturbances in muscular control over the speech mechanism due to damage of the central or peripheral nervous system. It designates problems in oral communication due to paralysis, weakness, or incoordination of the speech musculature. It differentiates such problems from disorders of higher centers related to the faulty programming of movements and sequences of movements (apraxia of speech) and to the inefficient processing of linguistic units (aphasia).'

Epidemiology/Risk Factors

Epidemiology as Related to Different Etiologies

Different underlying neurological disturbances are associated with different types of dysarthria. However, speech intelligibility is inevitably reduced in all. The dysarthria classification was proposed in 1969 on the basis of lesion sites. There are six single types of dysarthria: flaccid dysarthria, spastic dysarthria, ataxic dysarthria, hypokinetic dysarthria, hyperkinetic dysarthria, and unilateral upper motor neuron dysarthria, in addition to the category of mixed dysarthria, which encompasses all possible combinations of the six single types.

Dysarthria accounts for 54% of all acquired neurologic communicative disorders. The prevalence of dysarthria in movement disorders is high. Hypokinetic dysarthria is the dysarthria of idiopathic PD and atypical Parkinsonism, while hyperkinetic dysarthria is associated with involuntary movements as in Huntington's disease (HD). Eighty-nine percent of patients with idiopathic Parkinson's disease (IPD) have hypokinetic dysarthria. Mixed hypokinetic–hyperkinetic dysarthria is commonly associated with IPD, once patients develop on–off medication-related motor fluctuations and dyskinesias. In patients with atypical Parkinsonism such as progressive supranuclear palsy (PSP) and multiple system atrophy (MSA), speech impairment may be the first motor sign to appear. In PSP, dysarthria occurs in 48–88% of patients, while in MSA, in 34–100%, depending on the disease progression. Hypokinetic dysarthria is seldom the only type of dysarthria observed in atypical Parkinsonism. Mixed hypokinetic-spastic dysarthrias are most commonly associated with PSP, while mixed hypokinetic-ataxic-spastic dysarthrias mostly seen in MSA. Hyperkinetic dysarthria occurs when purposeful speech movement is interrupted by involuntary movements. Although it is identified as a single type of dysarthria, there are shared features yet remarkable differences in its actual speech characteristics, depending on where and how the involuntary movements interfere with speech movements. Any involuntary movements that involve muscle groups in the trunk, head, and neck area will likely cause hyperkinetic dysarthria. Hyperkinetic dysarthria is commonly associated with chorea in HD, palatopharyngolaryngeal myoclonus, tics in Tourette's syndrome (TS), dystonia involving head and neck muscles (cervical dystonia, laryngeal dystonia, and oromandibular dystonia), Essential tremor (ET), hemifacial spasm, tardive dyskinesias, and medication-induced dyskinesias.

Risk Factors

In idiopathic PD, the most important risk factors for developing dysarthria are progression of the disease, disease severity level, and 'on–off' motor fluctuations. In atypical Parkinsonism, the most important risk factors are presence of dysphagia, gait disturbances, and premorbid speech impairment. In movement disorders associated with hyperkinetic dysarthria, the risk factors involve muscle groups in the trunk, head, and neck area, and the extent, frequency, and intensity of the involuntary movements, as well as disease duration and progression.

Clinical Features/Diagnostic Criteria

Characterization

The main characteristic of any type of dysarthria is the reduction of speech intelligibility. The severity of hypokinetic dysarthria in PD is task dependent. The speech intelligibility is worse with spontaneous speech than with automatic speech such as counting, recitation, and reading when the content of speech is provided. In more advanced PD, the mixed hypokinetic–hyperkinetic dysarthria is medication related. The hypokinetic component is worse during 'off' time, while the hyperkinetic component is worse during 'on' time because of increased dyskinesias.

Salient Speech Features

Speech characteristics vary among different types of dysarthria. Salient speech features of hypokinetic dysarthria in IPD progress from early symptoms such as reduced loudness, monotone, monopitch, reduced pitch, and breathy and hoarse voice quality, to relatively later symptoms such as variable rate, short rushes of speech, hesitations, disfluency similar to stuttering, palilalia which is speech produced with significantly accelerated speaking rate with diminished volume, and significantly decreased articulatory accuracies. Hyperkinetic dysarthria associated with involuntary movements is characterized by unpredictable articulatory breakdowns and loudness and pitch variability. Dysarthria associated with cervical dystonia often manifests itself as spasmodic dysphonia. The salient speech features are strained and strangled vocal quality and frequent vocal arrests. Some patients may resolve to use whispering voice. Other types of dysarthria commonly associated with movement disorders are spastic dysarthria and ataxic dysarthria. Spastic dysarthria presents with strained–strangled vocal quality, low pitch, hypernasality, slow but regular speaking rate, and effortful speech. Ataxic dysarthria presents timing-related irregular articulatory breakdowns and variable pitch, loudness, and speaking rate.

Diagnosis of Dysarthria

Certified and licensed speech-language pathologists (SLP) are trained to diagnose dysarthria, using a combination of perceptual and instrumental tests to evaluate respiration, phonation, articulation, resonance, and prosody. A typical evaluation has the following components:

an in-depth medical history, a complete oral motor examination, and speech testing. On the basis of the findings, the SLP will be able to differentially diagnose the type or types of dysarthrias.

Pathophysiology

The precise pathophysiology underlying dysarthria in IPD, atypical Parkinsonism and other movement disorders is unclear. Rigidity and bradykinesia may be partially responsible for hypokinetic dysarthria, while for hyperkinetic dysarthria, the involuntary movements. Strained and strangled vocal quality and slow but regular articulatory movement patterns are consistent with increased spasticity in the muscles in spastic dysarthria. Irregular articulatory breakdowns and irregular loudness and pitch of ataxic dysarthria are consistent with dysfunction of the cerebellum.

Management

Medication

Hypokinetic dysarthria of IPD may appear early or late in the disease progression. The response to dopaminergic stimulation in speech is mixed. Drug-induced orofacial and respiratory dyskinesias interfere with speech movements resulting in mixed hypokinetic–hyperkinetic dysarthria in IPD.

Deep Brain Stimulation

Bilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) has gained increased acceptance, because it substantially reduces dyskinesias and fluctuations and improves the cardinal features of IPD. STN DBS does not improve speech; rather, one of its common adverse effects is worsened speech intelligibility. Speech deterioration may be from two sources: the progression of the disease itself and long-term stimulation-related changes. It has been suggested that the contact site and stimulation intensity may be partly responsible for the worsening speech.

Speech Therapy

Speech therapy that has demonstrated clear efficacy is Lee Silverman Voice Treatment (LSVT/LOUD), an intensive treatment program for treating hypophonia and hypokinetic dysarthria in patients with IPD, targeting a single treatment target of loudness with high intensity in its delivery mode and sensory retraining. It works best when the main symptoms are soft and breathy voice. More advanced symptoms such as inability to initiate speech, frequent hesitations, and palilalia have been reportedly controlled by altered auditory feedback (AAF) provided by a wearable device.

Prognosis

Dysarthria in patients with IPD or other movement disorders will worsen as the underlying disease progresses. Early onset of severe speech deficits such as palilalia in PD may indicate atypical Parkinsonism such as PSP or MSA especially when dysphagia and gait disturbances are present.

Acknowledgments

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See also: Alzheimer's Disease and Parkinsonism; Ataxia; Basal Ganglia, Functional Organization; Cognitive Assessments and Parkinson's Disease; Corticobasal Degeneration; Deep Brain stimulation; Dyskinesias; Dystonia; Hoehn and Yahr Staging Scale; Huntington's Disease; Levodopa; Multiple System Atrophy; Pallidotomy for Parkinson's Disease; Parkinson's Disease: Definition, Diagnosis, and Management; Progressive Supranuclear Palsy; Spasmodic Dysphonia: Focal Laryngeal Dystonia; Surgery for Movement Disorders, Overview, Including History; Unified Parkinson's Disease Rating Scale (UPDRS) and The Movement-Disorder Society Sponsored-unified Parkinson's Disease Rating Scale (MDS-UPDRS); Wilson's Disease.

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Relevant Websites

http://www.asha.org – American Speech-Language-Hearing Association (ASHA).
http://www.michaeljfox.org – The Michael J. Fox Foundation for Parkinson's Research.
http://www.nidcd.nih.gov – National Institute on Deafness and Other Communication Disorders (NIDCD).
http://www.lsvt.org – LSVT Global®.

Dyskinesias

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Glossary

Basal ganglia – The basal ganglia are neurons nuclei located at the brain base, comprising the substantia nigra, the striatum, the internal and external segments of the globus pallidus, and the subthalamic nucleus (STN) ganglia and playing a key role in the control of motor behavior through their in- and outputs.
Continuous dopaminergic stimulation – The mode of administration (pulsatile versus continuous) of dopaminergic antiparkinsonian medications seems crucial in the development of LIDs. Normal endogenous striatal dopamine receptor stimulation is supposed to be phasic and tonic at the level of a synapse, with a relatively stable continuous baseline release. Short acting drugs (such as levodopa) induce an abnormal pulsatile stimulation that disturbs the striatal relay of the motor system. Exposing an increasingly denervated striatum to pulsatile dopaminergic stimulation might then induce dyskinesia.
Deep brain stimulation – Chronic high frequency stimulation mimics the effects of ablative neurosurgery. This stimulation is obtained by means of an electrode with four contacts implanted into the target area and connected to a programmable stimulator under the chest wall.
Diphasic dyskinesias or 'onset- and end-of-dose-dyskinesias' – Diphasic dyskinesias correlate respectively with the rising and falling phases of levodopa plasma levels, can involve stereotypical rapid alternating movements, as well as unusual ballistic kicking or dystonia and tend to affect the legs predominantly.
Dyskinesias – Dyskinesias are abnormal involuntary hyperkinetic movements commonly observed in patients with PD chronically treated with levodopa (levodopa induced dyskinesias (LIDs)) and rarely with dopaminergic agonists.
Off dystonia – Off dystonia is painful dystonic posturing affecting the limbs particularly the legs and feet, occurring at the end of action of levodopa in levodopa-treated parkinsonian patients.
Peak-dose dyskinesias – Peak dose dyskinesias are the most common LIDs. They occur at the time of the peak concentration or peak benefit of the dose of levodopa when parkinsonian symptoms are improved. Typically, peak-dose dyskinesias involve the upper limbs more than the legs, trunk, or head and have a choreic phenotype.

Definition and History

The word 'dyskinesia' is derived from the Greek roots 'dys' (difficult, abnormal) and 'kinesis' (movement) to indicate abnormal, involuntary movements that can be associated with many neurological disorders. Here we will discuss levodopa-induced dyskinesias (LIDs) in Parkinson's disease (PD).

Treatment of PD with the dopamine precursor drug, levodopa, is initially remarkably effective. However, this 'honeymoon' period gradually vanishes with chronic levodopa exposure and disease progression, and many patients experience levodopa-induced motor complications within a few years. Such motor complications are of two main types: motor fluctuations in response to medication and to dyskinesias. LIDs are abnormal involuntary hyperkinetic movements commonly observed in patients with PD chronically treated with levodopa. Historically, LIDs were reported by Cotzias and colleagues in 1969 shortly after these authors described the dramatic antiparkinsonian efficacy of levodopa. LID is a historically honored term, but it includes dyskinesia induced with any form of dopaminergic drug therapy. For example, dopamine agonists likewise can induce the same types of dyskinesia, but because these problems are more frequently encountered with levodopa therapy than other dopaminergic drug classes, the term LID and the link to levodopa remain commonly used.

Clinical Manifestations of Dyskinesia

Different forms of LIDs are usually separated according to their phenomenology and their relationship with levodopa intake. These two classifications often overlap, so that the type of dyskinesia is usually distinctive depending on its temporal relationship to levodopa dosing. Further, multiple forms of dyskinesia can occur in the same patient. In spite of the prototypic types of dyskinesia, many patients have mixed forms, suggesting that the various LIDs are probably part of a clinical and pathophysiological continuum (**Figure 1**).

Phenomenology

LIDs are typically a mixture of chorea, ballism, and dystonia or more rarely myoclonus. LIDs have been reported to start frequently in the foot, ipsilateral to the side most affected by PD with inversion of the foot and ankle. This finding is consistent with early loss of dopaminergic innervation of the dorsolateral striatum, corresponding somatotopically to the foot area. In spite of this typical pattern, LIDs can affect any other part of the body (limbs, cervical, lingual–facial–buccal and/or even thoracic, respiratory, abdominal, or ocular musculature). Choreiform movements in the limbs, head, neck, and trunk are most common, but dystonic posturing in the limbs and craniocervical dystonia are not rare. Enhanced tremor, restlessness, and akathisia also occur in levodopa-treated patients. Although it is unclear whether these symptoms are drug-induced or part of advanced parkinsonism, they are not typically considered LIDs. The diagnosis of LIDs is therefore generally easy in most patients, but these last cases sometimes pose difficult differential diagnosis issues in a given patient, with consequent management problems. In such cases, careful direct examination of the

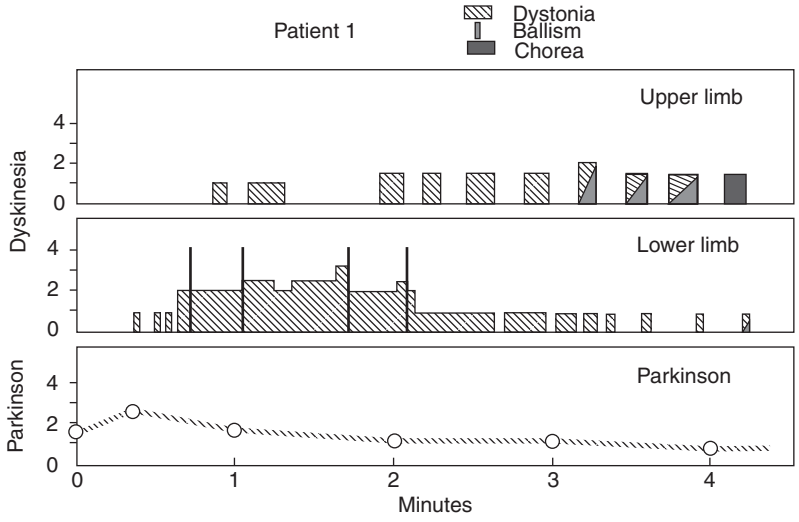

Figure 1 Phenomenology (dystonia, ballism, chorea) and topography (upper limb, lower limb) of LIDs in a patient with PD during the first 5 min of onset of 'on' (while the patient is switching from 'off' to 'on' after previous levodopa intake). Notice that LIDs are first occurring in the lower limb, as dystonic and ballic abnormal movements, then progressively spreading to the upper limb, becoming of the choreic type. Reproduced from Marconi et al. (1994) Levodopa-induced dyskinesias in Parkinson's disease phenomenology and pathophysiology. *Movement Disorder*.

patient over the cycle of 'off' (when levodopa-induced antiparkinson effects have waned) and 'on' (when levodopa-induced antiparkinson effects are present) conditions is helpful. LIDs markedly fluctuate in the same patient, depending on environmental/psychological factors and timing regarding levodopa intake (see later text). Stress and emotion can dramatically worsen LIDs, as it is the case for most hyperkinetic involuntary abnormal movements. Therefore, when examining a patient, mental calculation is commonly used as a facilitator to increase LIDs intensity as opposed to the resting condition in a quiet environment.

Relationship with Levodopa Dose

LIDs are also classified on the basis of their occurrence with regard to levodopa intake and such temporal classification allows the delineation of three main types of LIDs: 'peak-dose dyskinesias,' 'off-period dystonia,' and 'diphasic dyskinesias.' These three types of LIDs sometimes occur in the same patient at different moments. To document these patterns, it is sometimes helpful to perform an acute levodopa challenge in a given patient. In this case, the patient takes a typical dose of levodopa in the physician's office and stays there until the time of the next levodopa dose. This allows the physician to observe the entire cycle of the clinical response and the temporal changes in the spectrum of abnormal movements. This observation has practical importance, because different forms of dyskinesia are treated with different pharmacological strategies (**Figure 2**).

Peak-dose dyskinesias

These are the most common LIDs occurring at the time of the peak concentration or peak benefit of the levodopa dose, but they may also occur throughout the duration of the on-period (square-wave dyskinesias). Peak-dose dyskinesias usually consist of stereotypic, choreic, or ballistic movements involving the head, trunk, and limbs, and occasionally, the respiratory muscles. Typically, peak-dose dyskinesias involve the upper limbs more than the legs, trunk, or head, and have a choreic phenotype. They tend to be less disabling and less painful than diphasic-dyskinesia or off-dystonia. In some patients, however, peak-dose dyskinesias may evolve into athetosis and dystonia, thereby inducing significant social and/or functional disability as well as pain.

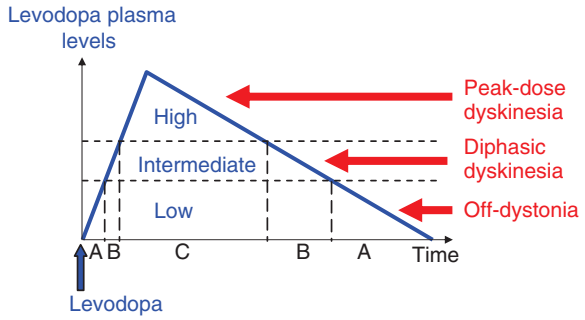

Figure 2 Schematic representation of the occurrence of different types of LIDs according to the temporal response to levodopa administration in a patient with PD. Notice that off-dystonia is observed when levodopa plasma levels are low and the patient is 'off' (a); diphasic dyskinesias are observed when levodopa plasma levels raise up or fall down to intermediate levels, and the patient is not completely 'on' nor fully 'off' (b); peak-dose dyskinesia are observed when levodopa plasma levels are at their maximum, above a threshold that turns the patient fully 'on' (c).

Off-period dystonia

The role of levodopa in such dyskinesias is debated, since they can occur in untreated PD patients. However, they also occur as a wearing-off phenomenon in levodopa-treated patients. They tend to affect the limbs, particularly the legs and feet of the more affected side. Patients typically experience a painful fixed dystonic posture (e.g., ankle intorsion with toe flexion or extension), especially early in the morning (early morning dystonia). Off-dystonia is frequently troublesome because of painful sensations and functional impairment.

Diphasic dyskinesia

This type of LIDs is also known as 'onset- and end-of-dose-dyskinesias.' They correlate respectively with the rising and falling phases of levodopa plasma levels, rather than the peak or nadir. They occur in ~15–20% of patients, which tend to affect the legs predominantly and can involve stereotypical rapid alternating movements, as well as unusual ballistic kicking or dystonia. In some patients, a mixture of dyskinesia and parkinsonian signs occurs concurrently, because the patient is in between 'on' and 'off' phases. Such LIDs can be very disabling, especially those inducing large ballistic movements of the limbs. It is sometimes difficult to recognize diphasic dyskinesias and separate them from peak-dose dyskinesias. This is especially true in the afternoon, when it is difficult to assess if a poor postprandial absorption of levodopa has led to low/intermediate plasma levels of levodopa, or on the contrary if levodopa has accumulated over the day, leading to very high plasma levels.

Rating Scales for Dyskinesias

An ideal scale for dyskinesia would score the phenomenology, severity, and impact on activities of daily living of the abnormal movements, and obviously be short and easy to use. Current rating scales do not fulfill these criteria. A unified dyskinesia rating scale combining elements of the AIMS and Rush scale along with a patient questionnaire has recently been introduced. The abnormal involuntary movements scale (AIMS) has been used to assess LIDs,

but it was originally developed for tardive dyskinesia and thus places predominant emphasis on lingual–facial–buccal movements. The UPDRS-IV scores global disability and duration of LIDs, along with the presence or absence of early morning dystonia and painful dyskinesia, but provides no information on anatomical distribution. The rush dyskinesias scale (or Goetz scale) introduces the objective assessment of dyskinesias during activities of daily living and focuses on disability from dyskinesias. LIDs can also be rated using diaries fulfilled during several consecutive days by the patient himself (possibly with the help of a caregiver) every 30 min over the waking hours. It is sometimes difficult to train the patient (and caregiver) to adequately rate his/her abnormal movements, separating, for example, tremor from LIDs and separating various types of LIDs. Patients can also be asked to rate whether they are 'on' with or without 'troublesome' or 'nontroublesome' LIDs, thus separating 'good on' from 'bad on.' Various instrumental techniques such as accelerometers have also been proposed to quantitatively assess LIDs. Their use remains exploratory and experimental until better validation is available.

Evolution and Impact of LIDs

Over the years of PD, the duration and severity of LIDs generally tend to progressively worsen in a given patient. The impact of LIDs on patients' health-related quality of life remains a matter of controversy, because it can markedly vary from one patient to another, depending on many factors including age, familial, professional, social and cultural environment, duration and intensity of LIDs, type of LIDs, severity of accompanying motor and nonmotor parkinsonian symptoms.

For most patients in the early stages of PD, LIDs are mild and nontroublesome, with minimal impact on daily quality of life. They are frequently unnoticed by the patients themselves and more embarrassing for the relatives and caregivers. Commonly, when asked, dyskinetic patients see LIDs as a kind of a 'marker' of their 'on' stage, a condition much more enjoyable for them than the 'off' episodes.

Conversely, in more advanced PD, LIDs frequently become troublesome and disabling. Severe LIDs can impair motor function and activities of daily living such as eating, washing, or walking, to a point that patients give up doing such tasks during the moments of the day they are dyskinetic. LIDs can also be socially embarrassing irrespective of their intensity, and this embarrassment depends largely on personal, familial, social, and cultural environments. Such embarrassment is a stress for patients, and because stress aggravates dyskinesia, patients experience a 'vicious' circle of increasing impairment. LIDs can also be painful, especially off-dystonia, to a point that affects the quality of life. Finally, peak-doses of LIDs often limit the use of levodopa, as their duration, if not their intensity, is worsened by higher doses of levodopa. Such dose-limiting effects can preclude the use of adequate doses of levodopa to optimally controlled parkinsonian symptoms, with consequent further impairment of the patients' quality of life.

Epidemiology and Risk Factors

LIDs have been reported to occur in 30–80% of levodopa-treated PD patients. In a community-based population study published by Schrag and colleagues in 2000, LIDs were present in 28% of PD patients with a mean time of 6.7 years from PD symptom onset to the development of LIDs. The variability of prevalence figures reported in the literature is mainly related to differences in the method of ascertainment of the presence of dyskinesias (self-assessment diary, objective measurement, use of activation procedures), and to differences in studied populations (community-based or hospital-based).

On an average, incidence of LIDs is estimated to be ~10% per year. Again, percentages can vary significantly from one trial to another, according to definitions and methods. The only prospective, placebo-controlled study assessing the effects of levodopa in early PD (ELLDOPA study, 2004) was conducted by Fahn and colleagues who reported LIDs in up to 16.5% of patients after only 6 months of levodopa therapy. This high incidence finding suggests that LIDs probably occur earlier than previously thought, although they probably go unnoticed at this stage by most patients and doctors. With the widespread use of dopamine agonists as initial monotherapy, the overall treatment exposure to levodopa may be decreasing, especially in the first several years of treatment. Early exposure to dopamine agonists as the primary treatment of parkinsonism is associated with a lower incidence of dyskinesia than when levodopa is the primary treatment (see below).

LIDs are much more common in PD than in patients with atypical parkinsonism. This observation suggests that pathophysiology of LIDs are likely to involve alterations in the level of postsynaptic dopamine receptors, since such receptors are relatively preserved in PD as opposed to atypical parkinsonian syndromes where the neuronal degenerative process involves the postsynaptic striatal neurons. However, dystonic facial LIDs can be observed in patients with multiple system atrophy and progressive supranuclear palsy.

The development of dyskinesia has been associated with several risk factors such as

- The age of the onset of PD: this is one of the most important risk factors for dyskinesias, and almost all patients with early onset of the disease develop dyskinesias whereas they are less frequent in patients with late onset of PD.

- PD severity: patients who have severe parkinsonian features at the onset of levodopa therapy develop more rapid and more severe LIDs than those who are less severely affected at the time of levodopa treatment. This is probably due to the severity of the underlying dopaminergic denervation at the time of first exposure and is in line with the observation that nonparkinsonian patients who are treated for many years with high doses of levodopa for other reason do not develop LIDs.
- Duration of the levodopa treatment: after 5 years of levodopa therapy, ~40% of patients experience LIDs, while nearly 90% do so after more than 10 years of treatment.
- Daily dosage of levodopa: LIDs are significantly more common in PD patients treated with high doses of levodopa compared to those exposed to low doses for the same period. In the ELLDOPA study, LIDs were reported after 6 months of levodopa therapy in 3.3%, 2.3%, and 16.5% of patients with early PD randomized respectively to 150 mg, 300 mg, or 600 mg day^{-1}.
- Use of levodopa versus dopamine agonists: several randomized controlled trials comparing the incidence of LIDs in patients with early PD randomized to levodopa therapy or a dopamine agonist (bromocriptine, cabergoline, pergolide, pramipexole, ropinirole) consistently demonstrated that the risk of developing LIDs was substantially less on agonist, at least as long as it was maintained as a monotherapy without levodopa. A genetic predisposition for the development of LIDs has not been established yet, although some positive gene polymorphism associations have been reported in a few small pharmacogenetic studies.

Pathophysiology of Dyskinesias

The mechanisms leading to the development of LIDs remain poorly understood. They are believed to be the consequence of complex alterations of the motor network circuitry of the basal ganglia. Animals with nigro-striatal dopaminergic denervation (6-hydroxy-dopamine (OHDA)-lesioned rat or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-intoxicated monkey) undergoing chronic levodopa therapy develop LIDs and are useful experimental models to provide new insights into the molecular, physiological, and pharmacological mechanisms generating LIDs. Studies of human brain tissues have also permitted a better, although partial insight into such mechanisms. A challenge in interpreting these studies is to determine if the observed changes are the cause or the consequence of the abnormal movements.

Briefly, LIDs are considered to be the result of the combination of several factors. First, there is loss of the dopamine striatal input caused by the degeneration of the nigrostriatal pathway. This loss induces alterations of synaptic connectivity within the striatum. Second, antiparkinsonian drugs, such as levodopa, imperfectly mimic normal transmission when used to compensate for the loss of endogenous striatal dopamine inputs. This artificial dopaminergic stimulation on an abnormal dopamine-depleted system generates inappropriate molecular postsynaptic messages, in turn leading to an abnormal neuronal cell signaling. As a consequence, researchers hypothesize that abnormal neuronal motor network activity is induced leading to abnormal motor programs and generation of abnormal movements such as LIDs. Interestingly, several of these changes are long-lasting and are known as the 'priming' phenomenon. Priming is possibly related to some kind of long-term molecular plasticity, as dopaminergic input to the striatum controls important processes such as long-term potentiation (LTP) and long-term depression (LTD) that are responsible for the maintenance of motor memory. Once 'primed,' it is not clear if this phenomenon is completely or only partially reversible, and to which extent 'depriming' strategies could switch the system back to normal.

Importance of Striatal Dopamine Depletion in the Genesis of LIDs

The importance of the extent of nigral dopaminergic cell loss is well documented by several experimental observations. As in humans, monkeys with normal dopaminergic nigrostriatal systems do not develop LIDs, unless they are treated with extremely large doses of levodopa. The rate of onset of dyskinesia is correlated with the extent of the dopaminergic lesion: animals with partial dopaminergic lesions hardly develop LIDs while those with severe dopaminergic depletion (>90%) develop marked LIDs within few days. Therefore, dopamine striatal denervation is an important facilitating factor for the development and expression of LIDs.

'Dopaminergic Continuous Stimulation' Theory

The mode of administration (pulsatile versus continuous) of dopaminergic antiparkinsonian medications seems crucial in the development of LIDs. Briefly, the dopaminergic continuous stimulation (CDS) theory considers that short acting drugs (such as levodopa with its 90 min elimination half-life and its erratic gastro–intestinal absorption responsible for peaks and troughs in plasma levels) induce an abnormal pulsatile stimulation that disturbs the striatal relay of the motor system. Normal endogenous striatal dopamine receptor stimulation is supposed to be both phasic and tonic at the level of a synapse, with a relatively stable continuous baseline release. Phasic dopamine release might occur preferentially within the synapse, while tonic release might be extrasynaptic. In the *early stages* of PD, levodopa might be stored in surviving dopaminergic

terminals in the striatum and released gradually in a relatively preserved physiological manner. However, as terminals are progressively lost with the disease progression, levodopa cerebral effects become more closely dependent on plasma levels of levodopa. Exposing an increasingly denervated striatum to pulsatile dopaminergic stimulation might then induce dyskinesia. This concept is supported by several experiments conducted in levodopa-naïve MPTP-intoxicated monkeys. Dopamine agonists with longer elimination half-life than levodopa (bromocriptine, ropinirole) induce significantly less LIDs than levodopa. One could argue that pharmacodynamic differences might also play a role, including differential effects of levodopa and agonists on dopaminergic receptor subtypes (D1- or D2-like) or on nondopaminergic (noradrenergic or serotonergic) receptors. However, conflicting or inconsistent pharmacodynamic explanations have generally been reported. Moreover, the importance of the mode of administration of the drug is supported by the fact that (1) combining entacapone, a catechol-*O*-methyl transferase (COMT) inhibitor that prolongs levodopa elimination half-life, with levodopa therapy induces fewer LIDs than levodopa alone, and (2) a short acting dopamine agonist like 4-propyl-9-hydroxynaphthoxazine (PHNO) can induce dyskinesias by itself when administered in a discontinuous pulsatile manner.

Changes Induced by Pulsatile Dopamine Stimulation in the Corticobasal Ganglia Circuitry

Such an irregular and disorganized dopamine response within the striatum is supposed to induce in turn an abnormal function of the cortico–subcortical neuronal networks that generate motor programs within the basal ganglia.

Healthy basal ganglia

The basal ganglia plays a key role in the control of motor behavior. They comprise the *substantia nigra*, *striatum*, *internal and external segments of the globus pallidus* (GPi and GPe, respectively), and *subthalamic nucleus* (STN) (**Figure 3**)

- The major inputs into the basal ganglia are:
  - the dopaminergic nigrostriatal pathway (#1, **Figure 3**)
  - the glutamatergic corticostriatal pathway (#4, **Figure 3**)

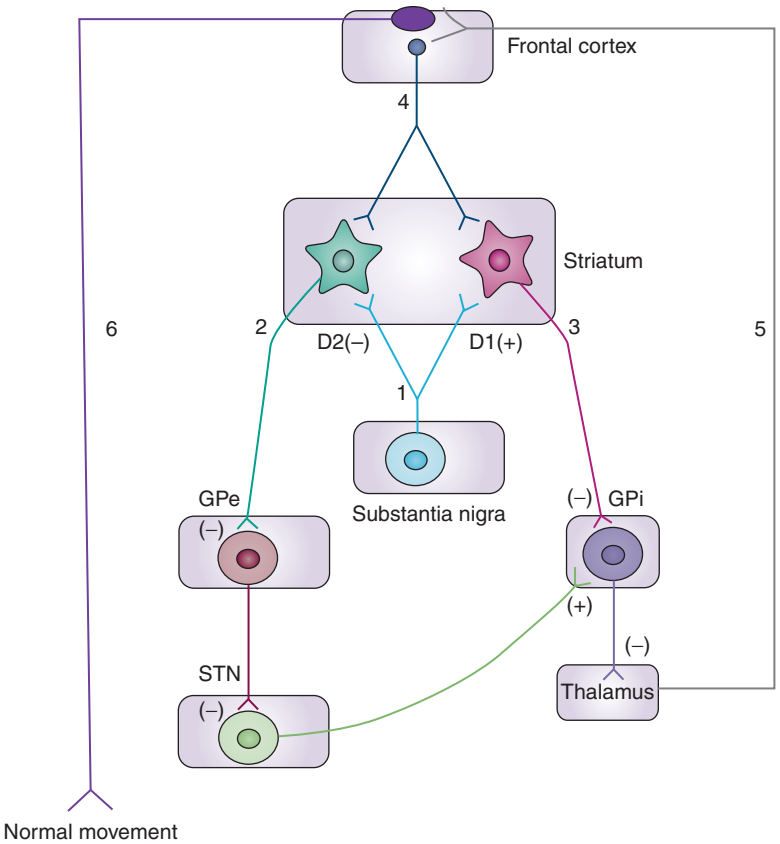

Figure 3 Schematic of normal basal ganglia (D1(+): dopamine D1 excitatory receptors; D2(–): Dopamine D2 inhibitory receptors; GPe: globus pallidus external segment; GPi: globus pallidus internal segment; STN: Subthalamic nucleus; (–): GABAergic inhibitory input; (+): glutamatergic excitatory input). Adapted from Jenner P (2008a), with permission from Nature Publishing Group.

- There are classically two major striatal outputs: the direct and indirect pathways composed of GABAergic inhibitory medium spiny neurons.
  - The neurons of the direct output pathway (#3, **Figure 3**) have *D1 dopamine excitatory receptors* on their cell bodies (D1(+), **Figure 3**). They project to the *GPi*.
- The neurons of the indirect output pathway (#2, **Figure 3**) have *D2 dopamine inhibitory receptors* on their cell bodies (D2(−), **Figure 3**). They project *to the GPe*, where they synapse with more GABAergic projection neurons. In turn, these neurons project *to the STN* and form synapses with the glutamatergic excitatory neurons that provide output to the GPi which sends in turn GABAergic inhibitory projections to the thalamus.
- The GPi therefore receives inhibitory inputs from the direct pathway and excitatory inputs from the indirect pathways. Normally, dopamine exerts inhibitory control over the indirect pathway, and by contrast, it exerts an excitatory effect on the direct output pathway. The balance between the direct and indirect pathways is thought to be responsible for a normal motor output of the system toward the thalamic nuclei that close the motor cortico–subcortical loop via thalamocortical projections (#5, **Figure 3**) and relay the message back to the frontal motor cortex for a normal efferent motor program (#6, **Figure 3**).

This classical view of the basal ganglia organization is overly simplistic and can be challenged in many ways. For example, axons projecting from the striatum are known to send collaterals to virtually every basal ganglia target, which is not in line with this 'sequential' schematic.

Changes in basal ganglia circuitry caused by striatal dopamine depletion (Figure 4)

In PD, degeneration of substantia nigra neurons causes loss of dopaminergic input to the striatum. This loss of dopaminergic input is supposed to provoke an imbalance in the activity of the direct and indirect striatal output pathways.

- Dopamine denervation increases the activity in the indirect pathway (loss of physiological dopamine inhibition). The GABAergic projection from the GPe to the STN becomes underactive as a consequence of this increased inhibitory GABAergic input. The STN glutamatergic neurons become in turn overactive, leading to increased activity of the inhibitory GABAergic neurons in the GPi that project to the thalamus.

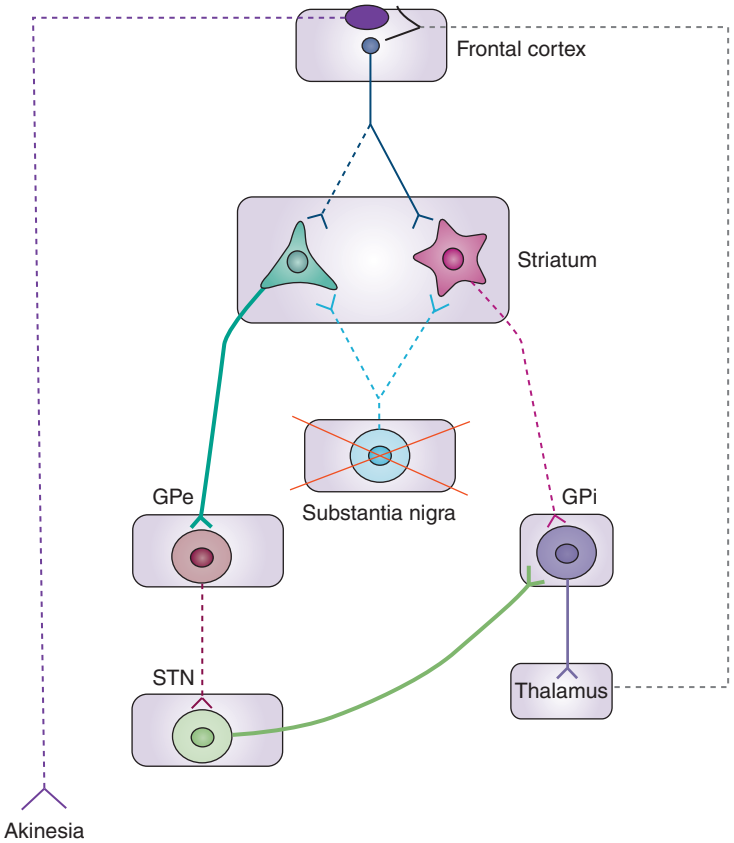

Figure 4 Schematic of changes occurring within the basal ganglia motor circuitry in Parkinson's disease. Adapted from Jenner P (2008a), with permission from Nature Publishing Group.

This decreases thalamic neuronal firing and alters input to the premotor cortex.

- Activity in the direct pathway decreases following the loss of dopamine physiological excitatory effects. This contributes to the increased activity of the GABAergic neurons that project to the thalamus with further increase in functional thalamic inhibition.

An abnormal motor program characterized by reduced voluntary movement (akinesia) is the final result of these changes in the basal ganglia output.

Changes in basal ganglia circuitry associated with LIDs in PD (Figure 5)

- The genesis of dyskinesia is generally explained by changes in the *direct and indirect output pathways* that are the opposite of those following dopamine depletion.
- It is suggested that D1 and D2 receptors are overstimulated by levodopa, leading to *underactivity of the indirect output pathway* and *overactivity of the direct output pathway*. This in turn leads to *decreased GABAergic input to the thalamus* and *increased firing of thalamic neurons toward the motor cortex*, resulting in involuntary movement.

It is easy to provide observations that illustrate the limits of this model. As an example, an upregulation of striatal dopamine receptors is expected as a result of *denervation supersensitivity* while a subsequent downregulation is expected after chronic dopaminergic treatment. However, there is a lack of any substantial detectable change in dopamine receptors in humans and in animals. Studies evaluating the involvement of the direct and indirect output pathways by their markers in animal models also show that many other different transmitters, including the opioid system, A2A adenosine, cannabinoid, noradrenergic, serotoninergic, and histaminergic receptors are modified in LIDs models. They probably play an important role, although yet poorly understood. This may serve as a useful basis for the development of future nondopaminergic antidyskinetic medications.

Corticostriatal Connectivity and the Role of Glutamate Transmission (Figure 6)

Cortical areas send dense glutamatergic innervation to the striatum (#3, **Figure 6**). The dopaminergic control within the striatum is supposed to integrate the glutamatergic

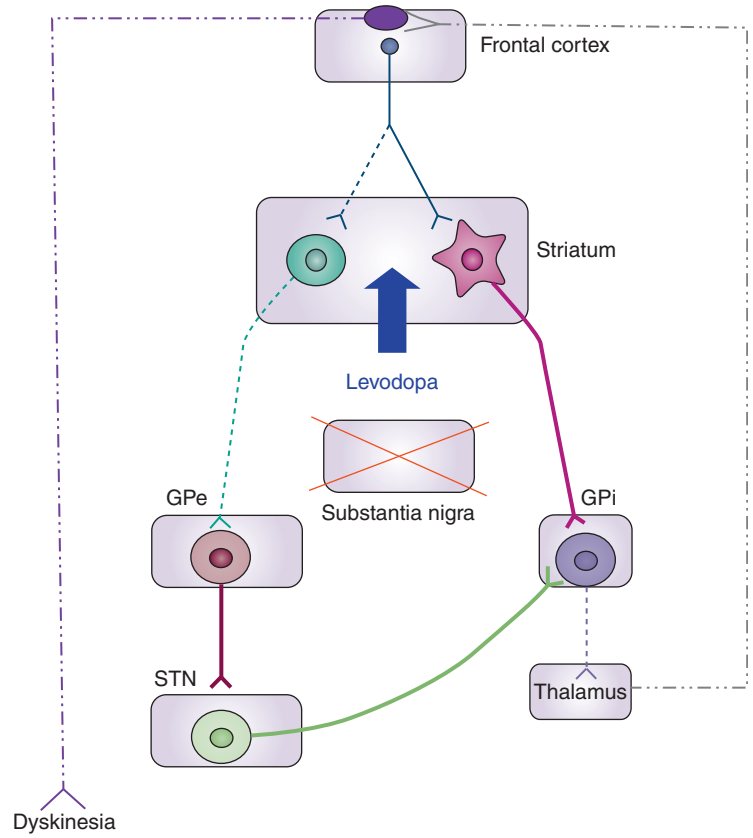

Figure 5 Schematic of alterations of the functioning of the basal ganglia motor circuitry in parkinsonian patients with levodopa-induced dyskinesias. Adapted from Jenner P (2008a), with permission from Nature Publishing Group.

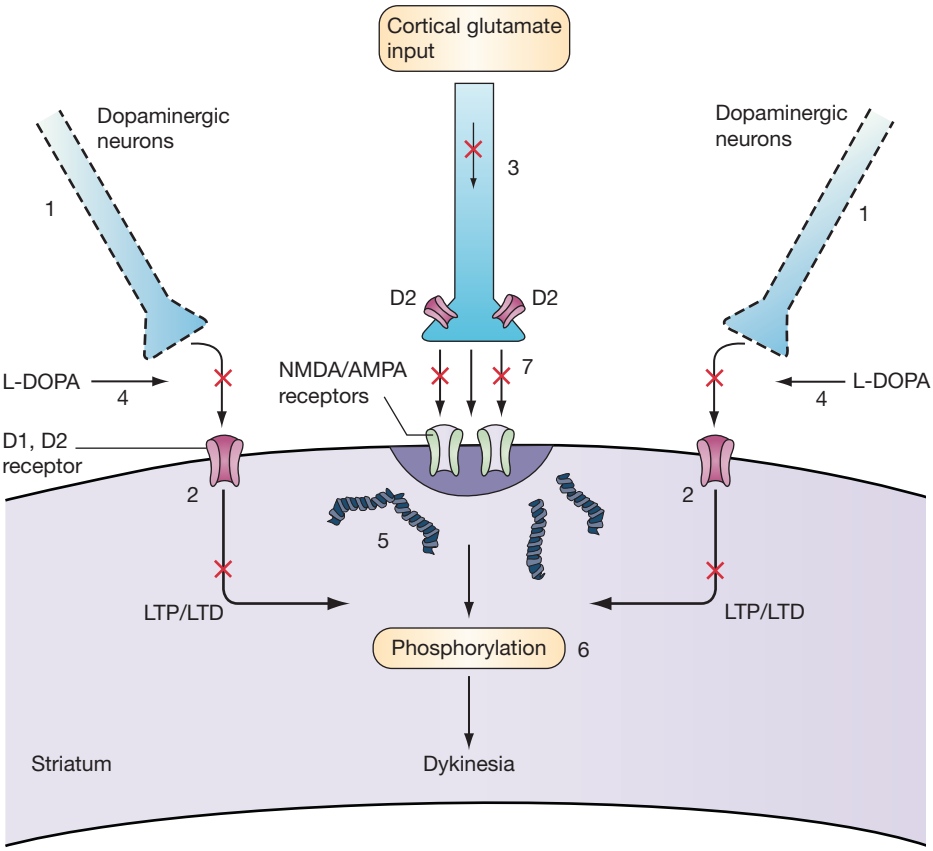

Figure 6 Altered transmission in the striatum that leads to dyskinesia expression. Adapted from Jenner P (2008a), with permission from Nature Publishing Group.

corticostriatal input with the GABAergic striatal output. The loss of striatal dopamine innervation in PD suppresses this dopamine-dependant integration. Morphologically, following the loss of striatal dopaminergic input, the medium spiny neurons lose the spines on which the glutamate receptors that receive input from the cortex are located. As the disease progresses, glutamatergic receptors might change in number and distribution, as a result of spine loss and changes in scaffold proteins (#5, **Figure 6**) which are important in fixing them in position to other glutamate and dopamine receptors on the spines. Moreover, important processes (such as state of phosphorylation) that are known to control glutamate receptor function are impaired by dopamine denervation and levodopa pulsatile stimulation. (#6, **Figure 6**). Taken together, these changes alter the consequences of glutamate activity (#7, **Figure 6**). As a consequence, the global effects of glutamate are modified, inducing abnormal intracellular signaling cascades with abnormal final striatal output and inappropriate motor programs. The striatal glutamatergic system thus appears to play a central role, with evidence of an abnormal NMDA-receptor- and AMPA-receptor-mediated responsiveness to glutamatergic corticostriatal input. This is supported by the fact that the NMDA glutamate antagonist amantadine reduces LIDs in parkinsonian monkeys and in PD patients.

Pharmacological Management to Prevent Dyskinesia

LIDs occur at an average annual rate of 10% when patients with early PD are started on levodopa therapy. In this context, it is pertinent to assess if the use of alternative medications as first line treatment may change the picture. This effect could be due to an indirect 'sparing' effect on levodopa use and/or to a more specific impact on underlying mechanisms, such as CDS.

Levodopa and COMT Inhibitors

According to the continuous dopaminergic stimulation hypothesis, prolonging the levodopa response with controlled-release (CR) formulations or early combination with a COMT inhibitor should induce less LIDs. Unfortunately, in contrast with expectations, two large randomized clinical trials (RCTs) showed that the early use of CR levodopa induced the same amount of LIDs than standard levodopa. Though an ongoing RCT aims at comparing the rate of LIDs between levodopa alone or in combination with entacapone (known as the STRIDE-PD study), this last strategy cannot be recommended for everyday practice as long as no clinical evidence is yet available.

Dopamine Agonists

There is consistent clinical evidence from several 2–5-year RCTs that the early use of a dopamine agonist, such as ropinirole or pramipexole, reduces the risk of emergence of LIDs as compared with levodopa first line treatment. The incidence of dyskinesias is nearly nil as long as the patient can be maintained on agonist monotherapy. The incidence goes up, however, once levodopa is added to the agonist. The latter is necessary in most patients after a few years of follow-up in order to keep adequate control of parkinsonian signs. The impact of this strategy on the prevalence of late disabling LIDs and on long-term health-related quality of life remains controversial. Moreover, there are other issues than LIDs to consider when starting a patient on an agonist early, since agonists can induce other troublesome adverse reactions such as daytime somnolence, hallucinations, and impulse control disorders.

Other Agents

The impact of an early treatment with monoamine oxidase Type B inhibitors (MAO-BIs), selegiline, or rasagiline, on the subsequent emergence of LIDs is not clearly understood. Selegiline may actually increase the risk of LIDs. No good level of evidence is available for anticholinergics or amantadine. The absence of information on amantadine is a serious scientific lacuna because the antiglutamate effects of amantadine could theoretically reduce the risk of subsequent development of LIDs.

Management Strategies to Reduce Dyskinesias

In some cases, no specific treatment of LIDs may be required especially when LIDs are mild and not troublesome to the patient. In other cases, LIDs require treatment because they are socially or functionally disabling or because they limit levodopa doses and thus compromise optimal control of parkinsonism. If LIDs deserve therapeutic management, it is then crucial to recognize their clinical pattern since off-period dystonia, diphasic dyskinesias, and peak-dose dyskinesia are not to be managed in the same manner.

Peak-Dose Dyskinesias

These dyskinesias are the most frequent LIDs. They can be managed using two different approaches (pharmacological or surgical), based on two different mechanisms each: indirect (levodopa dose reduction) and direct (specific antidyskinetic effects).

Adjustment of antiparkinsonian medications to reduce levodopa daily dose

This approach is often disappointing because of the risk of consequent worsening of parkinsonism, but several strategies can be tried:

- *Levodopa adjustments*: Manipulation of levodopa dosage (lower doses administered more frequently) may occasionally be helpful.
- *Dopamine agonist addition or adjustments:* The addition of a dopamine agonist, if the patient is not already receiving this class of drug, may permit a *reduction in levodopa dose* without worsening of Parkinsonism. If the addition of the agonist worsens the dyskinesias, a down-titration of levodopa dose can be tried. However, even patients who experience initial benefit can rarely be satisfactorily controlled in the long term. Substituting levodopa with high doses of a dopamine agonist has been reported, but at the risk of neuropsychiatric side effects.

Addition of a drug with direct antidyskinetic properties

- *Amantadine*: This is the most useful symptomatic antidyskinetic medication presently available. It is believed to work via NMDA receptors blockade. Amantadine added to levodopa improved antidyskinesia without worsening parkinsonism in placebo-controlled RCTs. High doses ($>200\,mg\,day^{-1}$) are more efficacious than lower ones, but less well tolerated because of cognitive side effects. Long-term benefit remains controversial.
- *Other drugs*: Clozapine is an atypical antipsychotic medication with poorly known mechanism of action (dopamine D1, D2, D4, and 5HT2 receptor antagonist and 5HT1A receptor agonist). It improves dyskinesia in one placebo-controlled RCT, but it can induce severe agranulocytosis, which prevents recommending it as a standard antidyskinesic treatment. A reduction in LIDs has been reported with low doses of other atypical antipsychotics (risperidone, olanzapine, quetiapine), but this cannot be recommended for common practice since even low doses can worsen parkinsonism. Non-dopaminergic drugs like sarizotan (5HT1A agonist), talampanel (glutamate AMPA antagonist), fipamezole (alpha2 agonist), and others have been reported to reduce dyskinesias in levodopa-primed MPTP-intoxicated primates, but such preclinical data remain exploratory and deserve clinical confirmation.

Use of continuous infusion therapies

- *Continuous subcutaneous infusion of apomorphine* (programmable pump usually during waking hours) was reported to control disabling motor complications, including dyskinesia in small open-label series of advanced PD patients. This effect is explained by the

more continuous delivery of dopamine stimulation and the concomitant reduction in levodopa daily dose. A limiting side effect is the occurrence of localized skin reactions.

- *Continuous intraintestinal infusion of levodopa.*

A water-soluble system for delivering continuous intrajejunal levodopa (Duodopa) has shown to be effective in controlling motor fluctuations without worsening dyskinesias in small open-label studies. This requires a surgical procedure to implant a permanent intraintestinal catheter.

Surgical approaches

Both ablative and deep brain stimulation (DBS) procedures are currently available to treat levodopa-associated motor complications that cannot be satisfactorily controlled with medical therapies. These techniques are based on the evidence indicating that the globus pallidus pars interna (GPi) and subthalamic nucleus (STN) are *overactive i*n PD. This overactivity is reversed by lesion or high frequency stimulation. Interestingly, while the *classic model* predicted that pallidotomy would worsen dyskinesia, these procedures produced a dramatic amelioration of dyskinesia, probably as a result of interference with abnormal firing patterns in basal ganglia output neurons.

- *Ablative procedures* (unilateral pallidotomy): Several controlled studies confirmed the efficacy of unilateral pallidotomy in improving dyskinesia. Benefits are long standing. Antidyskinetic benefits have been reported with lesions placed in an anteromedial location, a more ventral location, or anywhere in the posteroventral GPi. Ablative procedures are associated with a risk of *hemorrhage, infarction, and infection* (common to all stereotactic operations). Bilateral procedures are not recommended because they are associated with further risks, including *speech, swallowing, and cognitive problems*. With the development of DBS, ablative lesions are now more rarely performed.
- *Deep brain stimulation*: Chronic high-frequency 'deep brain' stimulation (DBS) mimics the effects of ablative neurosurgery. In this procedure, a stimulating electrode with four contacts is implanted into the target area and connected to a programmable stimulator with a long-life battery placed under the skin of the chest wall. The stimulator parameters (voltage, frequency, and pulse width) are gradually adjusted to reach the maximum benefits with the minimum side effects.

Several studies have confirmed that pallidal DBS is associated with a marked reduction in contralateral dyskinesia in addition to improvements in 'off'-periods. The duration of benefit is variable. Improvement in parkinsonian signs and dyskinesia may result from direct effects on two different anatomofunctional systems within the pallidum. The stimulation of the most ventral contact is effective on dyskinesia but may worsen akinesia and block the antiparkinsonian effect of levodopa. In contrast, stimulation through the most dorsal contact is most effective against akinesia but may induce dyskinesia.

Subthalamic nucleus (STN) DBS is efficacious to treat dyskinesia in advanced PD patients. It significantly improves motor function, dyskinesia, and quality of life compared with best medical management. Dyskinesia improvement is mainly explained by the concomitant reduction in levodopa daily dose. Long-term studies demonstrate the stability of this therapy.

Candidates for DBS are patients with typical PD, who are levodopa responsive but have troublesome motor complications that cannot be satisfactorily controlled with medical therapies and who do not have cognitive impairment.

DBS is expensive and associated with potentially serious side effects including those related to the *surgical procedure* (hemorrhage, infarction, infection), the *hardware* (lead breaks, lead displacement, ulceration, local infection), and *stimulation* (dysarthria, oculomotor disturbances, emotional problems, and cognitive impairment). In addition, the battery has a finite life and must be periodically replaced.

Off-Period Dystonia

Dystonia can improve with the same therapeutic strategies that reduce motor fluctuations and off periods: increasing levodopa dosage, increasing the frequency of dosing, combining a dopamine agonist (including apomorphine subcutaneous injections) to levodopa, adding a COMT-inhibitor or a MAO-B inhibitor. Injections of botulinum toxin may help alleviate prolonged painful foot dystonia.

Diphasic Dyskinesias

These dyskinesias are the most difficult to manage. Greater doses of levodopa may help, but generally at the cost of more severe peak-dose dyskinesias. Adjusting and modifying time and doses of antiparkinsonian medications are often disappointing. Subcutaneous apomorphine or intraduodenal levodopa may help, although the level of evidence to support the efficacy of these strategies is low. DBS of the subthalamic nucleus is an option in severe cases.

In summary, from a practical clinical perspective, the early use of a dopamine agonist rather than levodopa can be considered as initial treatment of PD in order to postpone the subsequent emergence of dyskinesia, especially in patients with early disease onset, as they are at greater risk for dyskinesia than older patients. Once present, and if disabling, dyskinesia should initially be managed by levodopa doses adjustment combined with

dopamine agonists. Usually this strategy is only transiently efficacious. Then, amantadine can be added for its antidyskinetic effects. If dyskinesia remains disabling in spite of such pharmacological adjustments, functional surgery is then indicated, especially STN DBS. For patients who cannot be operated, subcutaneous infusion of apomorphine or intraintestinal infusion of levodopa is to be considered.

See also: Chorea; Choreiform Disorders; Deep Brain stimulation; Direct Pathway; Dopamine; Dopamine Receptors; Dopaminergic Agonists in Parkinson's Disease; Indirect Pathway; Levodopa; Motor Fluctuations; Pallidotomy for Parkinson's Disease; Parkinson's Disease: Definition, Diagnosis, and Management; Subthalamic Nucleus.

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Dyskinesias: Animal Models

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Glossary

Channelopathies – Disorders related to dysfunctional ion channels.
Face validity – Phenomenological similarities between an animal model and the disorder in patients.
Long-term potentiation – Form of synaptic plasticity in which coincident activity of pre- and postsynaptic elements leads to a long-lasting facilitation of neuronal transmission.
Neuroleptics – Antipsychotic drugs with an antidopaminergic activity.

Definition and History

Dyskinesias are abnormal involuntary movements, including dystonic, athetotic, and choreic movements, which are heterogeneous with respect to etiology, triggers, and affected body parts. The First, descriptions of dyskinesias experimentally induced by drugs or neurolesions in animals can be found in the early 1970s. Furthermore, several mutant rodents have been reported to exhibit permanent dystonic symptoms. Animal models of dystonia and Huntington's disease are described elsewhere. Since the term dyskinesia is preferred for (1) hereditary paroxysmal dystonic and choreathetotic movements and

(2) drug-induced abnormal movements, this chapter focuses on a well-established genetic rodent model of paroxysmal dyskinesias and throughout drug-induced animal models on levodopa-induced dyskinesias (LIDs) in rats.

Genetic Animal Models of Paroxysmal Dyskinesias

Paroxysmal dyskinesias are a group of episodic movement disorders. Four major types of paroxysmal dyskinesias are differentiated by the precipitating and exacerbating factors: paroxysmal nonkinesigenic dyskinesia (induced by stress and caffeine; see below), paroxysmal kinesigenic dyskinesia (induced by sudden movements), exertion-induced dyskinesia, and hypnogenic paroxysmal dyskinesia. These episodic disorders have been suggested to be related to ion channelopathies, but the underlying mechanisms are unknown and are probably heterogeneous in various forms of dyskinesias. Clearly defined animal models of paroxysmal dyskinesias are restricted to the genetically dystonic hamster.

The *dt*^{sz} Mutant Hamster

In the *dt*^{sz} mutant hamster, an inbred line of Syrian hamsters, attacks of generalized dyskinesias occur in response to mild stress and, sometimes, also spontaneously. The vitality is normal in mutant hamsters, probably because of the paroxysmal nature of the movement disorder, and the age-dependent time-course of dystonia (see below) contributes to an unaltered fertility. These hereditary motor impairments, which are transmitted by an autosomal recessive gene, were initially misdiagnosed as epilepsy. Therefore, the original gene symbol was *sz* (for seizures). However, more detailed investigations (e.g., electroencephalography) revealed that the attacks are not epileptic seizures, but show the characteristics of paroxysmal nonkinesiogenic dystonic choreoathetosis (PDC) in humans. Since dystonia is the predominant symptom, the *dt*^{sz} mutant is also regarded as a model of (paroxysmal) dystonia. The responsible gene has not yet been identified, but the myofibrillogenesis regulator-1 (MR-1) gene, known as a causative gene for human PDC, could be excluded as the culprit in mutant hamsters.

In mutant hamsters, the severity of dyskinesia (determined by a score-system) is age-dependent with a maximum at an age of 30–40 days of life and with a complete remission of the stress-induced movement disorder at about 10 weeks. Nevertheless, paroxysmal dystonia in mutant hamsters is obviously not really transient because relapses of dystonia occur in females during late pregnancy and the prodystonic drugs lamotrigine and riluzole can provoke severe attacks in over 10-week-old male and female hamsters.

Among the drugs tested in *dt*^{sz} hamsters, pronounced beneficial effects were observed after acute treatments with various GABA-potentiating drugs, antidopaminergic compounds, and K_v7 potassium channel openers, while drugs which disturb GABAergic inhibition or which increase the dopaminergic activity worsened PDC. A dramatic aggravation of dystonia in mutant hamsters was provoked by the sodium channel blockers, lamotrigine and riluzole.

Pharmacological examinations in mutant hamsters are important to find more effective therapeutics and are also very helpful for interpretations of neurochemical findings. By neurochemical examinations, most changes were detected in the striatum and ventral thalamic nuclei of *dt*^{sz} hamsters. There is strong evidence that disturbed GABAergic inhibition and enhanced dopaminergic activity are critically involved. Measurements of levels of dopamine and its metabolites in tissue homogenates, examinations of tyrosine hydroxylase and of dopamine transporters did not disclose any abnormalities. As indicated by an unaltered density of nigral dopaminergic neurons, the dopaminergic system seems to be intact, but autoradiographic analyses have shown a lower dopamine D_1 and D_2 receptor binding in the dorsal striatum. This can be interpreted as a receptor downregulation, that is, as a consequence of an enhanced dopamine release, microdialysis in freely moving *dt*^{sz} hamsters revealed increased extracellular dopamine levels during dystonic episodes. In fact, striatal microinjections of the dopamine D_2 receptor agonist, quinpirole, significantly worsened the symptoms, while combined microinjections of D_1 and D_2 receptor antagonists exerted striking beneficial effects. However, the striatal dopaminergic overactivity could be secondary to impaired GABAergic inhibition. Reduced GABA levels, a decreased expression of the GABA-synthesizing enzyme, and changes in the density of benzodiazepine binding in the striatum, determined in mutant hamsters at the age of most marked severity of paroxysmal dystonia, but not in older animals after the remission of stress-induced dyskinesia, are in line with pharmacological observations. Systemic and intrastriatal injections of GABA-potentiating drugs, such as the $GABA_A$-receptor agonist muscimol, improved dyskinesia in the hamster model. These findings can be explained by a deficit of striatal aspiny GABAergic interneurons, found in *dt*^{sz} hamsters at an age of most marked expression of dyskinesia but not in older hamsters after spontaneous remission of PDC. The retarded development of striatal GABAergic interneurons possibly represents the primary defect in this animal model. As shown by recent studies, the density of striatal projection neurons seems to be unaltered in mutant hamsters.

The marked age-dependent deficit of striatal inhibitory interneurons is in line with electrophysiological findings in *dt*^{sz} hamsters. This structural defect obviously

leads, by disinhibition of striatal projection neurons, to an abnormal basal ganglia output. Thus, single unit recordings revealed a significantly increased basal activity of striatal GABAergic projection neurons in dt^{sz} hamsters, while the firing rate of entopeduncular GABAergic neurons was significantly decreased. Furthermore, the firing patterns were found to be more irregular in the entopeduncular nucleus (globus pallidus internus in primates). In line with an age-dependent normalization of the density of striatal GABAergic interneurons, the neuronal striato-entopeduncular activity reached normal levels in older dt^{sz} hamsters, that is, after remission of stress-induced dystonia. Deep brain stimulations of the entopeduncular nucleus improved dystonia in mutant hamsters, substantiating the importance of an abnormal basal ganglia output. In the globus pallidus (globus pallidus externus in primates), the neuronal activity only tended to be increased (+40%), but a wide range in the activity may indicate also an involvement of the indirect striato-pallidal pathway. In view of the paroxysmal nature of dyskinesia in dt^{sz} hamsters, the permanent deficit of striatal GABAergic interneurons, resulting in an enhanced striato-entopeduncular activity, seems not to cause motor disturbances by itself. However, this structural defect may lead to a disinhibition of stress-induced dopamine release in the striatum and thereby to the manifestation of a dystonic attack.

Drug-Induced Dyskinesias

Drug-induced dyskinesias are a severe problem in the chronic treatment of various diseases. The most common types of drug-induced dyskinesias are tardive dyskinesias, which can be caused by the treatment with neuroleptics, and LIDs as a side effect in the therapy of Parkinson's disease (PD). Although there have been excessive efforts in the last decades to develop new therapeutics for the treatment of PD, there is a lack of effective drugs with tolerable acute or chronic side effects. Animal models have been shown to give valuable insights into the pathophysiology of LID and represent a useful tool in the preclinical research. LID is only inducible in parkinsonian organisms. To generate animal models of PD, toxins can be administered either systemically (e.g., 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) or rotenone) or intracerebral, like 6-hydroxydopamine (6-OHDA). Probably, most popular is the induction of LID in MPTP-treated primates, but in respect to animal welfare and economic considerations, murine animal models of LID gain in importance. The unilaterally 6-OHDA-lesioned rat provides an excellent reproducibility and good face validity.

LID in the 6-OHDA-Lesioned Rat

LID in 6-OHDA-lesioned rats mimics the symptoms of peak-dose dyskinesias. In this most common type of LID, dyskinetic movements correspond to high concentrations of dopamine agonists in the brain, leading to an overactivation of postsynaptic dopamine receptors.

For generating hemi-parkinsonian rats, 6-OHDA is usually injected unilaterally into the substantia nigra or into the medial forebrain bundle. Additional application of the toxin into the striatum amplifies the depletion of striatal dopamine. Intracerebral injection of 6-OHDA induces degeneration of monoamine neurons, in general, but the selectivity for dopaminergic neurons can be increased by inhibitors of monoamine transporters, like desipramine, administered prior to the operation. The success of unilateral dopaminergic denervation can be detected by quantifying the rotational behavior after the application of dopaminergic drugs. Direct agonists of dopamine receptors like apomorphine provoke contralateral rotations to the lesion, caused by a hypersensitivity of dopamine receptors of the lesioned side. Drugs like amphetamine induce ipsilateral rotations, as only the intact side releases dopamine to stimulate dopamine receptors. The stepping or the cylinder tests also unmask lateral behavior, which reflects the parkinsonian symptoms, bradykinsia or akinesia, caused by the unilateral dopamine depletion. Chronic administration of levodopa (in addition with a decarboxylase inhibitor) induces LID. These involuntary choreoathetotic movements can affect orofascial muscles ('orolingual' dyskinesias), the limb (especially, the forelimb), and the whole body axis ('axial' dyskinesias) and appear contralateral to the lesioned side. An increased contralateral rotation ('locomotive' dyskinesia) can be induced by various dopaminergic drugs and should be distinguished from the three other subtypes of LID. According to Lundblad and coworkers, the severity of each subtype can be rated by a score system from 0 to 4: 0, absent; 1, present during less than half of the observation time (occasional); 2, present during more than half of the observation time (frequent); 3, continuous but interruptible by external stimuli; 4, continuous and not suppressible by external stimuli. Interestingly, the severity of dyskinesia is not predictable by the extent of dopaminergic depletion or levodopa dose.

In compliance with parkinsonian patients, D_2 receptor antagonists and the antiglutamatergic compound amantadine attenuated dyskinesia in the rat model of LID. Nevertheless, the therapeutic benefit of these drugs is only limited as D_2 receptor antagonists worsen parkinsonian symptoms and the glutamate receptor antagonist amantadine is only moderately effective, has side effects, and its efficacy declines over time. Although the combined administration of serotonergic drugs showed pronounced beneficial effects in the rat model of LID, there are contradicting reports to their antidyskinetic potency in patients. Recently, K_v7 channel openers proved to attenuate dyskinesias in 6-OHDA-lesioned rats, possibly pointing to a new therapeutical target in this disease.

Besides the preclinical drug research, neurochemical and electrophysiological studies give further insights into the pathophysiology of LID. It is known that the depletion of dopamine caused by degeneration of midbrain dopaminergic neurons results in an increased responsiveness of striatal GABAergic projection neurons to activation of dopaminergic receptors. During chronic levodopa treatment, when an intermittent increase of extracellular dopamine levels exists, this hyperresponsiveness gains in importance. Furthermore, serotonergic neurons have been shown to be able to convert levodopa to dopamine. However, in contrast to dopaminergic neurons, they lack of a feedback control for the release of dopamine. This could contribute to LID by causing unphysiological high levels of extracellular dopamine after administration of levodopa. Lundblad et al. propose an involvement of several different types of nerve fibres in the conversion of levodopa to dopamine. Otherwise, combined administration of serotonergic drugs, which reduce the release of synaptic vesicles containing serotonin and which convert dopamine by stimulating presynaptic autoreceptors had antidyskinetic potency in the rat model of LID (see above). There is also evidence for an implication of an altered corticostriatal glutamatergic neurotransmission. Picconi and coworkers demonstrated a loss of depotentiation in corticostriatal synapses in dyskinetic rats, consisting of an inability to downregulate long-term potentiation upon low-frequency stimulation of the corticostriatal pathway. This is in line with studies which revealed an enhanced striatal glutamate release in the rat model of LID.

These pathophysiological conditions probably lead to an increased activity of striatal GABAergic projection neurons. Especially, neurons of the 'direct pathway,' which express D_1 receptors, seem to be affected. These neurons show marked molecular changes in LID, including an upregulation of several GABA-related genes. An increased activity of these neurons presumably contributes to a reduced firing rate of neurons of the basal ganglia output structure, as shown in previous studies, which finally results in a disinhibition of the glutamatergic thalamocortical transmission.

Conclusions

Although the etiology of dyskinesias is different in the here described animal models, there seem to be common mechanisms in the pathophysiology. Striatal dysfunctions, leading to an abnormal basal ganglia output, are critically involved in the *dt*^{rz} mutant hamster as well as in LIDs in the rat model. This is in line with the current hypothesis on the pathophysiology in dyskinetic patients. Progress in the identification and in the understanding of shared mechanisms may be promising to find new therapeutic strategies in larger subpopulations of dyskinetic patients. The above described animal models can contribute to find new targets and are suitable for preclinical drug research.

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See also: Dyskinesias; Dystonia; Dystonia: Animal Models; DYT8, Paroxysmal Non-kinesiogenic Dyskinesia-PNKD; DYT9, Paroxysmal Dyskinesia with Spasticity; DYT10, Paroxysmal Kinesiogenic Dyskinesia-PKD; GABA and Movement Disorders; Parkinson's Disease: Definition, Diagnosis, and Management; Parkinson's Disease: Animal Models; Paroxysmal Exertion-induced Dyskinesia; Paroxysmal Movement Disorders.

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Dysphagia

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Glossary

Aspiration – Occurs when food or liquid enters into the airway below the true vocal folds.
Dysphagia – Difficulty in moving food from mouth to stomach.
Fiberoptic endoscopic evaluation of swallowing (FEES) – Is an instrumental assessment tool that allows direct visualization of the pharyngeal and laryngeal structures and their performance before and after the swallow.
Laryngeal penetration – Occurs when food or liquid enters the vestibule or entrance of the airway to any level but not below the superior surface of the true vocal folds.
Videofluoroscopic swallowing study (VFSS) – Is an instrumental assessment tool to determine the nature and extent of an oropharyngeal swallowing disorder. The studies are captured using fluoroscopy in video or digitized format.

Definition and History

Dysphagia is defined as the disordered movement of the bolus from mouth to stomach due to abnormalities in the structures critical to swallowing or in their movements. It comes from the Greek prefix *dys* meaning 'difficulty' or 'disordered' and *phagia* meaning 'to eat.'

The field that studies dysphagia and its treatment is relatively new. The field was in its infancy from the 1970s to the 1980s. The information regarding normal swallow physiology and abnormal swallow pathophysiology has been growing exponentially since the 1990s. The literature on dysphagia falls into three categories: on physiology of normal swallowing; on changes in physiology of swallowing as a result of a variety of medical conditions; and on methodologies for screening, diagnosis, and management of patients with dysphagia.

Pathophysiology

Swallowing, as a complex process, is divided into four stages: oral preparatory, oral, pharyngeal, and esophageal. The *oral preparatory stage* is highly volitional and characterized by chewing and mixing the bolus with saliva. The *oral stage* is characterized by the final formation of the bolus into a shape and posterior movement of that bolus through the faucial pillars and into the pharynx to trigger the pharyngeal stage of swallowing. In the *pharyngeal stage*, the bolus is moved through the pharynx and rostral esophagus. This striated muscle section of the esophagus is called the upper esophageal sphincter (UES). The *esophageal stage* involves movement of the bolus through the esophagus into the stomach. Dysphagia occurs when one or more of the four swallowing phases are impaired due to an underlying neurological condition such as PD or HD. The symptoms of dysphagia vary in different movement disorders at each of the swallowing stages. These differences may reflect the underlying etiology. For example, patients with PD often show a typical tongue movement pattern characterized by a repetitive upward and backward movement of the central portion of the tongue known as 'tongue pumping,' which may last 10 s or more before a full swallow can be initiated. The 'tongue pumping' movement pattern is similar to the festinating gait in PD, that is, many repeated attempts are made before a successful initiation of an intended movement. This may result from the dysfunction of the BG in its role in executing a planned movement sequence in a timely manner. In both Parkinson's disease and Huntington's disease, proprioceptive sensory deficits have been suggested to contribute to decreased sensitivity to aspiration. Other underlying movement disorders with frequent and significant dysphagia include cervical dystonia, oromandibular dystonia,

multisystem atrophy (MSA), progressive supranuclear palsy (PSP), and corticobasal ganglionic degeneration (CBGD), and tardive dyskinesia.

Epidemiology/Risk Factors

Epidemiology as Related to Different Etiologies

Dysphagia or swallowing disorders occur in nearly 100% of people with idiopathic Parkinson's disease (IPD) and Huntington's disease (HD), usually in relatively more advanced stage. In contrast, in atypical Parkinsonism such as MSA, PSP, and CBGD, dysphagia occurs earlier and is more severe in the course of the disease.

Risk Factors

In idiopathic PD, the most important risk factors for developing dysphagia are progression of the disease, disease severity level, and 'on–off' motor fluctuations. In atypical Parkinsonism, the most important risk factors are early signs of dysphagia, dysarthria, and gait disturbances. In all movement disorders, changes in swallowing muscle function and coordination could lead to dysphagia.

Clinical Features/Diagnostic Criteria

Dysphagia can occur at any or a combination of the four stages and it is a serious threat to one's health because of the risk of aspiration pneumonia, malnutrition, dehydration, weight loss, and airway obstruction.

Warning Signs Associated with Dysphagia and Aspiration Risk

Decreased alertness
- heavy sedation from medication
- playing with food
- taking too large or repeated bites without attempting to chew or swallow
- talking or emotional liability during attempts to swallow

Change in approach to food
- avoiding eating in front of others
- avoiding foods of specific consistency
- prolonged meal time; frequent use of liquid to 'wash-down' food
- moving head or neck in certain ways to try to get food down

Impaired functions associated with dysphagia and aspiration
- involuntary tongue movements or head movements that interfere with swallowing
- wet, hoarse voice, extremely breathy voice
- limited mouth opening due to increased spasticity
- drooling or oral spillage, pooling, and pocketing of food in mouth
- coughing and choking upon swallowing
- constant throat clearing during or immediately after meals

Patient complaints and observation
- "It is hard to swallow"
- "It feels like something is stuck in my throat"
- "My taste is changing"
- "It hurts when I swallow"
- "Food or drink comes out of my nose when I eat or drink"
- "It takes too long to eat"
- "I have trouble breathing when I eat or right after I eat"

Diagnosis of Dysphagia

Certified and licensed speech-language pathologists (SLP) are trained to diagnose dysphagia. The following testing procedures are routinely used for diagnosing dysphagia: (1) clinical swallowing study, also called as bedside swallowing study if the test is done in inpatient setting in a hospital; (2) the videofluoroscopic swallowing study (VFSS), also referred to as modified barium swallow (MBS), typically done in a hospital setting because the procedure requires both an SLP and radiologist; (3) the fiberoptic endoscopic evaluation of swallowing (FEES) is an instrumental assessment tool allowing direct visualization of the pharyngeal and laryngeal structures and their performance before and after the swallow. It may require the presence of an otolaryngologist in some states.

Management

Medication

There is limited evidence that medication used to treat PD may be beneficial to the swallowing function. On the other hand, drug-induced orofacial and respiratory dyskinesias can interfere with the swallowing process, which may result in oropharyngeal and/or pharyngeal dysphagia.

Deep Brain Stimulation

Bilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) has mixed results on swallowing. Currently, it is unclear about the exact effect of STN DBS on the swallowing function.

Dysphagia Management

Treatments for swallowing can be divided into compensatory and rehabilitative approaches. Compensatory techniques are aimed at an immediate effect on safety and adequacy of nutrition and hydration. They are applied

when a person is receiving rehabilitation but needs instant help for safe eating, or when a person cannot be expected to complete or profit from rehabilitative efforts. There are three broad categories of compensatory techniques. They are *change in the posture*, *change in the food and/or liquid consistency*, and *change in the approach to eating*. For example, a *postural adjustment such as chin tuck* is often used when a patient has penetration or aspiration due to a delayed swallowing initiation or poor airway protection. The rehabilitative techniques are of two basic types: *they aim to change the underlying pathophysiology such as weakness or reduced endurance and to increase skill*. For example, the Mendelsohn maneuver is used to enhance the anterior hyolaryngeal movement to increase the duration and extent of UES opening during swallow.

Prognosis

Dysphagia in patients with IPD or other movement disorders will worsen as the underlying disease progresses. Early onset of severe swallowing deficits usually indicates poor prognosis.

See also: Alzheimer's Disease and Parkinsonism; Ataxia; Basal Ganglia, Functional Organization; Cognitive Assessments and Parkinson's Disease; Corticobasal Degeneration; Deep Brain stimulation; Dyskinesias; Dystonia; Hoehn and Yahr Staging Scale; Huntington's Disease; Levodopa; Multiple System Atrophy; Pallidotomy for Parkinson's Disease; Parkinson's Disease: Definition, Diagnosis, and Management; Progressive Supranuclear Palsy; Spasmodic Dysphonia: Focal Laryngeal Dystonia; Surgery for Movement Disorders, Overview, Including History; Unified Parkinson's Disease Rating Scale (UPDRS) and The Movement-Disorder Society Sponsored-unified Parkinson's Disease Rating Scale (MDS-UPDRS); Wilson's Disease.

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http://www.nidcd.nih.gov – National Institute on Deafness and Other Communication Disorders (NIDCD).

http://www.dysphagiaresearch.org – Dysphagia Research Society.

http://www.swallowingdisorders.org – The Specialty Board on Swallowing and Swallowing Disorders (SBSSD).

Dystonia

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Glossary

Blepharospasm – Focal dystonia involving the periocular muscles.

Cervical dystonia – A focal dystonia of the neck also called spasmodic torticollis.

Dystonia – A neurological disorder marked by the presence of involuntary, sustained muscle contractions causing abnormal postures.

Generalized dystonia – Dystonia involving at least one leg, the trunk, and one other body area.

Geste antagoniste – A touch or sensory maneuver that reduces or abolishes the dystonic symptoms.
Occupational dystonia – A dystonia that occurs only during a specific activity, such as writer's cramp or musicians dystonia.

Definition

Dystonia is a neurological syndrome with sustained muscle contractions that result in twisting and repetitive movements or abnormal postures. The sustained movements of dystonia may have overlying spasms that resemble tremor but can be distinguished from essential tremor by the directional quality of the movement. Dystonia is a dynamic disorder that changes in severity depending on activity and posture. An example of this is writer's cramp, a dystonia that involves the hand and arm, which is present only during the action of writing but not apparent during any other activity. Another characteristic feature of dystonia is the sensory trick. The sensory trick (or geste antagoniste) is a touch or sensory maneuver that reduces or abolishes the dystonic symptoms. It occurs in approximately 60% of patients. These tricks may be effective in some patients if imagined but not performed physically.

Dystonia is categorized in several ways. Categorization by body distribution separates dystonia into focal (involving a single body area), segmental (involving contiguous body areas), and generalized (involving at least one leg, the trunk, and another body area). Less common body distributions include multifocal (two or more noncontiguous body areas involved) and hemidystonia (involvement of one side of the body). Categorization of dystonia by age of onset divides dystonia into young onset (age of onset less than 26 years) and adult onset (age of onset greater than 26 years). The third categorization is by etiology, which is broadly separated into primary and secondary dystonia (**Table 1**).

The body region at onset and age of onset are important clinical clues when assessing dystonia. Young-onset dystonia most often begins with symptoms in the limbs, with the leg most frequently involved at onset. Dystonia that begins in childhood spreads to other body areas to become generalized dystonia in over 50% of patients. In contrast, adult-onset dystonia most frequently begins in the neck, arm, or face and tends to remain focal or may spread to become segmental but not generalized in most adult patients. Hence, a child with onset in the neck or face or an adult with onset in the leg or an adult who develops generalized dystonia would be atypical and indicate the need for further evaluation for an underlying cause.

Table 1 Classification of dystonia

Age of onset	Young onset: $\leq$26 years
	Adult onset: $>$26 years
Body distribution	Focal: single body region
	Segmental: contiguous body regions
	Generalized: both legs and at least one other body region
	Multifocal: noncontiguous body regions
	Hemidystonia: involving one half of the body
Etiology	Primary:
	Dystonia is only sign; may be sporadic or inherited
	Secondary:
	Dystonia occurring associated with a defined etiology or associated with other neurological abnormalities

The third method of dystonia classification is by etiology (**Table 2**). This classification scheme has undergone modification as new etiologic and genetic forms of dystonia have been described. The two broad categories in this classification include primary and secondary dystonia. Patients with primary dystonia present with signs related solely to dystonia and have no additional neurologic, laboratory, or imaging abnormalities. If dystonia is associated with muscle weakness, spasticity, ataxia, ocular motility abnormalities, retinal abnormalities, cognitive impairment, or seizures, then it is categorized as a secondary dystonia. In primary dystonia, the onset and progression of symptoms are gradual and without fixed postures unless contractures from longstanding dystonia occur. Secondary dystonia arises from an underlying condition. Examples include perinatal asphyxia or exposure to dopamine receptor antagonist drugs prior to development of dystonia. The presence of other neurological abnormalities may provide the clue to the cause of the dystonia.

Pathogenesis

There are no consistent neuropathological findings in primary dystonia. The lack of cell degeneration suggests that primary dystonia is a dynamic disorder, arising from abnormal cell function. The anatomic localization and specific neurotransmitter defects of dystonia have also been elusive. The first clue that dystonia is a disorder of the basal ganglia came from studies of hemidystonia in which lesions of the contralateral basal ganglia were associated with ipsilateral dystonia.

Recent neuroimaging studies with positron emission tomography and functional magnetic resonance imaging have shown that dystonia is associated with abnormal

Table 2 Etiology of dystonia

1. Primary dystonia
   a. Genetic forms of dystonia
   b. Sporadic
2. Dystonia-plus syndromes
   a. Dopa-responsive dystonia (DRD)
      i. GCHI mutations (DRD or DYT5)
      ii. Tyrosine hydroxylase mutations
      iii. Other biopterin deficient states
   b. Dopamine agonist responsive dystonia due to decarboxylase deficiency
   c. Myoclonus-dystonia
3. Other inherited (degenerative) disorders
   a. Autosomal dominant
      i. Rapid-onset dystonia-parkinsonism
      ii. Huntington's disease
      iii. Machado–Joseph's disease/SCA3 disease
      iv. Other SCA subtypes
      v. DRPLA
      vi. Familial basal ganglia calcifications
   b. Autosomal recessive
      i. Wilson's disease
      ii. Gangliosidoses
      iii. Metachromatic leukodystrophy
      iv. Homocystinuria
      v. Hartnup disease
      vi. Glutaric acidemia
      vii. Methylmalonic aciduria
      viii. Hallervorden–Spatz disease
      ix. Dystonic lipidosis
      x. Ceroid-lipofuscinosis
      xi. Ataxia-telangiectasia
      xii. Neuroacanthocytosis
      xiii. Intraneuronal inclusion disease
      xiv. Juvenile parkinsonism (parkin)
   c. X-linked recessive
      i. Lubag (X-linked dystonia-parkinsonism or DYT3)
      ii. Lesch–Nyhan syndrome
      iii. Deafness/dystonia
   d. Mitochondrial
      i. MERRF/MELAS
      ii. Leber's disease
4. Due to acquired/exogenous causes
   a. Perinatal cerebral injury
   b. Encephalitis, infectious, and postinfectious
   c. Head trauma
   d. Pontine myelinolysis
   e. Primary antiphospholipid syndrome
   f. Stroke
   g. Tumor
   h. Multiple sclerosis
   i. Cervical cord injury or lesion
   j. Peripheral injury
   k. Drugs
      i. Dopamine receptor antagonists
      ii. Dopamine receptor agonists
   l. Toxins
   m. Psychogenic
5. Dystonia associated with parkinsonian disorders
   a. Parkinson's disease
   b. Progressive supranuclear palsy
   c. Multiple system atrophy
   d. Corticobasal ganglionic degeneration (CBGD)

activity in multiple regions of the brain, including motor cortex, supplementary motor areas, cerebellum, and basal ganglia. Abnormalities in blink reflex recovery and exteroceptive reflexes suggest a loss of central inhibitory mechanisms. Extensive electrophysiologic data in combination with functional imaging have suggested that the pathophysiology of dystonia, in particular the task-specific dystonias may arise to form a decrease of inhibition, an increase of plasticity or an impairment in sensory function.

Direct microelectrode recordings obtained in dystonia patients during electrode implantation for deep brain stimulation have shown alterations in mean discharge rates, somatosensory responsiveness, and altered patterns of neuronal activity in the globus pallidus. These recordings have given rise to new constructs for diagrams of the basal ganglia and its involvement in dystonia, in which the modulating influences within the basal ganglia change with activity, reflecting the movement-dependent nature of dystonia.

The underlying neurochemistry of dystonia is not known. Indirectly, abnormalities of dopaminergic activity in the basal ganglia are suggested by extrapolation from observations that dopamine receptor antagonism can cause acute and chronic dystonic symptoms (e.g., oculogyric crisis and tardive dystonia) and that dystonia is often associated with Parkinson's disease, a disorder with marked dopamine depletion. The occurrence of dopa-responsive dystonia further implicates a role for dopamine in the pathogenesis of dystonia. Response to anticholinergic agents implicates cholinergic mechanisms.

Epidemiology and Genetics

Investigations into the incidence and prevalence of dystonia are complicated by the difficulties in the ascertainment of affected individuals. The most cited prevalence figures are derived from a study conducted in the late 1980s in Rochester Minnesota, in which the prevalence of generalized dystonia was 34 per million population and the prevalence of focal dystonia was 295 per million, with cervical dystonia being the most frequent. However, subsequent epidemiological studies have shown a wide range in prevalence that may arise from differing methodologies of case identification, and the demographic and ethnic composition of the population assessed. In all studies, focal dystonia is more frequent, being estimated to be approximately ten times more frequent than generalized dystonia. Prevalence figures, however, have ranged from 6 to 732 persons per 1 000 000 population. In the absence of a reliable and validated screening tool that can be applied practically in large populations, underdiagnosis and misdiagnosis of dystonia are likely major confounds. In one study of familial dystonia, half the cases were not diagnosed. Recent efforts have been

directed toward development of diagnostic criteria and a reliable practical screening instrument that can be applied to large population studies.

There have been many recent advances in the area of dystonia genetics (**Table 3**), with identification of new genetic loci, increased understanding of genotype–phenotype interactions, and investigations into the role of the mutant gene products. DYTI dystonia is autosomal dominant but penetrance is reduced approximately 30–40%. The DYT1 gene accounts for about 90% of limb early-onset dystonia in the Ashkenazi population. In the non-Jewish population, however, only 40–65% of early-onset primary dystonia cases carry the gene. The DYT1 gene has a 3-base pair (GAG) deletion at 9q34, giving rise to mutated torsin A.

Torsin A is a member of the AAA+ superfamily and is present in all multicellular organisms. Wild-type torsin A colocalizes with cytoplasmic membrane structures and may be associated particularly with the endoplasmic reticulum. Recent studies of mutant torsin A have shown that it may be redistributed to other membrane structures, and demonstrates perinuclear staining, with the formation of distinct globular inclusions that contain vesicular monoamine transporter 2 (VMAT2).

Myoclonus-dystonia is a movement disorder characterized by alcohol-sensitive myoclonic jerks primarily affecting the arms and axial muscles combined with variable features of dystonia. Myoclonus-dystonia typically begins in the second decade and occurs equally in men and women. The dystonia may be mild, involving neck or limbs, and may occur in both in body areas affected by dystonia and affected areas. This form of dystonia may improve dramatically after alcohol intake. Myoclonus-dystonia is an autosomal dominant disorder with reduced penetrance.

Table 3 Genetic forms of dystonia

Locus	*Designation*	*Mode of inheritance*	*Clinical features*	*Chromosome, gene product and mutation*
DYT 1	Early-onset dystonia	AD	Typically begins in childhood; onset in limb often with progression to generalized dystonia	9q34; GAG deletion in DYT1 gene causes abnormality in ATP-binding protein, torsin A
DYT2	Autosomal recessive dystonia in Gypsies	AR	Childhood onset, generalized or segmental	Unknown chromosome, gene product
DYT3	Dystonia-parkinsonism 'Lubag'	X-linked recessive	Segmental or generalized dystonia with parkinsonism; predominantly in males from Panay island in Philippines	Xq13.1; unknown gene product
DYT4	Whispering dysphonia	AD	Whispering dysphonia; described in Australian family	Unknown chromosomal location, gene product
DYT5	Dopa-responsive dystonia/parkinsonism	AD	Dystonia with or without parkinsonism; dramatic response to levodopa	14q22: GCH1 locus; mutations in GTP cyclohydrolase I gene
	Segawa syndrome	AR	Dystonia with or without parkinsonism; diurnal variation, with worst symptoms in evening; marked response to levodopa	11p15.5; mutations in the tyrosine hydroxylase gene
DYT6	Adolescent-onset dystonia of mixed type; mennonite families	AD	Mostly segmental dystonia; mixed limb, cervical, cranial	8p; THAP1 gene
DYT7	Adult-onset focal dystonia; German family	AD	Adult onset with cervical dystonia, limb dystonia, dysphonia, or blepharospasm	18p
DYT8	Paroxysmal nonkinesigenic dyskinesia	AD	Episodes of dystonia/choreoathetosis not precipitated by exercise or activity	2q, myofibrillogenesis regualtro (MR-1)
DYT9	Paroxysmal choreoathetosis with episodic spasticity and ataxia	AD	Episodes of dystonia, diplopia, paresthesias with spastic paraplegia between attacks	1p Gene, product unknown
DYT10	Paroxysmal kinesigenic choreoathetosis	AD	Episodic choreoathetosis and dystonia brought on by exercise/activity	16p-q; gene, product unknown
DYT11	Myoclonus-dystonia	AD	Myoclonic jerks associated with variable features of dystonia; very alcohol responsive	7q; epsilon-sarcoglycan gene (SGCE)
DYT12	Rapid-onset dystonia-parkinsonism	AD	Onset of dystonia and parkinsonism over days to months	19q; Na/K ATPase alpha 3
DYT13	Multifocal and segmental dystonia	AD	Early-adult-onset segmental dystonia with cervical, cranial, and arm dystonia	1p; unknown gene product
DYT15	Myoclonus-dystonia	AD	Myclonus and dystonia	18p; unknown

AD = autosomal dominant; AR = autosomal recessive; ATP = adenosine triphosphate.
Bressman S (2007) Genetics of dystonia: An overview. *Parkinsonism and Related Disorders* 13: S347–S355.

Several loci for myoclonus-dystonia have been identified, one on chromosome 7q21, which harbors the gene for ε-sarcoglycan (SGCE), and another on chromosome 18p11. Other loci have been identified in two families, including a missense change in the D2 dopamine receptor (DRD2) gene on 11q23 and a novel 18-bp deletion mutation in the DYT1 gene on 9q34, indicating genetic heterogeneity for myoclonus-dystonia.

Dopa-responsive dystonia (DRD) manifests primarily as dystonia with onset in early childhood. Parkinsonism, including rigidity and bradykinesia, may develop during the course of untreated disease or be present at onset. Often, children with DRD are initially misdiagnosed as having a primary dystonia or cerebral palsy. The hallmark of this disorder is a marked, sustained response to levodopa. In the initial description of DRD, Segawa and colleagues reported a diurnal fluctuation in symptoms, such that symptoms worsened over the course of a day and improved following sleep. The diurnal fluctuation of symptoms may not be present in all patients with DRD. The most frequent form of DRD is autosomal dominant with a mutation in the gene for guanosine triphosphate (GTP) cyclohydrolase I. GTP cyclohydrolase I is involved in the biosynthesis of tetrahydrobiopterin, which is a cofactor for tyrosine hydroxylase, the rate-limiting enzyme in the synthesis of dopamine. It is also a cofactor for phenylalanine and tryptophan hydroxylase. Numerous mutations of the GTP cyclohydrolase I gene and mutations in can cause DRD, making gene testing difficult. Diagnostic testing that has been suggested includes assessing tetrahydrobiopterin and neopterin in the cerebrospinal fluid and a phenylalanine-loading test. In the clinical setting, the marked benefit of dystonia to a trial of levodopa slowly increased to doses of 600–1000 mg day^{-1} is usually the most useful for diagnosis although this does not differentiate from juvenile onset parkinsonism. In DRD, levodopa, usually at small doses, produces a marked sustained benefit, with virtual elimination of symptoms. DRD may be misdiagnosed as cerebral palsy.

Other genetic forms of dystonia combine features of dystonia with parkinsonism. Rapid-onset dystonia-parkinsonism is an autosomal dominant disorder in which symptoms of dystonia and parkinsonism with prominent dysarthria and dysphagia evolve over a period of hours to weeks. Onset occurs in adolescence and early adulthood. Despite reduced cerebrospinal homovanillic acid levels, this syndrome responds poorly to dopaminergic agents. Linkage to chromosome 19q13 has been found and six missense mutations in the gene for the Na+/K+-ATPase alpha3 subunit (ATP1A3) have been described. Genetic testing for the ATP1A3 gene is recommended when abrupt onset, rostrocaudal gradient and prominent bulbar findings are present.

Lubag is an X-linked dystonia-parkinsonism causing progressive dystonia, often accompanied by parkinsonism. This disorder affects Filipino males in their fifth decade Philippines. Women are also affected, with a recent study showing that in women, the clinical course is much more benign. Prominent pathologic findings include pronounced atrophy of the caudate and putamen. The disorder is poorly responsive to medication and patients usually survive with the disease for only about 10–12 years. Genetic studies have located the affected gene to Xq13.1.

The genetics of adult-onset, focal, and segmental dystonia has been more difficult to delineate. Many cases are likely to be hereditary. The DYT1 gene has been largely excluded as a cause in this form of dystonia. A gene locus has been described for several subgroups. Large Mennonite families with adult-onset, autosomal dominant, cranial-cervical dystonia have been described. The gene locus in these families is localized to chromosome 8 (DYT6).

Three additional genetic forms of focal and/or segmental dystonia have been described (DYT4, DYT7, DYT13). Cohort analysis suggests an autosomal dominant inheritance with variable penetrance. Although these families are rare, additional gene loci will be identified in the future.

Clinical Features

Early-onset dystonia typically begins in the lower body, affecting one leg. The initial symptoms are typically a posturing of the foot that is first noticed during more strenuous activities, such as running. Over time, the posturing will occur with less activity, being apparent during walking or standing. Subsequently, the dystonia occurs with minimal activation, and may be present at rest. In early-onset dystonia, approximately 50–90% of children will experience a spread of dystonia to other body areas, including the other leg, torso, arms, and upper body. Focal, young-onset dystonia tends to spread to become generalized dystonia usually within 5 years of onset. In primary dystonia, cognition and intellectual abilities remain intact despite the presence of significant movement abnormalities. Early-onset dystonia that begins in late childhood and adolescence may initially present in the arm and have less likelihood of subsequent spread to generalized dystonia.

In contrast to early-onset, late-onset primary dystonia often begins in the upper body, usually in the arm, neck, or face. Although symptoms may worsen in the area of involvement or spread to contiguous body regions (segmental dystonia), rarely does adult-onset dystonia become generalized. However, regional spread to contiguous body areas can occur, and is most frequently described with blepharospasm. In adults, the onset of leg dystonia is infrequent but can occur not associated with DYT1. Onset of generalized or hemidystonia in an adult is infrequent and warrants further investigation.

Late-onset focal dystonia may involve different body areas. Blepharospasm is a focal dystonia involving the

periocular muscles. Clinical manifestations include increased blinking and spasms of involuntary eye closure. Symptoms are bilateral but may be asymmetric. Typically, patients with blepharospasm complain of increased spasms under conditions of bright light or stress (such as driving a car in traffic). Pain is infrequently associated with blepharospasm, although patients may observe a feeling of irritation in the eyes as one of the first symptoms. Blepharospasm may be mild and not interfere with function, or it may cause significant disability through interference with vision as a result of the eye closure. Blepharospasm may be associated with dystonia of the lower face and/or jaw (Meige's syndrome or Brueghel's syndrome).

Cervical dystonia (CD) affects the muscles of the neck and shoulders. It may appear as horizontal turning of the head (torticollis), lateral flexion of the neck (laterocollis), forward flexion of the head (anterocollis), or posterior extension of the head (retrocollis). Some patients may have overlying dystonic spasms that resemble tremor, but are distinguished from tremor by the directional quality of the movement. Approximately half of patients with CD will complain of pain associated with the dystonia.

Arm dystonia is manifested as a posturing of the hand and/or arm. Overlying dystonic spasms may occur and resemble essential tremor. However, in contrast to essential tremor, dystonia is often unilateral, and triggered by specific activities, such as writing or typing. Dystonia of the arm and hand is often not present at rest and may be variably present with arms outstretched. Occupational or task-specific dystonia is only manifested during particular activities. Writer's cramp is the most common form. This focal dystonia is elicited by the act of writing, appearing as an involuntary flexion, extension and/or rotation of the fingers, wrist and less frequently the elbow and shoulder. The act of writing becomes effortful, and handwriting changes, becoming illegible in some patients. Other types of task-specific dystonia include typist dystonia, golfer's dystonia (yips), and musician's dystonia.

Oromandibular dystonia (OMD) and facial dystonia are characterized by involuntary movements involving masticatory, lingual, and pharyngeal muscles. OMD can be manifested as jaw clenching, jaw opening, jaw deviation, and tongue protrusion. It is often found in combination with dystonia of adjacent body regions, including blepharospasm and cervical dystonia. Symptoms can result in difficulty speaking and swallowing and may be cosmetically disfiguring. Occupational facial dystonia may manifest as embouchure dystonia, a dystonia of the lips, jaw, or tongue that affects musicians only during the act of playing their instruments, and is absent during other activities such as eating or speaking.

Spasmodic dysphonia is a focal dystonia involving the laryngeal muscles. The most common type of spasmodic dysphonia is the adductor type, with apposition of the vocal cords only during the action of vocalization. This causes voice breaks and a strained pattern of vocalization. Abductor spasmodic dysphonia is characterized by an abduction of the vocal cords during vocalization, resulting in a voice that is whispering and breathy. Vocal tremor arises from rhythmic movements of the vocal cords and produces an oscillation of vocal patterns.

Differential Diagnosis and Diagnostic Work Up

Dystonia is diagnosed based on its clinical features. Primary dystonia is separated from secondary dystonia by the absence of additional neurological abnormalities and the lack of possible acquired cause (**Table 4**). Laboratory testing in primary dystonia is of minimal usefulness but essential in the evaluation of secondary dystonia, or dystonia with atypical features. In primary dystonia, there are no abnormalities on MRI or computerized tomography scans. In secondary dystonia, the MRI findings vary with the etiology. In patients with early-onset dystonia (<26 years of age) or late onset but with an affected relative with early-onset dystonia, DYT1 gene testing is indicated with appropriate genetic counseling. Currently, testing for other genetic loci is not available for clinical use.

The assessment of secondary dystonia is extensive. Laboratory evaluations and brain imaging should be obtained and appropriately directed.

Management

The treatment of dystonia is symptomatic. No curative therapies are available. Treatment options include oral medications, chemodenervation, and surgical management. Oral medications have not been extensively studied

Table 4 Clinical features distinguishing primary dystonia

Presence of:
• Sustained involuntary movement, sometimes overlying spasms
• Consistent directional quality
• Involves same body region(s)
• Enhanced or produced by activity of involved area
• Varies with change in activity or posture
• Sensory tricks may reduce symptoms (*geste antagoniste*)
Absence of:
• Weakness
• Amyotrophy
• Spasticity
• Ataxia
• Ocular abnormalities
Abnormal eye movements
Retinal changes
• Cognitive impairment
• Seizures

in controlled trials. Many drugs have been reported to be of some benefit in a number of patients with dystonia. However, the therapeutic window for oral agents is narrow, with drug side effects frequently limiting achievement of adequate clinical benefit. Examples of oral agents useful for the treatment of dystonia are listed in **Table 5**.

Anticholinergic drugs, usually in high doses, have been of benefit in focal and generalized dystonia, as shown in one of the few controlled studies of treatments for dystonia. Peripheral side effects, such as dry mouth, blurred vision, and urinary retention, may be reversed using a peripheral cholinesterase inhibitor (glycopyrrolate). The central side effects, including memory loss and sedation, are dose limiting. Anticholinergic treatment is initiated at small doses, with a gradual dose escalation until acceptable improvement or unacceptable side effects occur. Discontinuation of anticholinergic agents should be gradual, as withdrawal effects may occur.

Carbidopa/levodopa is dramatically beneficial in DRD, in which small doses of levodopa may virtually eliminate dystonic symptoms for an indefinite period of time. In other forms of dystonia, the response rate with levodopa is approximately 15%. Dopamine receptor antagonists, although beneficial in some patients, are not used because of the possibility of tardive dyskinesia, a disorder that may be disabling and irreversible.

Tetrabenazine combines monoaminergic depletion and dopamine antagonist effects and has recently been approved

Table 5 Oral Medications useful for the treatment of dystonia

Pharmacologic agent	*Efficacy and comment*	*Side effects*
Dopamine agonists Carbidopa/Levodopa (Sinemet®)	Dramatic response in the dopa-responsive form of dystonia; effective in 10–15% of patients; more rapid upward titration possible	Nausea (especially at initiation of therapy); may worsen dystonia; rapid discontinuation possible
Anticholinergic/antihistaminic Trihexyphenidyl (Artane®) Benztropine (Cogentin®) Procyclidine (Kemadrin®) Diphenhydramine (Benadryl®) Ethopropazine (Parsidol®)	Effective in approximately 40% of patients; benefit limited by side effects; requires slow upward titration	Dry mouth (may lead to dental caries); blurred vision; exacerbation of acute-angle glaucoma; urinary retention; memory problems; sedation; confusion; hallucinations; heat intolerance
Baclofen (Lioresal®)	Effective in approximately 20% of patients; high doses tolerated in children; benefits limited by side effects; intrathecal baclofen minimally successful; *withdrawal effects on sudden discontinuation*	Nausea; sedation; dysphoria; muscle weakness (in those with spasticity associated)
Clonazepam (Klonopin®)	Effective in approximately 15% of patients; possibility for addiction; *withdrawal effects on sudden discontinuation*	Sedation; depression; confusion; dependence
Muscle relaxants Tizanidine Cyclobenzaprine	Limited benefit in some patients; side effects frequent	Sedation; dysphoria
Anticonvulsant medications Carbamazepine Gabapentin	Benefit in less than 10% of patients	Ataxia; sedation
Dopamine-depleting agents Tetrabenazine Reserpine	Tetrabenazine is not available in the United States; available from Europe/Canada; requires a very slow upward titration (4 weeks between dose increases)	Depression; dysphoria; parkinsonism
Dopamine antagonists	Effective in up to 25% of patients; clozapine requires weekly blood counts and may cause life threatening agranulocytosis	The possibility of tardive dyskinesia and the other adverse effects from this class of medications severely limits usefulness; not recommended for dystonia

in the United States for Huntington's disease. Tetrabenazine has been found to be beneficial in a variety of hyperkinetic movement disorders, including dystonia. Side effects, however, are frequent and include sedation, parkinsonism, depression, akathisia, nervousness, and insomnia.

Clonazepam is a benzodiazepine reported in uncontrolled studies to improve symptoms of dystonia in approximately one fifth of patients at doses ranging from 1.5 to 12.0 mg day^{-1}. Adverse effects from clonazepam include sedation, depression, confusion, and dependence.

Baclofen, a presynaptic γ-aminobutyric acid B receptor agonist, may be very effective at high doses in children with generalized dystonia, and less beneficial for treatment of focal dystonia because side effects, including nausea and sedation, may be intolerable. While administration of intrathecal baclofen allows for regionally elevated spinal fluid levels thereby reducing the occurrence of central side effects, it has yet to be established as an effective treatment for dystonia not associated with spasticity.

Botulinum toxin (BoNT) is a potent neurotoxin produced by clostridium botulinum that causes regional muscle weakness through its action as a zinc endopeptidase, cleaving specific proteins involved in vesicular fusion. Disruption of these fusion proteins interferes with the release of acetylcholine at the neuromuscular junction, resulting in localized muscle weakness. Although now applied to a variety of neurological and nonneurological disorders, BoNT has been used extensively for a variety of dystonias for over 20 years. Two serotypes, BoNT A and BoNT B are used commercially. Both are approved in the United States for treatment of cervical dystonia and BoNT A is approved for blepharospasm. BoNT treatment benefits from 50% to 85% of patients with these dystonias. It is also viewed as the treatment of choice for spasmodic dysphonia, limb dystonia and oromandibular dystonia. Adverse events are frequent and attributable to excessive weakness in injected muscles or diffusion into nearby muscles. These side effects are typically mild and transient. From 5% to 20% of patients receiving repeated large injections (greater than 300 units) of BoNT develop clinical resistance to the toxin. The availability of alternate serotypes provides options when resistance occurs.

Surgical treatment of dystonia is reserved for patients with severe dystonia who fail drug and chemodenervation treatments. Bilateral thalamotomy was used in the 1960s and 1970s for generalized dystonia, but complications from the procedure, including hemiparesis, spasticity, ataxia, dysphagia, and dysarthria were serious complications. Subsequently, deep brain microelectrode stimulation of the globus pallidus has been shown to dramatically improve symptoms of primary dystonia. The US Food and Drug Administration approved DBS for use in dystonia at centers with approved surgical protocols. Over the past year, DBS has been evaluated in open label and controlled studies for generalized dystonia and cervical dystonia. Other targets for DBS in dystonia include the subthalamic nucleus. DBS has not been as consistently effective for treatment of secondary dystonia, although several recent case reports indicate improvement in for some secondary cases including pantothenate kinase-associated neurodegeneration. A recent study indicates that accurate localization of stimulating electrodes in the area of the intercommissural plane provides for optimal outcome in generalized dystonia, and specific targets in the globus pallidus should be targeted for dystonia in specific body regions, reflecting the somatotopic organization of that structure.

Prognosis

Primary dystonia is usually a life-long disorder that may fluctuate in severity. Although remissions have been observed in up to 20% of patients, there is usually a recurrence of symptoms. In childhood-onset dystonia, especially with onset in the leg there is often spread of dystonia to involve other body areas, and over half will go on to develop generalized dystonia. In adult onset dystonia, symptoms tend to involve the face, neck and arm. These symptoms rarely spread to generalized dystonia. Although primary dystonia is not a life-threatening disorder, the symptoms may cause significant disability and impaired quality of life.

See also: Dystonia in Amish-Mennonite and Mennonite Families; Dystonia, Secondary; Dystonia, Task-specific; Dystonia, Traumatic; Dystonia: Animal Models; Dystonic Storm; DYT1; DYT2, Autosomal Recessive Generalized Dystonia; DYT4, Autosomal Dominant Type Dystonia or Whispering Dysphonia; DYT5; DYT6, Mixed Phenotype Primary Dystonia; DYT7, Autosomal Dominant Focal Dystonia; DYT8, Paroxysmal Non-kinesiogenic Dyskinesia-PNKD; DYT10, Paroxysmal Kinesiogenic Dyskinesia-PKD; DYT11, DYT15, Myoclonus-dystonia; DYT12, Rapid Onset Dystonia-parkinsonism; DYT13, Cranio-Cervical-Brachial; Hallervorden–Spatz Syndrome (PKAN); Spasmodic Dysphonia: Focal Laryngeal Dystonia.

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Dystonia in Amish-Mennonite and Mennonite Families

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Overview and History

The history of the Amish and the Mennonite populations spans four centuries and three continents. Due to persecution and religious differences, it is a story of migrations and splitting of groups. Dating the time of a founder mutation is helpful in determining which groups of Amish and Mennonites are at risk for certain disorders, as the oldest founder mutations may be represented in all groups and the more recent founders mutations will only be present in certain groups.

Begun in sixteenth century Europe, Amish-Mennonites and Mennonites were often persecuted, and migrated within and out of Europe to escape persecution. This often produced insular communities, and marriage was usually among individuals within the particular religious community. It is debated whether Anabaptism rose in separate places simultaneously or descended from one larger group; however, geographic clustering of two large groups, the Dutch and Swiss, were clear. Prior to the twentieth century, intermarriage between these two groups was uncommon.

Dutch/Northern German/Prussian/Russian

Menno Simons joined the Anabaptist movement in Holland around 1535, and followers of this group, called Mennonites, were primarily in Holland and Northern Germany. Some migrated from Holland directly to Pennsylvania in the late 1600s. Old Order Mennonites split from the Mennonite Church in the United States and Canada during 1870–1900 and, divisions in Indiana/Ohio, Ontario, Lancaster, PA, and Virginia arose.

Many Dutch Mennonites who remained in Holland migrated around this time to Prussia. Beginning in 1788–1789, some migrated further to Russia, and then from the 1870s to 1920s, moved again to midwestern and western Canada (especially southern Manitoba, and also Alberta) and the midwestern United States (Nebraska, Kansas). Later, waves of emigrants went to South America, particularly Paraguay. Hence, mutations that may have arisen after the migration to Pennsylvania in the 1600s might be seen only in the descendants of the Russian Mennonites. Descendants of both groups never practiced the Amish religion, thus were never Amish. However, other Russian Mennonites migrated to Ontario in the Kitchener–Walterloo areas, where some Swiss Amish-Mennonites had previously settled, thus leading to some mixing in the twentieth century.

Swiss/Alsatian/South German

Jakob Amman (hence Amish) led an Anabaptist movement in Switzerland in the 1690s. Both Old Order Amish (referred to here as Amish) and Amish-Mennonites descended from these groups. Descendants started migrating to the Alsace region in the late 1690s and eventually to southern Germany, and in the eighteenth century to Pennsylvania. In the beginning of the nineteenth century, there was another migration from Alsace-Lorraine and Bavaria to Ontario, Ohio, Indiana, and Illinois.

Because of high birth rates in the Amish communities, where contraception is not practiced and there are low infant mortality rates, the number of Amish has grown from ~3700 in 1900 to 231 000 in 2008. Therefore the likelihood that a common founder would be detected in the population is high. The adherence to stricter societal norms including not using electricity separates the Amish from Amish-Mennonites. However, even among groups who were originally Amish, many descendants no longer

consider themselves Amish, rather they are Mennonite, as splits among the Amish communities, led to different societal practices. This is the background in which the original DYT6 family was described as 'Mennonite.' Although they self-reported to researchers that they were of Mennonite background, it is not of the Dutch Mennonite described above, but rather of a Swiss Amish-Mennonite background, and to make this distinction, subsequent publications on DYT6 have labeled these families as 'Amish-Mennonites.'

Prior to the twentieth century intermarriage between those of Dutch and Swiss backgrounds was uncommon, so that individuals of Mennonite background differed genetically from those of Amish-Mennonite background, and founder mutations have been observed in one group but not the other.

Approach to Dystonia in the Amish-Mennonites and Mennonites

While the mixed phenotype primary torsion dystonia due to THAP1 mutations in the DYT6 gene has become synonymous with Amish-Mennonite dystonia, other etiologies of dystonia have been demonstrated in the Amish-Mennonites and Mennonites. Clinical patterns for the most part, guide a determination of the type of dystonia between families, although overlap may be present.

As in other forms of dystonia, determination of whether the dystonia is primary or secondary, that is, whether there are other neurologic features other than tremor, imaging abnormalities or a metabolic defect is key to classification.

Among Amish-Mennonites and Mennonites, three types of primary dystonia have been described.

DYT6 Dystonia

This type is characterized by early or adult onset primary dystonia which usually involves the arm or leg, and often has prominent cranial-cervical dystonia.

The DYT6 locus was first mapped in two Amish-Mennonite families who were not known to be related, although they shared a common haplotype and common genealogic ancestors were subsequently demonstrated. Together with additional members from these families as well as a third family, the gene region was narrowed, and the DYT6 gene, THAP1 was identified. THAP1 is a nuclear proapoptotic factor, whose causal relation to dystonia is not yet known. An exon 2 missense 5 bp insertion/3 bp deletion mutation which leads to premature termination of the THAP1 protein is responsible in the Amish-Mennonites. DYT6 is inherited in an autosomal dominant pattern with reduced penetrance of ~60%. Although more women than men are affected, no gender related penetrance is noted. Other DYT6 mutations have since been identified in other ethnic groups, and further research will demonstrate whether there is a genotypic heterogeneity even among Amish-Mennonites and Mennonites, as would be anticipated by their varied genetic backgrounds.

DYT6 was described as mixed, as it shared features with DYT1, early onset dystonia, the particularly arm involvement and early onset, as well as features with adult onset dystonia, the prominent cranial and cervical involvement, which is infrequently seen in DYT1, but is not a major feature of DYT1. Mean age of onset in the three Amish-Mennonite families was 16 years with a range of 5–38 and more than half of the cases starting before 16 years. Arm was the most frequent site of onset (approximately half), and dystonia eventually involved the arm in almost all. Other sites at onset included cranial muscles and neck, but leg was rare (4%). This is in contradistinction to DYT1 where leg onset is frequent. Speech involvement was a prominent feature in half of the affected individuals, and cranial and neck dystonia were present in 80%. While the leg became involved in over 50%, the severity of leg dystonia was much less than DYT1, which more commonly leads to difficulty ambulation.

DYT1 Dystonia

As noted, above, the affected sites and the severity of sites may distinguish DYT6 dystonia from DYT1. Therefore the DYT1 diagnosis made in a man of Amish-Mennonite background, who had childhood onset dystonia with prominent bilateral leg, trunk dystonia which impaired walking, as well as bilateral arm and mild neck dystonia and no cranial dystonia or speech involvement was diagnosed with DYT1 dystonia, was not surprising. However, in this man of Amish-Mennonite background, the DYT1 mutation was not a founder, rather, it was determined to be a de novo mutation, as a small proportion of DYT1 mutations are. Thus, DYT1 dystonia should be considered in individuals of Mennonite and Amish-Mennonite background, but this consideration should be driven by the clinical picture.

Non-DYT6, Non-DYT1 Primary Dystonia

Two Amish-Mennonite families with dystonia have also been described who have neither DYT6 nor DYT1 mutations. These families have prominent cervical dystonia, and older average age of onset than DYT6. Characteristic features of cranial dystonia and early onset were lacking, suggesting that the phenotype was different from both DYT6 and DYT1. The type of dystonia seen in these families is more suggestive of focal cervical dystonia, one of the most common forms of dystonia. The hope is that these families may also lend insight into other genetic etiologies of this type of primary dystonia.

Secondary Dystonia

Dystonia may also be accompanied by other neurologic symptoms and signs, and this falls into the rubric of secondary dystonias. All of these disorders are autosomal recessive. These include (but are not limited to):

- Pantothenate kinase-associated neurodegeneration (PKAN), which has two founder mutations in the Amish. MRI is notable for iron accumulation leading to the 'eye of the tiger' sign. Clinical features also include optic atrophy, pigmentary retinopathy, spasticity, and progressive dementia.
- Ataxia-telangiectasia, which is observed in both the Amish-Mennonites and the Dutch-Russian Mennonites, and is a disorder of DNA repair associated with low or missing ataxia-telangiectasia mutated protein. It is usually associated with early childhood onset ataxia, chorea, oculomotor apraxia, neuropathy, and conjuctival telangiectasias although in cases of variant ataxia-telangiectasia, ataxia, oculomotor abnormalities or telangiectasias may be mild or absent.
- Glutaric acidemia type 1 is a disorder due to deficiency of glutaryl-coA-hydrogenase. It is of increased frequency in the Amish. It often presents with acute encephalopathy with subsequent dystonia and chorea, but may present as macrocephaly and subdural hematomas.
- Homocystinuria, due to an Amish founder mutation in methyltetrahydrofolate reductase is associated with growth deficiency, microcephaly, developmental delay, mental retardation, spasticity, weakness, and seizures.

Hence, while DYT6 dystonia is often known as Amish-Mennonite dystonia, the differential for dystonia in the Amish-Mennonites and Mennonites is broad, and should be guided by the history, examination, and clinical features.

See also: Ataxia-Telangiectasia; Basal Ganglia; Dystonia; Dystonia in Amish-Mennonite and Mennonite Families; Dystonia, Secondary; Dystonia: Animal Models; DYT1; DYT2, Autosomal Recessive Generalized Dystonia; DYT4, Autosomal Dominant Type Dystonia or Whispering Dysphonia; DYT5; DYT11, DYT15, Myoclonus-dystonia; DYT12, Rapid Onset Dystonia-parkinsonism; Fahn–Marsden Rating Scale; Generalized Primary Torsion Dystonia; Hallervorden–Spatz Syndrome (PKAN); Wilson's Disease.

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Dystonia, Drug-induced (Acute)

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Glossary

Acute dystonic reaction – Often affects the face and neck musculature, with a sense of pain, discomfort, or tightness. Almost all occur within 5 days of medication change, usually a D2 dopamine receptor blocking agent. Younger persons are more susceptible. Treatment with anticholinergic and antihistamine medication causes prompt resolution.
Drug-induced movement disorders – Includes parkinsonism, dystonia, tardive dyskinesias, and akathisia. Most though not all are due to dopamine-blocking medication. Some appear early (acute), while others delay (tardive). Treatment and prognosis are variable depending on the condition. More than one drug-induced movement disorder may be present at a time.
Dystonia – Involuntary twisting and turning movements caused by coactivation of agonist and antagonist muscles. The position may be fixed, affected by movements, and associated with jerky

irregular tremor. Dystonia is due to dysfunction of the basal ganglia. There are many different causes of dystonia.
Neuroleptic – Literally, 'that which grips the nerve.' These medications block the dopamine receptors, and are effective in treating psychosis (and are often called 'antipsychotics'). Neuroleptic medications blocking the D2 dopamine receptors may cause drug-induced movement disorders, including acute dystonic reactions.

Definition and History

An acute dystonic reaction consists of cocontraction of agonist and antagonist muscles temporally related to either introduction of a new medication or increase in dosage. Acute dystonic reactions linked to neuroleptics were first noted in the late 1950s. About half of acute dystonic reactions occur within the first 48 h and nearly 90% within 5 days of medication change. The presentation is often marked, though milder cases may not present for a few days. The most common medications associated with acute dystonic reactions are neuroleptics with D2 dopamine receptor blocking properties.

Pathogenesis and Pathophysiology

There are two competing theories for acute dystonic reactions. According to the 'mismatch' hypothesis, increased dopaminergic input occurs acutely after treatment with dopamine D2 receptor blocking agents. D2 autoreceptor stimulation inhibits neurotransmitter synthesis and release. Blockade of the D2 receptors would be expected to produce increased striatal dopamine release in the short term. Acute dystonic reactions tend to occur when plasma levels fall after a single antipsychotic dose which supports this theory. Also, acute dystonic reactions are rare in the elderly. Striatal dopamine D2 receptor density decreases with age, 'protecting' the elderly from transient hyperdopaminergic states.

The more generally accepted theory is that acute dystonic reactions result from a hypodopaminergic state induced by dopamine D2 receptor blockade. Potent D2 receptor blockers are more likely to cause this than weaker blocking agents; presynaptic dopamine depleters can produce acute dystonia, and dopamine agonists may exert an antidystonic effect.

Interestingly, one study reported diurnal variation in acute dystonia with more than 80% occurring between noon and 11 p.m. This variation could not be accounted for sleep, fatigue, or time since last dose.

Rarely, nondopaminergic medications, particularly the selective serotonin reuptake inhibitors (SSRIs), have been linked to acute dystonic reactions. While the antihistamine diphenhydramine (Benadryl) provides prompt relief (see section Management), an acute dystonic reaction has been reported in a child with the antihistamine cetirizine, a medication approved by the Food and Drug Administration for treating allergic disorders in children younger than 5 years of age.

The author suggests reading the chapter by Mazurek and Rosebush (see Further Reading) for further details.

Epidemiology and Risk Factors

The incidence of acute dystonic reactions among patients taking antipsychotics varies widely. Earlier studies tended to quote lower risks. Using pooled data from nine studies of patients not on prophylactic anticholinergics, almost 15% developed dystonia regardless of the antipsychotic agent used compared to over 50% of patients receiving high-potency antipsychotics. The risk of an acute dystonic reaction in patients treated with conventional neuroleptics for first-onset psychosis is reported to be between 34 and 60%. A reasonable overall estimate based on the available information is 20–40%.

No particular psychiatric illness predisposes one to develop an acute dystonic reaction.

Acute dystonic reactions are most common in children and young adults, with the frequency declining with age. While it has been generally reported that males are more prone to developing acute dystonia, this is not the universal opinion. Young males tend to be treated more often with antipsychotic agents than young females, which may account for this perceived bias. In prospective follow-up of their own patients, Mazurek and Rosebush report rates of $<10\%$ in males and $<20\%$ in females above the age of 40 years.

Medications that are potent D2 receptor blockers (such as haloperidol) are more prone to producing an acute dystonic reaction. Lower potency D2 receptor blocking agents are less prone, perhaps because some have prominent anticholinergic activity as well. High dose and parenteral administration also increase the risk.

The incidence of drug-induced acute dystonia requiring treatment was similar in a prospective study of neuroleptic-naïve patients comparing oral haloperidol (34%) with oral risperidone (26%) (a high potency second generation 'atypical' antipsychotic).

Risk factors reported for developing an acute dystonic reaction include male gender, potency of D2 blockade, young age, high dose, and parenteral administration.

Cocaine use increases the risk of an acute dystonic reaction more than fourfold. Cocaine may trigger an

acute dystonic reaction in the absence of dopaminergic blocking agents.

HIV infection more than doubles the risk of developing an acute dystonic reaction, likely because the basal ganglia tend to be vulnerable to HIV infection.

Clinical Features and Diagnostic Criteria

Acute dystonic reactions most commonly affect the neck, followed by the cranial musculature including the jaw, throat, and tongue (including actual tongue swelling). Movements at the neck are typically rotational (torticollis) or extensional (retrocollis), though flexion (anterocollis) is also seen. Sensation of pain, tightness, or pulling almost always accompanies acute dystonia. Cranial dystonia includes eye blinking or closure (blepharospasm), facial grimacing, jaw clenching (trismus), and jaw opening. Acute dystonic reactions may involve the limbs and occasionally the trunk. Backward arching of the trunk (opisthotonus) may be mistaken for a psychogenic movement disorder. Some report that lower limb involvement is uncommon (though it is more common in younger persons). Upper limb involvement includes wrist flexion with extension of the index finger and flexion of the other fingers.

Laryngeal dystonia is an uncommon but potentially fatal presentation as it may progress to laryngospasm.

Oculogyric crisis occurs in ~10% cases, often with retrocollis and/or torticollis accompanying the tonic upward (and often lateral) deviation of the eyes. Patients may have difficulty speaking and, in rare cases, dystonia of the vocal cords causes respiratory distress. Oculogyric crisis was first noted in cases of acute encephalitis lethargica seen in the early twentieth century. There may be associated feelings of depression, fear, or anxiety which improve with treatment.

Dystonic movements and posturing may last up to 30 min, waxing and waning, before gradually resolving. Younger patients are more prone to have generalized dystonic reactions, while in older patients, the dystonia is usually restricted to the cervical musculature.

Differential Diagnosis

Conditions that could be mistaken for acute dystonia include tonic seizures or painful tonic spasms of Multiple sclerosis (MS). Tonic seizures are usually brief, lasting for a few seconds to a minute or two, and are associated with altered consciousness and EEG changes. Painful tonic spasms of MS most often affect the lower limbs. Paroxysmal nonkinesiogenic chorea may have dystonic features; the kinesiogenic form is brief and should not cause sustained postures. Hypocalcemia or hypomagnesemia may produce carpopedal spasm. Acute laryngospasm in a case of neuroleptic-induced laryngeal dystonia has been mistaken for an anaphylactic reaction.

Dystonia is commonly diagnosed as a psychogenic movement disorder by persons who have not seen dystonia. This is particularly a concern in a population at risk who already have a psychiatric diagnosis requiring neuroleptic treatment.

The role of medications may go unnoticed by those unfamiliar with acute dystonic reactions. The most serious problem is laryngospasm. Acute drug-induced dystonia should be considered in those with dyspnea and stridorous voice with normal pulmonary exam and investigations; this is the key for primary care and emergency room physicians.

With the appropriate history of drug exposure, no particular investigations are needed. Often general labs including calcium and a toxicology screen (specifically cocaine) are tested in young adults.

Management

Mild acute dystonic reactions may improve after simply withholding medications.

Prompt treatment with the anticholinergic benztropine (Cogentin) 1–2 mg i.m. or i.v. and the antihistamine diphenhydramine (Benadryl) 25–50 mg results in resolution within 20 min. Sometimes diazepam (Valium) 5–10 mg i.m. or i.v. or lorazepam (Ativan) 1–2 mg i.m. or i.v. is used for similar effect. Usually benztropine 1–2 mg bid (oral) for up to 7 days is prescribed to prevent recurrence.

While prophylactic oral anticholinergics (such as benztropine, biperiden, and trihexyphenidyl) reduce the risk of an acute dystonic reaction, the routine use of these agents is controversial. An elderly person at low risk of an acute dystonic reaction and at definite risk of adverse effects from anticholinergics (confusion, constipation, urinary retention, blurred vision) should likely not be treated, while a young male patient treated with a high potency D2 receptor blocking agent may warrant prophylactic anticholinergics at least initially. For patients isolated because of agitation, anticholinergic prophylaxis is recommended to reduce the risk of potentially fatal laryngospasm.

It is essential that the causal medication be documented so that the patient is not rechallenged in the future. Physicians should also be aware that an acute dystonic reaction may occur with similar medications.

Prognosis

A full and prompt recovery is expected with treatment. An acute dystonic reaction increases the risk of recurrence. In one prospective study of patients who had an acute

dystonic reaction, 51/89 (57%) had at least one more reaction while in the hospital. Recurrent episodes tended to be more widespread.

See also: Dystonia; Dystonia, Drug-induced (Acute); Neuroleptic-induced Nonhuman Primate Models of EPS and TD; Neuroleptics and Movement Disorders; Tardive Dystonia.

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Dystonia, Secondary

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Glossary

Athetosis – Writhing limb movements, sometimes accompanied by rapid, flicking movements (chorea). A common setting for choreoathetosis is kernicterus or other causes of birth injury. Since many of the children with athetosis in this setting go on to develop dystonia, it has been suggested that athetosis is a form of mobile dystonia.

Deep brain stimulation – A surgical procedure wherein a high-frequency current is delivered to a small area of the brain using an implanted electrode. The full effects of this stimulation on the brain are not completely understood.

Dystonia – A symptom consisting of sustained involuntary muscle contractions usually resulting in abnormal postures, sometimes accompanied by tremor or jerking.

Parkinsonism – A syndrome with many or all of the signs and symptoms of Parkinson's disease (PD), but the underlying pathophysiology is presumed to differ from the typical degeneration of the substantia nigra seen in PD. Sometimes called Parkinson-plus syndromes, these diseases almost always have pathological abnormalities not seen in PD and usually involve cell loss in the substantia nigra, although usually without the Lewy bodies characteristic of PD.

Psychogenic – A controversial term applied to symptoms that are believed to be an unconscious adaptation to psychological stress. This usually implies the absence of detectable physical or biochemical dysfunction in the brain; recently, however, evidence has emerged that such symptoms may be accompanied by measurable metabolic changes in the brain.

Tardive – Signifies delayed. When applied to movement disorders caused by centrally acting drugs that block the dopamine D2 receptor, this initially is referred to the appearance of involuntary movements only after prolonged exposure to the blocking agent. Most neurologists now use the word to signify persistence of the involuntary movements even if the blocking agent is discontinued.

Secondary Dystonia

In the past, secondary dystonia referred to the symptom dystonia in the setting of another identified neurological disease, and primary dystonia referred to a condition of unknown cause in which dystonia was the only symptom. This distinction is breaking down. We now know that most cases of primary dystonia in childhood and some adult cases are genetic in origin. There are currently blood tests for a few of these genetic diseases, and we hope someday to have tests for all of them. There are several conditions in which dystonia is combined with a single other neurological symptom: parkinsonism (dopa-responsive dystonia, rapid

onset dystonia-parkinsonism) or myoclonus (myoclonus-dystonia syndrome), and some have proposed a third category of 'dystonia plus' for these diseases. However, these distinctions seem increasingly arbitrary. (For example, some cases of primary dystonia also have a superimposed tremor, which might reasonably put them in the category of dystonia-plus.) Although most patients with dystonia have the symptom during the entire waking day, there are rare patients in whom the dystonia is present in discrete episodes generally called paroxysmal dystonia.

There are many causes of secondary dystonia. I have divided the causes into degenerative diseases, with dead or dying brain cells, and nondegenerative diseases. The nondegenerative diseases include tardive dystonia and acute dystonic reactions (caused by exposure to the centrally acting dopamine receptor blocking medications), psychogenic dystonia, dystonic tics, dystonia triggered by peripheral injury, and others.

There are a large and growing number of known causes for degenerative dystonia, most of them are rare. These can be divided into nongenetic and genetic causes. The nongenetic causes include dystonia after birth injury (static encephalopathy), delayed onset dystonia after birth injury, head trauma, cerebrovascular disease, CNS tumors in the basal ganglia, demyelinating diseases (multiple sclerosis, central pontine myelinolysis, etc.), Parkinson's disease (PD), and nongenetic Parkinson's plus syndromes, multiple toxins, and infections. Patients with these conditions may have stable dystonia after a brain insult, but sometimes, as in the case of dystonia after birth injury, the onset of dystonia may be delayed after the insult, and the dystonia may progress long after the injury is over.

There are many inherited degenerative diseases, which can cause dystonia. Almost all of these are rare, and they are usually associated with other neurological signs and symptoms in addition to dystonia. Autosomal dominant diseases include dominant forms of juvenile parkinsonism, Huntington's disease (HD), some of the dominant spinocerebellar atrophies, neuroferritinopathy, and others. Autosomal recessive diseases include Wilson's disease, neurodegeneration with brain iron accumulation (NBIA) (including Hallervorden–Spatz Disease, or PKAN), Niemann pick type C, glutaric aciduria (GA), ceroid lipofuscinosis, and many others. There are other genetic inheritance patterns that have been identified for diseases causing dystonia: X-linked recessive (Lubag, a dystonia/parkinsonism syndrome found almost exclusively on the island of Panay in the Philippines, and deafness-dystonia syndrome, a mitochondrial disease) and maternal inheritance (mitochondrial cytopathies such as Leigh's syndrome, mitochondrial encephalopathy with ragged red fibers or MERRF, Leber's optic neuropathy, and others).

Why make the distinction between primary and secondary dystonia? First, in order to determine what diagnostic tests to perform. There are far too many rare causes of dystonia to test for all possible diseases in every patient. With the possible exception of MRI of the brain, the distinction between primary and secondary dystonia is initially clinical. Second, the most important therapeutic decision is whether to treat the symptom dystonia or whether there is also an underlying disease that requires treatment.

What are some of the clinical features distinguishing primary and secondary dystonias? If there are family members affected with primary dystonia, it is more likely (but not certain) that the patient has primary dystonia. In many primary dystonias, the involuntary movement appears only during action, sometimes with a specific action (task specific dystonia) such as writing, talking, playing a musical instrument, typing, or certain types of sports maneuvers (e.g., a golf swing). The presence of sensory tricks usually indicates a primary dystonia. Sensory tricks are movements that a patient can make to relieve symptoms of his/her dystonia. They are often effective when the disease is mild and sometimes lost as it becomes more severe. However, tardive dystonia and dystonia related to birth injury are two secondary dystonias in which onset with action and sensory tricks are common.

Similarly, there are some features which are characteristic of the secondary dystonia. As noted above, other neurological abnormalities are the rule in most of the degenerative dystonia syndromes, including parkinsonism, dementia, ataxia, corticospinal tract dysfunction, neuropathy, myoclonus, abnormal extraocular movements, or an abnormal fundus. Hemidystonia often, but not always, indicates a basal ganglia lesion in the contralateral hemisphere. Fixed dystonia at or shortly after onset of the disease is highly suggestive of secondary dystonia. Early speech disturbance, excluding laryngeal dystonia, also suggests a secondary dystonia. Give-way weakness, change in dystonia with suggestion, and other incongruous findings may indicate a psychogenic cause for dystonia. In addition, primary dystonia from most causes involves parts of the body at characteristic times, so that dystonia of the legs starting in adult life is rarely due to primary dystonia.

The most common setting for dystonia in our center and most large movement disorders centers is PD or 'Parkinson plus' syndromes. The most common non-Parkinson-related secondary dystonias at our center are tardive dystonia, 19% of our secondary population; dystonia after hypoxic/ischemic injury, 12%; and psychogenic dystonia in 6%. This article briefly discusses the most common causes for dystonia and some of the less common but significant or interesting causes of dystonia.

Parkinsonism

Dystonia can be present before treatment in idiopathic PD, especially in young onset patients and in most

parkinson syndromes (especially cortical-basal ganglionic degeneration). The dystonia may be painful or painless, and it may only be present with action initially. In young patients with PD, hemidystonia (dystonia limited to one side of the body) may be more prominent at the onset than rigidity and bradykinesia, and such patients sometimes undergo testing for the causes of dystonia until the underlying parkinsonism becomes apparent. In very young patients, the symptoms and response to treatment of juvenile parkinsonism and dopa-responsive dystonia may be identical at the onset, leaving some doubt as to the correct diagnosis. Fluorodopa PET is normal in dopa-responsive dystonia and shows reduced signal in juvenile parkinsonism. The treatment of dystonia in the setting of PD is complex. In PD, levodopa may help the dystonia, worsen the dystonia, or have no effect. In the young, other medications for dystonia such as anticholinergics and baclofen, may help. Deep brain stimulation (DBS) (usually of the globus pallidus) sometimes helps dystonia in PD. Patients with Parkinson plus syndromes and dystonia usually have fixed dystonia that does not respond to medication. Botulinum toxin (BTX) injections usually do not improve function in that setting, but may relieve pain from muscle spasm. Rarely, focal dystonia such as blepharospasm or spasmodic dysphonia may precede Parkinson symptoms in a young patient. This may be coincidence, but it is hard to be sure.

Treatment, especially treatment with levodopa, may produce dystonia in patients with parkinsonism of all ages. Two patterns have been identified: peak dose dystonia which occurs when the blood (and presumably brain) levels are at a peak, and dystonia which occurs shortly after taking medication and as the medication effects wear off (dyskinesia-improved-dyskinesia or DID pattern). The DID dystonia is often painful. Any strategy which reduces fluctuations in the levodopa levels may help these forms of drug induced dystonia. Finally, dystonia may occur during the time when the medicine is not working ('off' state). A typical example is the painful toe cramping in the early morning in patients who have not taken medicine since the previous evening. Reducing off periods helps this type of dystonia.

Pallidal, and possibly subthalamic nucleus, DBS can help all these forms of dystonia. The use of BTX is usually limited when widespread muscles are involved. In patients with blepharospasm, torticollis, or pain from localized muscle spasm, the injections can be helpful.

Acute Dystonic Reaction

Acute dystonic reactions happen almost exclusively shortly after exposure to the centrally acting dopamine receptor blocking agents and usually resolve within hours to days of stopping the agents. The risk of developing this reaction seems to be higher in more potent blockers of the dopamine D2 receptor and decreases with increasing age of the patient. These reactions usually improve with anticholinergics or antihistamines.

Tardive Dystonia

Tardive syndromes are persistent movement disorders starting during or after exposure to centrally acting dopamine receptor blocking agents. The tardive syndromes include tardive dyskinesias, tardive dystonia, and tardive akathisia, although most patients have combinations of these symptoms. Less common syndromes include tics, myoclonus, tardive oculogyria, and possibly tremor and other movement types. Tardive dyskinesias are more common in older patients, whereas tardive dystonia is more common in younger patients. The prevalence of tardive dystonia has been estimated at 1.5–2% in most studies, although one VA study of young patients found a prevalence of 21%. There have been many estimates of the prevalence of idiopathic dystonia, with the largest being ~0.03%. Therefore, dystonia is ~50 times more common in the neuroleptic treated population than in the population at large. As with other tardive syndromes, there are occasionally spontaneous remissions in tardive dystonia when the dopamine receptor blocker is stopped. In the series from Columbia, which is a referral based series, we estimated the remission rate at 12% after 5 years. This is in contrast to an estimated remission of over 30% in patients with pure tardive dyskinesias.

The distribution of symptoms is somewhat different in tardive dystonia than idiopathic dystonia. Jaw, trunk, and legs are more likely to be effected in adults with tardive dystonia than primary dystonia. Blepharospasm (eyelid dystonia) is more common in young adults with tardive dystonia than in young adults with primary dystonia. Although tardive dystonia can be indistinguishable from primary dystonia, many patients with tardive dystonia have very rapid dystonic jerks, often with truncal or neck extension and intorsion of both arms, occasionally resulting in flailing movements when proximal muscles are involved. Unlike most patients with primary dystonia, the movements sometimes improve with walking and worsen with lying down. The only diagnostic test at present for tardive dystonia is the presence of other tardive movements and the history of exposure to dopamine receptor blocking agents. Patients will sometimes forget exposure to such drugs, and obtaining pharmacy records and hospital records is sometimes helpful. It is also important to remember that several antinausea agents (such as metoclopramide and prochlorperazine) are dopamine receptor blockers. Similarly, the tricyclic agent amoxapine is also a dopamine receptor blocker and has been associated with the development of tardive dystonia. Some cigarette smoking cessation programs include dopamine receptor blockers, and patients in hospitals may receive dopamine receptor blockers without their knowledge for behavior control.

The treatment for tardive dystonia and tardive syndromes in general are complex. Briefly, any drug that produces Parkinsonism as a side effect may help tardive dystonia. Treatment with most dopamine receptor blockers may suppress symptoms but worsen the underlying disease. Dopamine depleters such as reserpine and tetrabenazine often help the symptoms but have substantial side effects and are often not tolerated in optimal doses. Anticholinergics are sometimes effective. BTX is effective for focal symptoms as with all other causes of dystonia. Pallidotomy and now pallidal DBS seem to be effective for tardive dystonia, especially for retrocollis and truncal hyperextension.

Postischemic Dystonia

Dystonia after birth injury occurs in two settings. Children with early evidence of motor and intellection developmental delay may have early chorea or athetosis (writhing postures) which convert to dystonia later. In addition, there is a syndrome in which children survive birth injury without stigma but develop pure dystonia later in childhood. This dystonia may worsen for decades. The MRI in these cases is often normal or shows only generalized atrophy. The phenomenology of dystonia after ischemic stroke or hemorrhage in adult life divides into two groups: fixed postures (sometimes with pain) and posturing with superimposed tremor or writhing movements. The kinetic form of dystonia after ischemic injury usually involves lesions of the thalamus. The pain may be a combination of central (thalamic) pain and peripheral pain from muscle spasm. Surprisingly, dystonia arising after ischemic injury early in life may improve with the same medicines that treat primary dystonia, but postischemic dystonia arising in adult life is very difficult to treat. Pain arising from muscle spasm responds to BTX injections. The efficacy of pallidal DBS in postischemic, adult onset dystonia is not clear.

Psychogenic Dystonia

Psychogenic movements arise from a psychological disorder rather than from identified brain dysfunction. Recently, PET studies indicate that there are physiological changes in the brain corresponding to psychogenic movements. It is possible that in the future, we will consider psychogenic disorder as a biochemical disorder of the brain similar to depression, bipolar disorder, obsessive–compulsive disorder, and schizophrenia. For now, it is important to diagnose psychogenic dystonia and distinguish it from dystonia that is produced voluntarily (malingering). Many physicians are reluctant to make a diagnosis of psychogenic dystonia because of the stigma associated with the psychiatric disease ('give the patient the benefit of the doubt'). I believe, it is no worse to mistakenly diagnose psychogenic dystonia than it is to mistakenly diagnose organic dystonia. Both deprive patients of appropriate counseling and therapy. Psychogenic dystonia is a serious disease that destroys quality of life and can end in death by suicide. It is at least as treatable as most other forms of secondary dystonia. Management of psychogenic dystonia involves cooperation of several disciplines: the neurologist has primary responsibility for making the diagnosis; the psychiatrist and possibly the physical therapist have primary responsibility for making specific psychiatric diagnoses and treatment. Unusual features suggesting psychogenic dystonia include shuddering, unusual tremors or speech, elaborated startle, complex head shaking, deliberate slowness of gait, rapid and unpredictable change of direction, and unpredictable change in direction of dystonic tremor. Nonphysiologic features include give-way weakness, complex ataxia without falling, nonphysiologic numbness or anesthesia, and change in movements with suggestion or placebo. Inconsistent features include fluctuating weakness, disappearance with distraction, and fluctuating pressure (the more you resist the dystonia, the more forceful the contractions). Inconsistent course includes abrupt onset and disappearance for brief periods of time. When considering this diagnosis, be humble, but do not be timid.

There is no formula for the successful treatment of psychogenic dystonia. Some reasonable principles include: (1) destigmatize the diagnosis: we tell the patients that stress causes biochemical changes in the brain that can produce many symptoms such as ulcers and involuntary movements, (2) it is helpful to engage patients as partners in the effort to improve: set achievable daily goals, (3) we have relied primarily on individual psychotherapy with family therapy when needed, and (4) we do not use medications for dystonia, but do use antidepressants, antianxiety medications, hypnosis, and ECT when appropriate. It is essential to convince the patient that you believe they have a serious problem.

Wilson's Disease

Wilson's disease is rare: the prevalence is estimated at ~1 in 30 000, compared to the estimated prevalence of primary dystonia of 0.03% or 9 in 30 000. However, Wilson's disease is a treatable disease, especially when diagnosed early, and it is one of the few causes of secondary dystonia in which dystonia may seem to be the only symptom. In fact, personality change and psychiatric symptoms (sometimes subtle) usually precede motor symptoms. In addition, cranial parkinsonism is often present, with open mouth, drooling, and impaired postural reflexes, even when dystonia or tremor dominate. The presentation of Wilson's disease generally depends on age: hemolytic anemia and renal disease in infants, dystonia in children, and tremor in young adults, although a wide variety of

movement disorders have been seen in Wilson's disease, making the diagnosis difficult. The gene for Wilson's disease has been identified as a copper-transporting ATPase, but the large number of mutations makes genetic screening difficult. When the possibility of Wilson's disease is considered, screening for low serum ceruloplasmin will detect ~95% of cases, detection of Kaiser–Fleischer rings in the cornea will detect almost all cases with neurological symptoms, but liver biopsy with copper staining is the test of last resort. Copper chelation and liver transplant when necessary are the treatments for Wilson's disease. Treatment is complicated because many patients will worsen (sometimes permanently) at the onset of treatment. A new agent, tetrathiomolybdate may have less initial worsening than other agents, but this is currently under study. Treatment of dystonia is necessary only in severe cases, since treatment of the disease will ameliorate symptoms in mild to moderate cases. Successful treatment of dystonia with medications and pallidal DBS has been reported in a small number of cases.

Mitochondrial Syndromes

Many mitochondrial syndromes can occasionally produce a syndrome dominated by dystonia, including MERRF, Leber's hereditary optic neuropathy, infantile bilateral striatal necrosis, deafness-dystonia syndrome, and Leigh's syndrome. As with all mitochondrial cytopathies, these can arise from mutations in the mitochondrial genes (e.g., *MERRF*, Leber's disease), nuclear genes (deafness dystonia syndrome), or both (e.g., Leigh's syndrome). Perhaps the most common dystonic mitochondrial syndrome is Leigh's syndrome (oxidative phosphorylation defects), caused by mutations in both mitochondrial genes (pyruvate dehydrogenase complex, cytochrome oxidase) and nuclear genes (for elements of the respiratory chain complex). Leigh's syndrome can also result from CoQ10 deficiency. The syndrome is defined by the pathology, which includes necrosis, vascular proliferation, and spongiosis (resembling Wernicke's disease) in the brainstem, striatum, thalamus, dentate, substantia nigra, white matter, and optic nerves bilaterally. The presentation depends on the age at onset. Dystonia is common in the early childhood presentation that may produce ataxia, motor and intellectual regression, axial hypotonia, dystonia and/or chorea, respiratory dysrhythmia, ocular palsies, optic atrophy, and peripheral neuropathy. The symptoms often worsen during concurrent illness. Leigh's syndrome can be suspected when there is a multisystem disorder, including combinations of the above neurological deficits and an MRI with increased T2 signal in the basal ganglia, brainstem, dentate nucleus, and white matter. Once Leigh's syndrome is suspected, diagnosis can be confirmed if there are defects of the cytochrome oxidase system in muscle biopsy or any of the known mutations. Many attempts at treating these conditions have produced little success. CoQ10, idebenone, thiamine, riboflavin, biotin, vit E, succinate, creatine, and carnitine have produced minimal, if any, benefit. Efforts are underway to discover effective treatments, including introduction of wild-type genes and selective inhibition of mutant genes. There is little data on the symptomatic treatment of dystonia in mitochondrial cytopathy. The few patients we have treated have not done well. BTX should reduce painful muscle spasm. The effectiveness of pallidal DBS in mitochondrial disease is not known.

Glutaric Aciduria Type 1 (GA1)

The mitochondrial enzyme glutaryl-CoA dehydrogenase is necessary for the metabolism of lysine/tryptophan and hydroxylysine. Absence of the enzyme (usually autosomal recessive) results in mitochondrial dysfunction and production of the toxins glutaric acid and 3-OH-glutaric acid. Thus, GA1 is a mitochondrial cytopathy plus. The disease usually starts in the first year of life, occasionally later, as an acute encephalopathy with dystonia or chorea triggered by intercurrent illness. The pathological basis is striatal necrosis. Most children have only one or two such episodes, although there probably is some gradual worsening in the absence of crises. Occasionally, there is gradual progression without crises. Dystonia is often the overwhelming symptom: spasms of retrocollis and truncal arching can be extreme but alternate with periods of extreme axial hypotonia. Other signs include spasticity, chorea, hypoglycemia, acidosis, seizures, and ataxia, but intelligence is often relatively preserved. About 75% of infants with GA1 have macrocephaly from birth or infancy. Serum and urine GA are usually elevated, but there are low GA excretors. Glutaryl carnitine is always elevated in the urine. The MRI findings are suggestive of the diagnosis: bilateral increased T2 signal in putamen > caudate < globus pallidus, bilateral increased T2 signal in anterior and posterior white matter, generalized atrophy especially pretemporal ('bat wing' dilatation of the Sylvian fissures), and sometimes increased signal in corpus callosum, dentate, medial lemniscus, substantia nigra bilaterally. Dietary lysine restriction (reduced production of GA) and carnitine supplementation (detoxifies some of the toxic metabolites) may prevent neurologic disease in asymptomatic patients, but it is not clear if this helps symptomatic patients. The dystonia may be helped by anticholinergics, baclofen, and possibly pallidal DBS.

Neurodegeneration with Brain Iron Accumulation

There are several forms of NBIA. Probably the most common is autosomal recessive disease associated with mutations in the *PANK2* gene for pantothenate kinase

necessary for regulation of the Co-A synthesis, formerly known as Hallervorden–Spatz disease. Most patients with mutations in this gene have decreased signal in the globus pallidus surrounding a small area of increased signal, or 'eye of the tiger.' Others have decreased signal without the 'eye.' At this time, there appears to be a spectrum of presentations of this form of NBIA depending on the age at onset. Patients with symptoms in the first decade of life have severe dystonia, loss of ambulation, mental retardation, often optic atrophy, or retinitis pigmentosa. Children presenting later have less severe dystonia with preserved gait and intelligence, parkinsonism, tics, behavior disorders, and only occasional optic atrophy. The dystonia in NBIA may respond to medical therapy with anticholinergics, baclofen, BTX injections, and pallidal DBS, but the proportion of patients responding to treatment is not known. Less is known at this time about the treatment of the Parkinson features.

X-linked Dystonia-Parkinsonism (Lubag Disease)

Lubag disease is an X-linked recessive condition found almost exclusively in men from the island of Panay, Phillipines. There is occasionally a milder form in women who carry a single mutation. Young onset patients start with dystonia but usually develop parkinsonism later in life. Old onset patients may have exclusively parkinsonism. The dystonia of Lubag may improve with anticholinergics, clonazepam, zolpidem, or BTX injections. The parkinsonism seems particularly resistant to the treatment.

Huntington's Disease

Many adults with HD will develop some dystonic posturing as the disease progresses. Often this does not require treatment, although some patients have symptomatic blepharospasm. Juvenile HD results from a large repeat length, especially over 60 CAG repeats and is usually inherited from the father. Patients with juvenile HD may have significant generalized dystonia, and dystonia may dominate the picture. There is little data about the treatment of the dystonia.

Paroxysmal Dystonia

Paroxysmal dystonia is used to describe the syndromes in which dystonia (and sometimes other involuntary movements such as chorea) occurs in discrete episodes, while movement symptoms are absent at other times. These disorders have been categorized either by duration of the attacks or by precipitating factors. The two most common are paroxysmal kinesigenic dyskinesia (PKD – usually triggered by sudden movement and lasting at most several minutes) and paroxysmal nonkinesigenic dyskinesia (PNKD – not triggered by movement and lasting from many minutes to many hours). Both of these syndromes can be inherited, but both also have secondary forms. PKD has been reported after a large number of insults, most commonly multiple sclerosis and ischemic/traumatic brain injury. Similarly, PNKD also occurs in multiple sclerosis, after birth injury and many other causes. Psychogenic PNKD is very common. The dystonia of PKD may be unilateral, bilateral, or alternate sides. All the involuntary movements in idiopathic PKD (and many cases of secondary PKD) improve markedly with anticonvulsants. The dystonia of PNKD is usually accompanied by other movement types and is very difficult to treat. Some of the genetic forms respond to benzodiazepines, but there has been no consistent medication response in the various forms of secondary PNKD.

See also: Botulinum Toxin; Camptocormia; Cock-walk; Complex Regional Pain Syndrome; Dystonia; Dystonia, Traumatic; DYT3, X-linked Dystonia-parkinsonism (Lubag); DYT10, Paroxysmal Kinesiogenic Dyskinesia-PKD; DYT11, DYT15, Myoclonus-dystonia; DYT12, Rapid Onset Dystonia-parkinsonism; Factitious Disorders; Gaucher's Disease; GM1 Type 3 Gangliosidosis; GM2 Gangliosidosis; Hallervorden–Spatz Syndrome (PKAN); Kernicterus; Leigh Syndrome; Manganese; Mitochondrial Encephalopathies; Myoclonus-Dystonia/Essential Myoclonus; Neuroferritinopathy; Neuronal Ceroid Lipofuscinosis; Niemann–Pick Type C; Parkinson's Disease: Definition, Diagnosis, and Management; Spinocerebellar Ataxias Genetics; Tardive Dystonia; Tardive Syndromes; Wilson's Disease.

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Dystonia, Task-specific

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Glossary

Dystonia – Hyperkinetic movement disorder characterized by repetitive, involuntary, twisting movements typically producing sustained postures.
Embouchure dystonia – A dystonia that affects the muscles of the face, tongue, or jaw used to control the speed and force of air flow into the mouthpiece of a woodwind or brass instrument.
Focal, task-specific dystonia – Hyperkinetic movement disorder characterized by repetitive, involuntary, twisting movements typically producing sustained postures triggered by a specific task.
Focal, task-specific dystonia of musicians' hands – Dystonia triggered by playing a musical instrument with one's hands.
Writer's cramp – Dystonia triggered by the task of writing.

Definition and History

Dystonia is a hyperkinetic movement disorder characterized by repetitive, involuntary, twisting movements typically producing sustained postures. When the movement is triggered by a specific task, it is referred to as focal, task-specific dystonia (FTSD). This phenomenon was first described as early as 1830 when Charles Bell described cases of writer's cramp affecting the clerical staff of the British Civil Service. By the late 1800s, Gowers, among others, had described FTSD affecting the hands of musicians (FTSDmh). Historically, some referred to these movements as 'occupational neuroses,' and many thought there was a significant psychiatric etiology.

Pathogenesis/Pathophysiology

The underlying pathophysiology of dystonia is incompletely understood. Dystonia is caused by the simultaneous contraction of agonist and antagonist muscles. Lack of reciprocal inhibition of antagonist muscles contributes to this cocontraction, with dysfunction either at cortical or spinal levels. When task-specific dystonia spreads to related skills, there is a decrease in 'surround inhibition' as a result of faulty cortical inhibitory connections. In addition to motor dysfunction, there are abnormalities of sensory perception and representation. While primary sensory modalities are normal in these patients, there are disturbances in stereognosis. Interestingly, abnormalities in sensory discrimination have been demonstrated bilaterally in patients with lateralized focal dystonia. Furthermore, in animal studies, repetitive stereotyped movements have been associated with disorganization of the sensory cortex and an increase in size of cortical sensory receptive fields. Studies have also demonstrated an increase in neuronal plasticity resulting in excessive corticospinal excitability and decreased cortical inhibition. Structurally, imaging techniques have demonstrated abnormalities in subcortical and cortical structures. Studies have demonstrated an increase in putaminal volume by 10% as well as an increase in size of the primary sensory cortex.

Epidemiology/Risk Factors

FTSD is a diagnosis of young adults, affecting both sexes. Writer's cramp commonly presents in the third to fifth decades and earlier reports described a male predominance. With changes in the workforce over the years, writer's cramp no longer has a predilection for males. The epidemiology of writer's cramp was studied in Rochester, Minnesota between 1950 and 1982 and found to have a prevalence rate of 69 per million people. An underlying cause is rarely found; only about 5–10% of patients identify local trauma as a possible precipitant. Despite earlier claims that writer's cramp was a psychogenic illness, formal studies have failed to reveal a higher incidence of psychopathology in patients with this disorder. Approximately 5% of patients identify family members with similar symptoms, and some studies have suggested autosomal dominant inheritance with incomplete penetrance.

FTSDmh occurs at a mean age of 35.7 years and has a significant male predominance (80%). Up to 1 out of 200 musicians may be affected during their musical career, and as many as 8–14% of patients evaluated at performing arts medical centers receive this diagnosis. The type of hand dystonia that develops in musicians is dependent on the technical demands specific to the instrument. Some patients report a recent increase in practice time, a focus on a particularly challenging musical piece, or a change in musical technique immediately before developing dystonia. However, similar to writer's cramp, FTSDmh

develops insidiously and has no clear precipitant. While most patients with FTSDmh deny a family history of dystonia, careful examination of relatives has demonstrated an increased incidence of dystonia. One recent study of FTSDmh described three families in which family members were afflicted with focal dystonia, mainly writer's cramp.

Embouchure dystonia is another FTSD with a male predominance. The embouchure is the pattern of muscles of the face, tongue, and jaw used to control the speed and force of air flow into the mouthpiece of a woodwind or brass instrument. Risk factors, such as preceding trauma and dental work, are uncommon. The presence of writer's cramp in several of these patients also suggests a genetic contribution. Like FTSDmh, environmental influences are significant in embouchure dystonia with phenotype depending on the instrument.

Clinical Features and Diagnostic Criteria

FTSD is seen with skilled, over-learned tasks. This phenomenon has been described with various tasks and occupations, including writing, playing sports (golf, darts), operating a machine (typing, computer mouse, telegraph), or playing a musical instrument. It usually develops gradually over weeks to months and rarely has a precipitating event. Patients often develop a sensory trick (geste antagoniste) that provides relief from the dystonic movement. This may involve applying pressure to a critical area or change in position or grip.

Writer's cramp has been divided into three distinct types: simple, progressive, and dystonic. In simple writer's cramp, dystonia is limited to the task of writing. Progressive writer's cramp involves the spread of dystonia to other hand activities, and dystonic writer's cramp patients experience impairment in writing and similar manual tasks from onset. Abnormal postures commonly involve the fingers, wrist, and elbow. Dystonia may begin with difficulty in picking up a pen and declares itself shortly after starting to write. Patients have an excessively tight grip that may cause the pen to slip out of the hand. A classic posture is an exaggerated flexion of the wrist, thumb, and fingers and hyperextension of the distal interphalangeal joint of the index finger. Ulnar deviation at the wrist and elevation of the elbow may also occur. Patients may describe their symptoms as an ache, as clumsiness, or as a lack of motor control. Rather than pain, patients may describe muscle tension. Paresthesias can develop over time, as dystonic postures lead to compression neuropathies. Patients commonly describe fatigue and worsening of dystonia with persistent writing, requiring them to take breaks. Sudden jerks of the hand are common, resulting in random pen strokes across the paper. Tremor occurs in one-third of patients and is usually unilateral. Patients acquire compensatory maneuvers such as holding the pen vertically between the index and middle fingers or with a closed fist. Some may need to stabilize their writing hand with the assistance of the unaffected limb. Interestingly, some patients may still be able to write on a chalkboard, using more proximal muscles. Others have found ease in writing with a pen that has a thicker point. Approximately one-third of patients will resort to learning to write with their opposite hand because of the deterioration in their penmanship. While writing with the contralateral hand, these patients may produce dystonic movements with the primarily affected hand. These movements have been referred to as 'mirror movements.' Unfortunately, about 25% of patients will develop dystonia of their contralateral hand, although it may take years to manifest.

Patients with FTSDmh describe a loss of flexibility and automaticity, which motivates them to increase rehearsal time. This strategy, however, only exacerbates the problem. The hand that performs the more complicated task is predisposed to developing dystonia. Thus, the right hand is affected among pianists and plucked string players, while the left hand is predominantly affected in bowed string players and flutists. Both hands are equally affected in woodwind, percussion, and brass players. Dystonia usually begins in one finger, usually the third finger, and eventually spreads to adjacent digits. The ulnar aspect of the hand is disproportionately affected, perhaps due to the greater technical demands placed on this part of the hand. Biomechanical constraints may increase the risk of injury when the wrist is ulnarly deviated. The dystonic phenotype that develops is dependent on the instrument. Flexion dystonia is common in pianists, violinists, and guitarists, and isolated extension of the third finger is common in woodwind players. Once the phenotype is established in a given patient, it rarely varies, even if the patient takes a hiatus from playing their instrument. This raises the possibility that an abnormal, dystonic sensorimotor network somehow becomes selected and entrained. Certain triggers may be identified such as ascending-versus-descending scales in a specific key. Again, pain is uncommon and should raise the suspicion of an alternative diagnosis.

Patients with embouchure dystonia begin experiencing symptoms decades after learning to play their instrument. These patients describe a loss of embouchure control, loss of clarity of articulation, and involuntary movements of the lips, jaw, or tongue. Once again, frank pain is uncommon; however, patients may complain of vague oral discomfort. Various phenotypes of embouchure dystonia have been described, including tremor, lip pulling, lip lock, jaw dystonia, tongue dystonia, and Meige. The tremor is fast, involves the upper and lower lids, and is audible and visible. Lip-pulling refers to lateral or forward movement of the upper or lower lips. Lip lock describes the clamping together of the lips, triggered as the patient begins to play and thus either delays or cuts off the sound.

Jaw dystonia refers to involuntary jaw closure or lateral movements of the mandible when playing. Tongue dystonia refers to incoordination of the tongue, particularly during passages requiring tongue activation. Meige is involuntary movement of the upper and lower face triggered by playing an instrument. The different dystonic movements usually begin and remain limited to a specific pitch range. Gradually, the symptoms may spread to neighboring pitches. A specific musical style such as sustained legato or staccato can also be a specific trigger for dystonia. Certain trends have been observed in musicians according to musical instrument. Tremor and lip pulling is more common in high-register brass instruments such as trumpet and French horn. Lip lock dystonia tends to occur in patients who play low-register brass instruments such as trombone and tuba. Jaw and tongue dystonia is more commonly seen in musicians playing woodwind instruments. About 5% of patients with embouchure dystonia have writer's cramp, which presents years prior. Embouchure dystonia spreads to other oral tasks in about 15% of cases. It is more common for jaw, tongue, and Meige phenotypes to spread to other oral tasks such as speaking, chewing, or drinking. Once the spread has occurred, the dystonia is likely to persist even if patients stop playing their instrument.

Differential Diagnosis

Dystonia can be distinguished from other hyperkinetic movement disorders based on clinical examination. Task-specificity and sensory tricks are unique to dystonia. Abnormal postures can occur with musculoskeletal or peripheral nerve disorders and dystonia can be distinguished from these processes based on signs and symptoms such as pain, paresthesias, and muscles weakness. Focal dystonias, such as writer's cramp, may also be the initial presentation of a progressive neurological disease such as Parkinson's disease, multiple sclerosis, spinal muscular atrophy, or spinocerebellar degeneration.

Diagnostic Workup/Tests

The diagnostic evaluation of adults who present with focal dystonia should begin with a careful history and physical examination. A history of task-specificity and sensory tricks is classic for FTSD. Review of all medications (prescription and nonprescription) should search for a history of possible exposure to dopamine receptor blocking agents. For musician's dystonia, particular attention should be paid to the motor examination, with careful testing of all intrinsic and extrinsic hand muscles. Sensory deficits in ulnar, median or C6, C7, or C8 distributions are not uncommon in musicians and should be specifically addressed. Typically, cutaneous sensation is normal, but there are problems with stereognosis. When the history is classic for FTSD and there are no other abnormalities on the neurological examination, imaging of the brain or spine is unnecessary. An EMG can demonstrate cocontraction of agonist and antagonist muscles, with prolonged bursts of activity and overflow into other muscle groups. With a classic history of dystonia and otherwise unremarkable physical examination, EMG is unnecessary to make a diagnosis of task-specific dystonia; however, this neurophysiologic test should be pursued if there is a concern for a peripheral nerve injury based on neurological examination.

Management

Treating patients with focal dystonia may involve oral pharmacological agents, botulinum toxin injection, assist devices and compensatory techniques, rehabilitation, and surgical procedures. The goals of therapy may be directed toward decreasing the intensity of symptoms, developing ways to compensate for dystonia, and changing neuronal function. Until the genetic and environmental triggers are better understood, prevention remains the preferred goal.

Oral medications are available for the management of dystonia, but the data supporting the use of these agents for focal task-specific dystonia are limited. Trihexyphenidyl and tetrabenazine are two drugs that have been studied in randomized controlled trials and shown to be effective. A major limitation to oral medications is the side effect profile and thus these agents are not the mainstay of treatment.

Implementing assist devices or modifying technique are strategies to adapt to task-specific dystonias. Patients with writer's cramp may attempt to alter their grip, use a pen with a wider diameter, or use a uniquely designed writing device that allows one to take advantage of more proximal muscles. For musicians with hand dystonia, altering technique or adding appendages to the instrument may be helpful. For example, woodwind players who have difficulty with the extension of the middle finger may benefit from changing the placement of the instrument's keys or adding appendages to key levers. In 2001, Priori employed a more radical solution, splinting and immobilizing the hand of affected musicians for 6 weeks and then retraining the hand once the splint was removed. While preliminary results with patients with early dystonia were encouraging, subsequent trials involving patients with more established dystonia have not replicated these findings. Most patients with embouchure dystonia attempt to compensate by using other muscle groups or techniques to produce the desired result.

This strategy has been more successful in patients with the tremor type of embouchure dystonia.

The approval and introduction of botulinum toxin injection in the United States in the late 1980s revolutionized the treatment of focal dystonia, particularly blepharospasm, torticollis, and spasmodic dysphonia. Botulinum toxin injection was then used to treat writer's cramp and FTSDmh, with hand weakness being the most common side effect. Injections are performed under EMG guidance, and they usually need to be repeated every 3–4 months as the toxin's effect wears off. Initial reports suggested that many FTSDmh patients initially benefited from injections, but they discontinued the injections after a year or two due to inadequate efficacy or lack of functional improvement. More recent studies, however, have shown that many musicians with focal dystonia benefit significantly from expertly administered injections. Patients should understand that the injections provide symptomatic relief, not a cure.

Several treatment approaches attempt to reset or retrain the abnormal somatotopic cortical map in the affected hand in focal dystonia. Byl proposed a learning-based sensorimotor retraining strategy that was comprehensive, including improved posture, aerobic fitness, and specific retraining of sensorimotor function. Another approach, sensory motor tuning, involves constraining fingers adjacent to the dystonic finger triggering the dystonia. This strategy employs a series of daily exercises to retrain the affected fingers. While interesting, success has been variable. Other similar treatments have been used, including teaching affected patients to read Braille. The nature of the intervention may matter less than the fact that an intervention is performed that targets and requires attention, progressive learning, reinforcement, and sensorimotor integration.

A more invasive approach has been used in Japan, where botulinum toxin injection is not available. Taira performed thalamotomy of the nucleus ventrooralis of the thalamus contralateral to the affected hand in FTSDmh and writer's cramp with surprisingly good results. Other patients have been successfully treated with deep brain stimulation of the thalamic nucleus ventrooralis and ventralis intermedius nucleus. These treatment options need to be investigated further in clinical trials.

Prognosis

Spontaneous remission in FTSD is rare. There is a five percent remission rate in writer's cramp and even then, recurrence is common. Despite symptomatic therapy, the degree of improvement in musician's dystonia is usually inadequate for an individual to continue with their performing career. Patients with embouchure dystonia, particularly the jaw and tongue phenotype, should be advised of the risk of spread to other activities such as chewing or speaking that may remain permanently. It is critical for the treating physician to offer emotional support to musicians who face this diagnosis, as they may experience significant depression and anxiety during the process of diagnosis and treatment.

See also: Dystonia; Dystonia, Secondary; Dystonia: Animal Models; Spasmodic Dysphonia: Focal Laryngeal Dystonia; Writer's Cramp.

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Dystonia, Traumatic

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Glossary

CRPS (complex regional pain syndrome) – A syndrome consisting of pain, autonomic dysfunction, and skin changes in a traumatized body area.
Hemidystonia – Dystonia involving both upper and lower extremities on the same side of the body.
Torticolls – A form of cervical dystonia with head rotation.

Definition and History

Dystonia following peripheral injury or head trauma was first reported in the 1970s to 1980s, although head turning associated with atlantoaxial dislocation (Grisel syndrome) had been described much earlier. It is now clear that dystonia can follow trauma to the head or body, but the association between the antecedent trauma and the subsequent dystonia remains a matter of controversy. A causal relationship between trauma and dystonia has been questioned because trauma is common while dystonia is not, and because case reports and retrospective studies are influenced by recall bias and lack of clear diagnostic criteria. However, the preponderance of evidence supports trauma causing or precipitating dystonia in some patients. Dystonia associated with head trauma will be discussed below separately from dystonia associated with peripheral injury.

Dystonia and Head Trauma

Dystonia can develop following a variety of cerebral insults including head trauma. It is most commonly associated with damage involving the basal ganglia, especially the putamen, but has also been reported with damage to the thalamus, the cerebellum, the brainstem, or their connections. The antecedent head trauma need not be severe. However, movement disorders including dystonia may be less likely with mild or moderate trauma and the latency between the trauma and dystonia onset may be longer for those with severe compared to those with milder head trauma. Dystonia may be more likely to develop in those who sustain trauma at a young age.

Head trauma is an uncommon cause of dystonia and dystonia is not the most common movement disorder following head trauma. Although 13–66% of survivors of head trauma have at least one movement disorder, the most common type is tremor. Dystonia may be present in about 18%, often accompanied by tremor or another movement disorder. The dystonia is transient in about 50% of trauma survivors, resolving within 1–12 months of the accident.

Dystonia associated with head trauma often develops secondary to brain injury sufficient to cause hemiplegia, and usually occurs in the previously hemiplegic limbs even after weakness has improved or resolved, leading to hemidystonia. Hemidystonia with involvement of upper and lower limb on one side is rarely seen with idiopathic dystonia. However, post-head trauma dystonia can also be focal, bilateral, multifocal, or generalized and can progress or spread from the original site of onset. Dystonia in the setting of brain trauma may be accompanied by neurologic deficits such as spasticity, rigidity, weakness, or hyperreflexia which are not seen in primary idiopathic dystonia. While dystonia after head trauma can resemble idiopathic dystonia clinically, it may be less likely to be action specific.

Dystonia usually develops months to years after the head trauma rather than acutely, although it has been proposed that an initial hemiplegia may mask the presence of dystonia. The delay in onset of dystonia following head trauma and the spread to areas beyond the hemiplegic limbs make it likely that dystonia does not result directly from trauma, but rather arises from remodeling associated with recovery from brain injury. Aberrant cerebral plasticity, sprouting, and remyelination have been postulated to result in dystonia, especially in patients who have a putative genetic predisposition.

Dystonia and Peripheral Trauma

A causal relationship between peripheral trauma and dystonia is even more controversial. Dystonia has been reported not only following severe injury from a wide variety of causes, but also with mild trauma such as soft tissue sprains, overuse, immobilization, casting, minor dental procedures or from electrical injury. The likelihood of developing dystonia following peripheral injury is impossible determine, especially if 'injury' is defined to include everyday sprains and common medical procedures. Five to twenty-one percent of patients with dystonia report trauma

in the preceding year. Sixty-eight percent of patients with fixed dystonia reported by Schrag gave a history of peripheral trauma within the preceding year.

Jankovic et al. proposed criteria that would limit the diagnosis of peripheral trauma-induced movement disorders arbitrarily to those arising within a year of the injury, in order to minimize the inclusion of subjects whose movement disorder was unrelated to trauma. Additionally, the injury must have been severe enough to cause local symptoms persisting for at least 2 weeks or requiring medical attention within 2 weeks, and the movement disorder had to arise in an area anatomically related to the site of injury. The diagnosis was further supported if no other cause for movement disorder could be identified, if features atypical of an idiopathic movement disorder were present, and if there was a poor response to medication. While these criteria may be helpful in defining a select cohort whose movement disorder is most likely related to trauma, many reported subjects with posttraumatic dystonia do not meet these criteria, often because of a delay in the onset of dystonia beyond 1 year.

Certain aspects of the dystonia have been proposed that may serve to differentiate peripheral trauma-associated dystonia from idiopathic dystonia. In particular, peripheral posttraumatic dystonia may be characterized by fixed postures or tonic rather than phasic muscle contraction, less task specificity, the absence of an effective geste antagoniste, higher likelihood of pain, lack of improvement after sleep or persistence during sleep, poorer response to treatment, including botulinum toxin injection, a more rapid rate of progression and, perhaps, a younger age of onset. Even if peripheral trauma initially or prominently affects the traumatized area, the dystonia can subsequently spread to become bilateral, multifocal, or generalized. Focal posttraumatic dystonia can be characterized by the body area affected.

Posttraumatic Cervical Dystonia

Local injury to the neck and shoulders, from automobile accidents with whiplash, lifting heavy objects, falling, blunt force, and repetitive strain have been implicated in 5–21% of cases of cervical dystonia (CD). An interval from injury to the onset of CD as short as hours and as long as 3 years have been reported. It may be difficult to differentiate posttraumatic dystonia from nondystonic abnormalities of neck posture such as those associated with occipital condyle fracture, atlantoaxial subluxation, spinal cord tumors, muscle inflammation, or fibrosis. Laterocollis (head tilting) is the most common pattern, followed by torticollis (head turning to one side), both of which may be accompanied by shoulder elevation and prominent neck muscle hypertrophy. Anterocollis and retrocollis are reported less frequently. Isolated neck or shoulder muscle hypertrophy may be variants of focal posttraumatic CD.

Tarsy compared those developing CD within 1 month of an injury to those whose dystonia presented 3 months to 1 year after injury and to a cohort without any antecedent trauma. Those with acute onset of dystonia developed pain, spasm and a fixed posture within days of the injury, along with shoulder elevation and muscle hypertrophy. Dystonia in the acute-onset patients also did not respond to sensory tricks, activating movements or botulinum toxin. Several patients with acute posttraumatic dystonia had complex repetitive discharges on electromyography. Interestingly, those with later-onset posttraumatic CD did not differ in any of these parameters from those with idiopathic CD. Tarsy therefore proposed that acute-onset posttraumatic CD might be a different disorder from late posttraumatic dystonia and idiopathic CD and might, in fact, be nondystonic.

In patients receiving botulinum toxin injections with CD arising within 1 year of head or neck trauma compared to a control population of patients with idiopathic CD, Samii found nonsignificant lower age of onset and more frequent pain in those with trauma, but no differences in the incidence of spontaneous remission, direction of head deviation, presence of an effective geste antagoniste, presence of tremor or response to botulinum toxin injection.

Posttraumatic CD may be more common in women even though trauma is more common in men. A psychogenic etiology for posttraumatic CD, as well as other posttraumatic dystonias, might be considered in those with the sudden onset within minutes to weeks of fixed painful spasmodic torticollis with rapid progression to fixed postures after minor trauma, especially if other nonphysiological symptoms like give-way weakness and nonanatomic sensory loss are present, as well as in those with pending litigation related to the injury.

Posttraumatic Craniofacial Dystonia

Cranial dystonias including blepharospasm, oromandibular dystonia (OMD), Meige syndrome (OMD with blepharospasm) and orofacial dystonia have been reported to follow eye disease or irritation, face and head surgery, facial trauma and dental procedures. Twelve percent of patients reported by Grandas had eye disease such as infection, trauma, or surgery within the year preceding the onset of blepharospasm and 17% of patients reported by Sankhla sustained trauma within the year before with OMD onset. There was no correlation between the severity of the trauma and the subsequent severity of the dystonia. After onset, more than half of the patients had spread to other cranial or cervical muscles. The patients reported by Sankhla did not differ significantly from

OMD patients without a history of a trauma precipitant in age at dystonia onset, the presence of pain, the effectiveness of sensory tricks, response to botulinum toxin, or a history of tremor. However, the nontraumatic cohort more frequently had spread of the dystonia, coexistent writer's cramp or spasmodic dysphonia and a family history of dystonia. Schrag similarly found, in eight cases of craniofacial dystonia arising within days to weeks of dental procedures, that posture was often fixed, pain was prominent and gestes were ineffective. A relationship between head or facial trauma and subsequent cranial dystonia, however, is not supported by all studies. Martino found the same self-reported incidence of head and maxillofacial trauma preceding hemifacial spasm as in patients with craniofacial dystonia.

Posttraumatic Limb and Segmental Dystonia

Upper limb, lower limb, and segmental dystonia have been reported following peripheral trauma. 28% of subjects with lower limb dystonia reported by McKeon sustained a distal or proximal (back, pelvis, or gluteal) injury to the affected extremity within 1 week of injury in half of the subjects and between 4 and 13 months in the others. Dystonia was accompanied by pain and 80% had a fixed dystonic posture. The dystonia was severe enough to interfere with walking in 30%.

Ten percent of patients with writer's cramp report previous trauma to the affected hand. Excessive repetitive use of a hand, as in musicians who practice many hours a day for years, could represent mild, chronic trauma and has long been considered a precipitant of focal hand dystonia. Posttraumatic focal hand dystonia may arise with trauma to the limb or neck. Its association with complex regional pain syndrome (CRPS; previously reflex sympathetic dystrophy) deserves particular mention. CRPS is characterized by persistent pain out of proportion to the precipitating event, autonomic dysregulation and trophic skin changes that follow trauma. In both CRPS and peripheral trauma-induced dystonia, the antecedent trauma may be trivial. Dystonia and CRPS may each follow soft tissue injury or limb immobilization as with casting. Movement disorders are present in up to 65% of patients with CRPS. Dystonia is the most common movement disorder in CRPS, present in 14–90% of those with movement disorders associated with CRPS, often in combination with tremor or myoclonus. In patients with CRPS, the dystonia typically takes the form of flexion of the fingers and wrist if the upper extremity is affected and inversion and plantar flexion of the foot with clawing of the toes if the lower extremity is affected. The dystonia in patients with CRPS can spread proximally, can become bilateral and can generalize. Patients with posttraumatic CRPS and dystonia tend to be younger than those with CRPS without dystonia. The onset of the dystonia may be abrupt or gradual, the dystonia may be sensitive to tactile or auditory stimuli, and may be fixed or mobile. In patients with dystonia and CRPS reported by van Rijn, the median interval between the onset of CRPS and dystonia was 61 days; however, about 25% of patients developed dystonia within 1 week and 3% more than 5 years after the development of other CRPS symptoms. Rarely, the dystonia presents before other CRPS symptoms affecting the same limb.

Pathophysiology

While a peripheral explanation might suffice for dystonia confined to the area of injury, only a central mechanism can explain the progression of dystonia to body areas other than that injured. It has been proposed that peripheral trauma leads to alterations in sensory feedback and sensitization of peripheral nociceptors, and subsequently to changes in spinal cord circuits eventually resulting in central sensitization and remodeling at cortical and subcortical levels.

As with head trauma, peripheral trauma is common but subsequent dystonia is not. It has been hypothesized that an underlying genetic predisposition may predispose patients to the development of dystonia following peripheral trauma. Bressman et al. failed to find the DYT1 gene in four patients with posttraumatic dystonia or other secondary dystonias. A genetic predisposition, however, is supported by reports of trauma precipitating or significantly worsening dystonic symptoms in patients with familial idiopathic generalized dystonia. It is also supported by the physiologic study of Bohlhalter. In this study, a patient with foot dystonia following an ankle injury, her brother with craniocervical dystonia and an unaffected sister all had abnormalities in motor cortical excitability assessed with transcranial magnetic stimulation similar to those previously reported in patients with idiopathic dystonia.

Treatment and Prognosis

The treatment of dystonia following either head or peripheral trauma is symptomatic and often ineffective. Typical medications used for idiopathic dystonia, including anticholinergic medications, baclofen, and benzodiazepines can be tried as well as physical and rehabilitation therapies. Early in the course of CRPS, intrathecal baclofen may provide relief of both pain and dystonia. Botulinum toxin helps some patients but may be less effective than in idiopathic dystonia. Stereotactic neurosurgery, such as pallidotomy or thalmatomy offer relief to some

patients but may be less effective in posttraumatic and other secondary dystonias than in idiopathic dystonia. Preliminary reports suggest that deep brain stimulation may be as effective as ablative surgery.

See also: Basal Ganglia; Blepharospasm; Botulinum Toxin; Cervical Dystonia; Complex Regional Pain Syndrome; Deep Brain stimulation; Dystonia; Meige's Syndrome.

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Dystonia: Animal Models

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Glossary

Glutamic acid decarboxylase – The enzyme that catalyzes the conversion of glutamate to GABA.
Knockin mouse – A mouse that has had genetic information, such as a specific disease-causing mutation, inserted into the gene of interest.
Knockout mouse – A genetically engineered mouse in which a specific gene has been inactivated.
Transgenic mouse – A mouse that carries a foreign gene that is randomly inserted in the genome.
Voltage-gated calcium channel – Ion channels that open and conduct calcium upon membrane depolarization.

Definition and History

Dystonia is a movement disorder characterized by excessive and, sometimes, sustained muscle contractions. The abnormal contractions and resulting twisting movements and postures may arise as a result of brain injury or occur as a sporadic or inherited disorder. Dystonia is classified by the distribution of the affected muscle groups. Generalized dystonia is characterized by involvement of muscles throughout the body. Focal or segmental forms of the disorder involve a small number of muscles, such as those of the hand in writer's cramp or of the upper face in blepharospasm. Dystonia has no clear neuropathological signature. Most cases are not a degenerative disorder, and no single neural pathway is yet implicated in the disorder. In fact, functional imaging studies

generally implicate several brain regions including cerebellum, cortex, brainstem, and basal ganglia. Because our understanding of the etiology and pathophysiology of dystonia is limited, animal models are essential for understanding this systems level disorder. One of the first animal models of dystonia, the dystonia musculorum mouse mutant, was described in the early 1970s, and many models have been developed since. These models are used to facilitate the identification of anatomical, physiological, or biochemical processes involved in the expression of the motor syndrome. Some of the most commonly studied animal models of both generalized and focal dystonia are described.

Models of Generalized Dystonia

Genetic Models of Generalized Dystonia

$Ca_v2.1$ calcium channel mouse mutants

Mice bearing mutations within the *Cacna1a* gene, which encodes Cav2.1 (P/Q-type) calcium channels, are models of dystonia; dystonia is a prominent feature of the *tottering*, *rocker*, *leaner*, and *Cacna1a knockout mice*. Tottering mice exhibit paroxysmal generalized dystonia. Attacks of generalized dystonia last for 30–40 min and are experimentally induced by stress, caffeine, or ethanol. Tottering mice carry a point mutation in the *Cacna1a* gene that results in a reduction in Cav2.1 calcium current density. No gross neuropathological abnormalities are identified in the tottering mouse brain. During a dystonic attack, neuronal activation is observed throughout the olivocerebellar circuit, and lesions of the cerebellum alleviate the dystonia suggesting that the cerebellum is necessary for the expression of dystonia in *tottering* mice.

Leaner mice and *Cacna1a* knockout mice exhibit severe chronic generalized dystonia. Dystonia develops at ~2–3 weeks of life. This debilitating dystonia causes death, indirectly by interfering with feeding in weanlings. The motor dysfunction in these mutants is more severe dystonia in the knockout mice than in leaner mice. The leaner mutation causes a gross disruption in the channel protein, resulting from a G to A point mutation of a splice donor site near the 3′ end of the gene. The mutation produces aberrantly spliced mRNA species that causes a reduction in open-probability of the channels and an overall reduction in P/Q-type calcium current density. Prominent degeneration of cerebellar granule and Purkinje cells, particularly in the anterior cerebellum, is observed in both leaner mice and the null mutants.

Dystonia musculorum mice

Dystonia musculorum mice exhibit generalized dystonia caused by a mutation in the Bpag1 gene, which encodes a cytoskeletal linker protein. The mutation causes loss of neuronal cytoskeletal organization, axonal swelling, and abnormal axonal transport. Neuropathological studies reveal lesions of sensory nerves and dorsal root ganglia, cerebellum, and red nucleus plus degeneration of muscle spindles. Additionally, myelination is abnormal in both the peripheral and central nervous system. The precise mechanisms underlying the motor dysfunction are unknown.

dt^{sz} hamster

The *dystonic* (*dt^{sz}*) hamster exhibits generalized paroxysmal dystonia. Attacks of dystonia are stress induced and last for hours. The attacks begin after the second week of life, peak in severity between the fourth and sixth week, and disappear after eight weeks of age. The phenotype is caused by a recessive mutation, but the gene defect is unknown. The dystonia correlates with overactivity of striatal projection neurons and reduced basal ganglia output. Irregular patterns of electrical activity are observed within caudate, putamen, and globus pallidus, which may result from significant increases in corticostriatal and striatopallidal excitability. The overactivity is associated with a marked reduction in the number of striatal GABAergic interneurons, and an increase in striatal dopamine overflow during a dystonic attack, implicating the basal ganglia as the source of dystonic attacks.

dt rat

The chronic generalized dystonia exhibited by the dystonic (*dt*) rat is caused by a recessively inherited mutation in *Atcay*, the gene encoding caytaxin. Dystonia is observed starting 10 days after birth and becomes increasingly severe with age. Viability is compromised since animals have difficult eating and drinking. Neither gross neuroanatomical abnormalities nor neurodegeneration is apparent. Neurochemical abnormalities in cerebellum, include an increase in GABA synthesis and concentration in Purkinje cells, but a reduction in glutamic acid decarboxylase activity and GABA receptor density in the deep cerebellar nuclei. *dt* rat Purkinje neurons exhibit reduced complex spiking and abnormal patterns of simple spike bursting. Neurons within the deep cerebellar nuclei exhibit increased rhythmic bursting, with the most severe changes in activity observed in older animals with advanced dystonia. It is likely that both physiological and biochemical abnormalities result from abnormal Purkinje cell innervation by climbing fiber afferents from the inferior olive. Removal of the cerebellum or lesions of the deep cerebellar nuclei alleviate the dystonia in *dt* rats, further implicating the cerebellum in the disorder.

Genetically engineered models of dystonia

The focus of genetically engineered mouse models of generalized dystonia has been *DYT1* dystonia, a primary dystonia caused by an in-frame 3 base pair deletion of GAG in the *TOR1A* gene, which encodes the torsinA

protein. The dominant mutation exhibits partial penetrance and exerts its effects through mechanisms that are not fully understood. Both transgenic and knockin/out lines of mice carry the *DTY1* mutation. Transgenic mice overexpress a copy of the mutant gene along with normal endogenous gene. Several different promoters were used to drive expression of mutant torsinA in transgenic mice, including the mammalian neuron-specific enolase promoter, the human cytomegalovirus promoter, and the mammalian prion protein promoter. Perinuclear inclusions, blebbing of the nuclear membrane and torsinA-containing aggregates are observed in the brainstem of some, but not all transgenic lines. Dopaminergic dysfunction is also observed in many lines. Striatal dopamine concentrations are generally normal, but dopamine turnover and release are reduced. Striatal D2 dopamine receptor-mediated N-type calcium channel inhibition and GABAergic signaling are also altered. Although each line exhibits some motor abnormality, none has a motor disorder resembling human dystonia. It is important to note that transgenic lines overexpressing normal torsinA also exhibit abnormalities similar to those observed in the mutant torsinA transgenic lines including changes in motor behavior and perinuclear inclusions. Therefore, some abnormalities in the transgenics may reflect the consequence of overexpression or ectopic expression, rather than the consequence of mutant torsinA expression per se.

Mice homozygous for the Tor1A null mutation and knockin mice homozygous for the *DYT1* GAG deletion in the *Tor1A* gene die perinatally and exhibit abnormalities of the nuclear membrane. Gross brain histology of both heterozygous knockin and knockout mice is relatively normal but protein aggregates are observed in brainstem neurons. Heterozygous knockin mice are somewhat hyperactive and impaired on the beam-walking test without overt dystonia.

There are also genetically engineered mouse models of disorders in which dystonia is frequently observed, such as Lesch–Nyhan disease, Parkinson disease, and Wilson disease. Like DYT1, the models are a mix of transgenic, knockin and knockout mice, but few carry precise human mutations as knockins. None of these models exhibit dystonia with the exception of α-synuclein transgenic mice. This may be due to intrinsic differences in neural circuits between man and mouse or simply the lack of models expressing exact genocopies of the human disorders.

Drug-Induced Models of Generalized Dystonia

Generalized dystonia may be induced in otherwise normal animals using a variety of drugs. Drug-induced models are useful in defining defects common to many forms of dystonia, similar to the manner in which drug-induced animal models of Parkinson disease have elucidated the pathophysiology underlying that disorder.

Kainic acid-induced dystonia

Low doses of the excitatory glutamate receptor agonist kainic acid microinjected into the mouse cerebellum produce generalized dystonia. Dystonia peaks 30–40 min after injection and mice return to baseline motor activity 2 h after injection. The severity of the dystonia is dose dependent. Kainate-induced dystonia in normal mice is associated with neuronal activation within cerebellum, deep cerebellar nuclei, red nuclei, and other cerebellar relay nuclei; it is not associated with neuronal cell death. Non-N-methyl-D-aspartic acid (NMDA) glutamatergic antagonists injected into the cerebellum do not cause dystonia but block kainate-induced dystonia demonstrating that non-NMDA receptor activation, not simply a distortion of glutamatergic signaling, is necessary to induce dystonia. Microinjection of kainate into basal ganglia does not induce motor dysfunction, nor does kainate induce dystonia when injected into the cerebella of mice lacking Purkinje cells, indicating that output from cerebellum is necessary for expression of the dystonia.

3-Nitropropionic acid intoxification

In humans, ingestion of sugarcane tainted with the *Arthrinium* fungus causes a movement disorder that includes dystonia and chorea accompanied by lesions within striatum and globus pallidus. The contaminating toxin, 3-nitropropionic acid (3-NPA) induces similar motor dysfunction in mice, rats, and nonhuman primates. This model has been difficult to work with in rodents because 3-NPA is highly toxic and causes death in at least one-third of mice. In surviving mice, lesions occur in the dorsolateral striatum and cell loss is observed in the globus pallidus and substantia nigra pars reticulata and compacta. Loss of striatal projection neurons and increases in striatal dopamine are observed in both rodents and nonhuman primates after 3-NPA intoxification, suggesting a reduction in striatonigral inhibition. Thus, 3-NPA-induced striatal lesions predict dysfunctional basal ganglia output as the cause of dystonia.

Dystonia caused by L-type calcium channel activation

Low doses of systemically administered Bay K 8644, an L-type calcium channel agonist, cause slowing of movements with occasional momentary abnormal limb positions. Higher doses cause abnormal severe flexion of the trunk with flexion of the head toward the abdomen, which often causes the mouse to fall. Activity returns to baseline after ~120 min. With EMG, significant increases are observed in resting muscle activity and movement-related phasic bursting is prolonged and of high amplitude. A similar motor syndrome is evoked by intracerebral injection of Bay K 8644, demonstrating a central effect of the drug. Additionally, systemic administration of FPL 64176,

another L-type calcium channel agonist induces a similar syndrome. L-type calcium channel antagonists, such as nimodipine and nitrendipine, block the syndrome. Neuronal activation after Bay K 8644 challenge is apparent in the striatum, cortex, hippocampus, locus coeruleus, and cerebellum. The broad distribution of activation suggests that Bay K 8644 may induce dystonia through several different motor regions.

Models of Focal Dystonia

Genetic Models of Focal Dystonia

Rocker mice

Rocker mice carry a point mutation in the *Cacna1a* gene that results in a modest reduction in Cav2.1 calcium current density. Like the Cacna1a mouse mutant tottering, rocker mice exhibit paroxysmal dystonia. Attacks of dystonia are often limited to a single limb or segmental and occur only in female mice. Few obvious neuropathological abnormalities are observed in the rocker mouse brain with the exception of abnormal Purkinje cell dendritic arbors.

Lethargic mice

Lethargic mice carry a point mutation in the *cachb4* gene, which encodes the beta auxiliary subunit of voltage-gated calcium channels. Lethargic mice exhibit brief attacks of paroxysmal dystonia induced by short periods of exercise. Attacks of dystonia may be focal, segmental, or generalized. Surgical removal of the cerebellum eliminates the paroxysmal dystonia demonstrating that the cerebellum is necessary for the paroxysmal dystonia.

Induced Models of Focal Dystonia

Blepharospasm in rat

Blepharospasm is a focal dystonia of the upper face characterized by exaggerated involuntary blinking caused by spasms of the orbicularis oculi muscle. The rat model of blepharospasm was developed based on the hypothesis that dystonia results from a combination of abnormal sensory input plus basal ganglia dysfunction. To implement this two-hit model, a partial lesion of the facial nerve to reduce orbicularis oculi innervation was combined with a small unilateral 6-hydroxydopamine lesion of the substantia nigra pars compacta to induce mild dopamine depletion. Both insults alone produce small increases in trigeminal reflex blink excitability. In combination, the lesions cause increased blinking and spasms of lid closure, resembling blepharospasm in humans. Lid spasms persist even after reinnervation of the orbicularis oculis muscle suggesting long lasting and irreversible modifications to central processes mediating blink responses.

Hand dystonia in owl monkey

Most hand dystonias are task specific and may occur in response to excessive and repetitive movement. Abnormal hand representation in the somatosensory cortex is associated with the disorder. To mimic the conditions of task-specific overuse, owl monkeys were trained to squeeze a handgrip with as many as 3000 rapid opening and closing cycles daily for up to 25 weeks. Performance declined in several monkeys due to the emergence of abnormal movements resembling hand dystonia. After training, hand receptive field size in somatosensory cortex was strikingly enlarged, similar to observations in humans that develop task-specific dystonias following overuse. It is unclear whether the changes in receptive fields are a cause or an effect of the dystonia. This model has not been widely studied. Dystonia induced through this repetitive movement paradigm has been observed only in four owl monkeys and others have not yet replicated the model.

Summary

Animal models of both generalized and focal dystonia have been developed in numerous species and are critical tools for understanding the mechanisms underlying dystonia in humans. These models have been used to elucidate novel disease mechanisms and pathophysiology and should prove useful for identifying novel therapeutics.

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See also: Blepharospasm; Dystonia; Kainic Acid Model of Dystonia; Leaner Mouse; Tottering Mouse - a Definition.

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Dystonic Storm

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Glossary

CRPS (complex regional pain syndrome) – A syndrome consisting of pain, autonomic dysfunction, and skin changes in a traumatized body area.
Neuroleptic malignant syndrome – Life-threatening syndrome including fever, muscle rigidity, and autonomic instability usually associated with the use of neuroleptic medication.
Rhabdomyolysis – Muscle breakdown.

Introduction

Dystonic storm (status dystonicus) (DS) is used to describe episodes of acute or subacute severe generalized dystonia accompanied by fever and rhabdomyolysis in those with preexisting dystonic syndromes. Often refractory to medical management, DS can be life-threatening.

History and Epidemiology

Jankovic and Penn first described DS, in 1982, in a child with idiopathic torsion dystonia who had several exacerbations of dystonic spasms, high fever, and myoglobinuria leading to acute renal failure. Various medications, including Sinemet, baclofen, and tetrabenazine, were only transiently effective. The child ultimately improved following bilateral thalamotomy.

DS is rare, with only single cases and small series reported. DS affects subjects with underlying dystonic disorders – both primary dystonias, such as DYT1-positive and DYT1-negative primary torsion dystonia, and secondary dystonias, including posttraumatic dystonia, dystonia associated with cerebral palsy, Wilson's disease, pantothenate kinase-associated neurodegeneration (PKAN), complex regional pain syndrome, and neuroacanthocytosis. DS may be more common in males and in those with childhood-onset dystonic disorders. Although most commonly seen in those with generalized dystonia, it has been reported rarely in patients with focal or segmental dystonia.

Signs and Symptoms

The most prominent and disabling symptoms of DS are continuous, severe dystonic muscle contractions. The onset may be heralded by intermittent, less-severe attacks, or exacerbations of the underlying dystonia over days, weeks, or months before more abrupt progression to the characteristic widespread, continuous spasms, which are extremely painful. Dystonia may be accompanied by other abnormal movements, including tremor, myoclonus, or chorea. Severe spasm affecting the upper airway, including the larynx, leads to upper airway compromise with stridor, aspiration, dysphagia, and anarthria. Spasm of the respiratory muscles contributes to respiratory insufficiency so that intubation and mechanical ventilation are often necessary. The intensity of uncontrolled muscle activity also causes high fever, dehydration, acidosis, and rhabdomyolysis with an elevated creatine kinase level and myoglobinuria, which can subsequently cause acute renal failure.

Episodes of DS can last days to years. Intervals between episodes as short as hours and as long as years have been reported. A precipitant, such as respiratory or urinary tract infection, can be identified before many episodes. Some episodes were reported to begin shortly upon the initiation of medications, including clonazepam or zinc sulfate or D-penicillamine for Wilson's disease. In other patients, a decrease in dose or withdrawal of medications, such as intrathecal baclofen, lithium, or tetrabenazine, seems to initiate a spell.

The differential diagnosis of DS includes neuroleptic malignant syndrome and malignant hyperthermia, which are differentiated by the medical history and the background of occurrence in those with preexisting dystonia.

Management

Urgent management of DS includes protection of the airway, maintenance of ventilation, and correction of metabolic abnormalities, along with control of the muscle spasms and the associated pain. Admission to the intensive care unit is usually advisable.

The first line of care includes close hemodynamic and metabolic monitoring. Antipyretics, hydration, cooling blankets, and correction of acidosis may all be required. Dialysis may be used to prevent renal damage from myoglobinuria. Patients with DS often require sedation and may require mechanical ventilation. Sedation lessens the severe spasms thereby decreasing muscle breakdown and preventing rhabdomyolysis, as well as allowing adequate ventilation. The choice of sedating agent and muscle relaxant may not be important. Midazolam, propofol, thiopental, and lorazepam are commonly used, although it has been suggested that midazolam which has a direct action on spinal cord circuitry may be especially effective. Once started, intubation and ventilation may be required for a prolonged period. Among 12 DS patients reported by Manji, intubation was required for a mean of 52 days, but as long as 300 days. Sedation should be lifted periodically to determine if DS spasms have subsided.

Specific treatment for the dystonic spasms often begins with increases in the dosages of medications the patient is already on. A wide range of medications have been reported as possibly helpful for DS, including neuroleptics (haloperidol, chlorpromazine, pimozide, sulpiride, clozapine, risperidone), tetrabenazine, anticholinergics (trihexyphenidyl/benzhexol), acetazolamide, antispasmodics (dantrolene, baclofen), anticonvulsants (phenytoin, carbamezepine, valproic acid), and L-dopa. High doses may be required; neuroleptics are often pushed to the point of parkinsonism. Marsden et al. proposed initial treatment with high doses of an anticholinergic followed by the addition of tetrabenazine and pimozide, if needed. Several reported patients benefited significantly from intrathecal baclofen. Unfortunately, antidystonic medications are often ineffective or only partly effective. Some medications that appear to be working initially quickly lose benefit requiring higher doses or additional medications.

A number of neurosurgical procedures appear to be able to halt DS. Pallidotomy and thalamotomy have both been successful in a number of patients. Deep brain stimulation (DBS) may prove to be equally efficacious.

Prognosis

The long-term outcome varies widely. No prognostic factors have been identified that allow one to predict which subjects will have a good outcome. Following an episode of DS, many patients recover completely and return to their baseline level of dystonia. Some are permanently worse and some patients die, often of intercurrent infection associated with prolonged hospitalization and intubation. With surgery, pallidotomy, thalamotomy, or DBS, there are now reports of patients improving beyond their pre-DS condition.

See also: Dystonia; Dystonia, Secondary; Dystonia, Traumatic; DYT1; DYT12, Rapid Onset Dystonia-parkinsonism; Generalized Primary Torsion Dystonia; Neuroacanthocytosis Syndromes; Wilson's Disease.

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DYT1

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Glossary

Dystonia – Sustained muscle contractions of agonist and antagonist muscles causing involuntary repetitive movements or abnormal postures, which are usually directional in nature.
Expression – Describes the type and severity of disease (e.g., DYT1 dystonia has variable expressivity, such that one carrier may manifest with severe generalized disease and be unable to walk, and another may have only mild non-debilitating writer's cramp).
Generalized dystonia – Dystonia involving both legs or the leg and the trunk and at least one other body region.
Geste antagoniste – Specific sensory modality (e.g., touching) used by a patient suffering from dystonia to lessen the abnormal posture or repetitive movements (also called sensory trick).
Null point – Position in which a dystonic contraction disappears, may be helpful in discriminating dystonic tremor from other types of tremor.
Penetrance – The rate at which a gene carrier develops disease (e.g., ~30% of DYT1 carriers will develop dystonia).
Primary dystonia – Dystonia is the only neurologic feature on examination (with the exception of tremor), there are no laboratory or imaging data to suggest an acquired or degenerative cause, there is no response to levodopa and there is no history to suggest an environmental or pharmacologic cause.

Definition and History

Dystonia is an involuntary hyperkinetic movement disorder characterized by sustained twisting and posturing movements which are usually directional in nature. It involves agonist and antagonist muscle contraction. Dystonia can be classified according to the body part(s) involved, the age of onset, or the etiology (see **Figure 1**). The term primary dystonia is used when dystonia is the only movement disorder (with the exception of tremor) and there is no secondary etiology. Secondary dystonia, on the other hand, is used when dystonia is associated with other movement disorder(s) and/or is due to an exogenous cause, such as dopamine receptor blocking medications or stroke or when structural changes are noted on imaging. The primary dystonias can be further classified according to the age of onset: *early* (age of onset <26 years, this is often due to mutations in DYT1), *late* (age of onset >26 years, most genetic etiologies are not known), and *mixed* (early and late onset within families (typically DYT6 and DYT13)).

DYT1 dystonia is the prototype of primary torsion dystonia. It is also called dystonia musculorum deformans 1, early-onset torsion dystonia, idiopathic torsion dystonia and Oppenheim dystonia. It is an early-onset dystonia, with patients almost always presenting before the age of 26 years with involvement of an arm or leg. DYT1 classically progresses to multifocal or generalized dystonia, but some DYT1 carriers will have dystonia that remains focal, with only brachial involvement, for example.

Although there is some debate regarding the first report of dystonia, the clearest description of primary dystonia was written by Hermann Oppenheim in 1911, who reported four children with features of abnormal muscle tone, includingtwisting postures with muscle spasms which affect the trunk and limbs, and described their 'dromedary gait' with flexion and twisting of the trunk. Labelled 'dystonia musculorum deformans,' these cases most likely represent DYT1 dystonia. DYT1 was incorrectly assumed to be an autosomal recessive disorder due to infrequent parent child transmission, but work by Zeman and coworkers demonstrated that the transmission was autosomal dominant with reduced penetrance. His work also led to better characterization of the DYT1 phenotype and an understanding that the condition was of increased frequency in Ashkenazi Jews. Linkage to chromosome 9q34 was reported in a French-Canadian family. In 1997, ~80 years after the first description this condition, the DYT1 gene, which encodes the protein torsin A was cloned by Ozelius and colleagues. It is important to note that while DYT1 is the major etiology of early-onset dystonia in the Ashkenazi Jews, DYT1 dystonia is not limited to French-Canadians and Ashkenazim, and has been reported in populations around the world, including other Caucasian, Asian and African populations.

Pathogenesis/Pathophysiology

Mutations in the DYT1 gene on chromosome 9q34 are responsible for DYT1 dystonia. This mutation consists of a three base pair (GAG) deletion in the hydroxy terminus

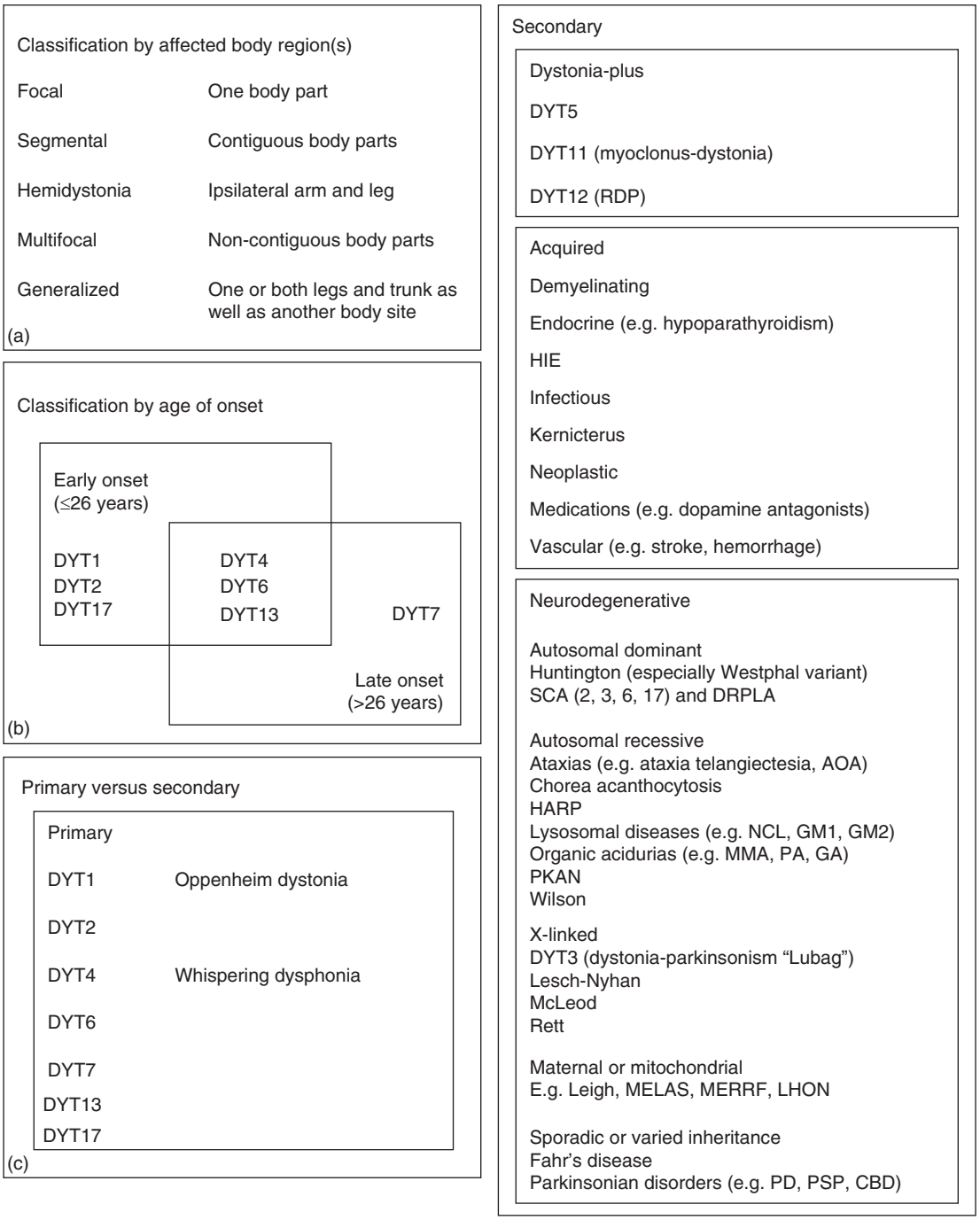

Figure 1 Dystonia classification. AOA: ataxia with oculo-motor apraxia; CBD: corticobasal degeneration; DRPLA: dentatorubral pallidoluysian atrophy; GA: glutaric aciduria; HIE: hypoxic ischemic encephalopathy; LHON: Leber hereditary optic neuropathy; MELAS: mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes; MERRF: myocclonic epilepsy associated with ragged red fibers; MMA: methylmalonic aciduria; NCL: neuronal ceroid lipofuscinosis; PA: proprionic aciduria; PD: parkinson's disease; PKAN: panthotenate kinase associated neurodegeneration; PSP: progressive supranuclear palsy; RDP: rapid-onset dystonia parkinsonism; SCA: spinocerebellar ataxia.

of the gene resulting in the loss of a pair of glutamic acid residues in the C-terminal region of the protein. The same mutation is present in virtually all patients, regardless of their ethnicity.

DYT1 dystonia is transmitted in an autosomal dominant fashion with reduced penetrance (30–40%), and varied expression. Reduced penetrance is most likely due to a combination of genetic and environmental causes. Thus far,

only one uncommon genetic change is known to decrease penetrance of DYT1. This change is a polymorphism in the coding sequence in *cis* with the DYT1 deletion which has been shown to be associated with markedly reduced penetrance. DYT1 dystonia also has variable expression, even within families. In the same sibship, one sibling may have a severe generalized dystonia requiring a wheelchair for mobility while another may never seek medical attention because of an isolated writer's cramp.

The DYT1 gene encodes for the protein torsin A. This protein is widely expressed in the human brain and has been found to have a greater expression in the neurons of the striatum, substantia nigra pars compacta, thalamus, hippocampus, cortex, and cerebellum (in Purkinje cells). The role of this protein is not yet fully understood: it is a member of the AAA + superfamily of heat shock and regulatory proteins, which are known to be important in protein folding and regulation. Both in vitro and in vivo studies suggest that torsin A is involved in protein trafficking, fusion of vesicles with the presynaptic membrane, movements of organelles, cytoskeletal dynamics, and protein folding.

Torsin A has been localized to the small vesicles of the presynaptic terminals in adult striatum. This may suggest that the protein also has a role in dopaminergic modulation. Torsin A may be important for dopaminergic transmission – in a neuropathological study, patients with DYT1 dystonia had larger appearing nigral dopaminergic neurons than normal. Moreover, another postmortem study revealed that both dopamine and homovanillic acid levels are decreased in the striatum of affected patients. Finally, torsin A has also been shown to be present with α-synuclein in Lewy bodies and ubiquitin positive perinuclear inclusions were found in the periaqueductal grey matter as well as in the reticular formation. Despite all of these elements suggesting that dopamine may play an important role in the pathogenesis of DYT1 dystonia, the significance of this role remains uncertain. An argument against the dopaminergic hypothesis is that patients with DYT1 dystonia do not have parkinsonian sign or symptoms, and the response to dopaminergic therapies is not marked.

Epidemiology/Risk Factors

DYT1 dystonia is the most common form of early-onset primary dystonia. Early-onset dystonia is caused by DYT1 dystonia in 80–90% of Ashkenazi Jews and in ~50% (30–60%) of non-Jewish patients. DYT1 is more prevalent among Ashkenazi Jews (1/3000 to 1/9000) compared to non-Jewish individuals (1/9000 to 1/27 000). The increased prevalence of the disease in Ashkenazi Jews is thought to result from a founder mutation that was postulated to have appeared in Lithuania or Byelorussia, ~350 years ago. De novo mutations have been reported in patients in varying ethnic backgrounds but their rate is unknown.

The most important risk factor for the development of DYT1 dystonia is being a carrier of the known gene mutation. It has been postulated that both environmental and genetic factors may be important for the development of the disease, but to date only the histadine polymorphism in *cis* with the GAG deletion has been clearly demonstrated to reduce the risk of developing the disease.

Clinical Features and Diagnostic Criteria

The diagnostic criteria for primary dystonia include: (1) dystonia is the only abnormality (exception: postural or/and kinetic tremor), (2) no evidence of an acquired or degenerative cause (by laboratory or imaging data), (3) lack of a marked and sustained response to levodopa, and (4) no identifiable environmental or pharmacological cause such as past or current use of neuroleptics or antiemetics (e.g., metochlopramide). DYT1 patients all meet these criteria. There may be a partial response to levodopa in some, but the improvement is not as dramatic or sustained as occurs in dopa-responsive dystonia (DRD).

As noted, while there is phenotypic heterogeneity in DYT1 dystonia, there are also classic clinical features. In 90% of cases dystonia starts in the arm or leg, and almost always one or more limbs become affected, with 95% of cases have at least one affected arm. In half of the cases, there is generalization with both legs or one leg and the trunk becoming affected. Trunk and cervical muscles may become involved in approximately one-quarter to one-third of the cases. While it is unusual to start in the cranial muscles, spread to these muscles occurs in up to 15–20% of cases. Also as noted, early age of onset is a major feature of DYT1, with average age of onset at 12.5 years. The reported ages of onset are quite variable, ranging from 3 to 64 years, but most cases with onset before the age of 21 and almost all before the age of 26. Earlier age of onset of dystonia is associated with a more severe phenotype. It is rare for adult onset focal dystonia to be attributed to a DYT1 mutation.

As the only definitive method of diagnosing DYT1 dystonia is through genetic testing. Guidelines for genetic testing suggest consideration of testing in individuals with onset of primary dystonia <26 years old, individuals with an older onset if there is a family history of early-onset dystonia or if writer's cramp is a prominent feature. Genetic counseling should be sought in combination with testing. If genetic testing is not available in a case of young-onset dystonia an empiric trial of L-dopa should be considered to evaluate the possibility of DRD (see below).

Several features lead the clinician away from the diagnosis of DYT1 dystonia: age of onset after the age of 40 years, focal or segmental craniocervical dystonia (including spasmodic torticollis or cervical dystonia,

spasmodic dysphonia, blepharospasm, oromandibular dystonia), dramatic and sustained improvement with levodopa, abnormal brain imaging, additional abnormal findings on examination (e.g., parkinsonism), and a history suggesting acquired cause (e.g., perinatal asphyxia, remote or current use of neuroleptics).

Because the disease is inherited in an autosomal dominant manner with incomplete penetrance, no family history may be apparent, especially in small families. Further, because there is tremendous phenotypic variability, family members may not realize that severe dystonia and very mild writer's cramp, for example, are both expressions of the same condition.

Differential Diagnosis

The differential diagnosis for DYT1 dystonia includes other forms of primary dystonia; including the mixed age of onset (DYT6, DYT13) and late age of onset (DYT7). DYT5 or DRD, which is also an early-onset dystonia with onset in a limb (usually the leg) which frequently spreads to generalized dystonia, may be confused with DYT1. Diurnal fluctuations are characteristic of DRD, but are not always seen, whereas they are uncommon in DYT1 dystonia. Parkinsonian features as well as a spastic gait and hyperreflexia may also be seen in DRD, but are not present in DYT1. Treatment of these two conditions is different; DRD patients typically respond dramatically to low doses of levodopa, while DYT1 patients may have a mild but not a dramatic and sustained response. If genetic testing for DYT1 is not readily available, or the test is negative, a levodopa trial should be undertaken. Because there may be some partial response to L-dopa in DYT1 dystonia, some clinicians may choose to continue the medication even if DRD is excluded by the lack of a marked and sustained response. **Table 1** summarizes the principal characteristics of the primary dystonias and dystonia-plus syndromes, according to their inheritance.

Among the secondary causes of dystonia, hereditary neurodegenerative conditions should also be considered in the differential diagnosis, especially Wilson's disease, as it is a highly treatable, but otherwise degenerative disorder. Wilson's disease typically presents with liver disease in the pediatric population, especially before the age of 12 years. The neurological and psychiatric presentations are more typical of adolescent and adult patients. When suggested by the clinical impression, testing for other diseases (e.g., Lesch–Nyhan syndrome, pantothenate kinase associated neurodegeneration (PKAN)), should be performed. However, this group of diseases typically involve other neurological symptoms or signs in addition to dystonia.

Dystonia may result from acquired injuries to the basal ganglia. In the pediatric population this is typically from a perinatal hypoxic–ischemic insult. Dystonia is also seen in patients with Kernicterus. In these later two conditions, even though the insult occurs in the neonatal period, it is typically only in early to mid childhood that the patients develop dystonia, often accompanied by choreoathetosis. Other acquired conditions may lead to dystonia include basal ganglia stroke, hemorrhage, tumor, and exposures to medications such as neuroleptics.

Other types of hyperkinetic movement disorders are part of the differential diagnosis; the most important being essential tremor. As previously mentioned, tremor may be a clinical feature of DYT1 dystonia and could resemble the postural and kinetic tremor of essential tremor. The presence of a tremor, especially if there is a positive family history suggesting an autosomal dominant mode of transmission, may lead to an erroneous diagnosis of essential tremor. A few characteristics of the tremor may help the clinician to differentiate these two entities: in the case of a dystonic tremor, the tremor is typically irregular both in amplitude and frequency, it has a directional nature, there may be a null point and the patient may use a sensory trick (geste antagoniste) to reduce the intensity of the tremor. In the case of an essential tremor, all of the above mentioned characteristics are absent. The other hyperkinetic movement disorders are tics, chorea, and myoclonus. They are less often mistaken for dystonia. Certain tics may have dystonic features (dystonic tics), but the association with an urge, the ability to temporarily suppress, the lack of predictability and ability to reproduce them with specific actions all help in differentiating them from dystonia. Chorea, on the other hand is primary distinguished from dystonia by its random quality, its dance-like pattern and its unpredictability. Myoclonus is very rarely confused with dystonia because of its rapid, shock-like jerks, although there is an overlap syndrome of myoclonus-dystonia, and patients with primary dystonia may have superimposed myoclonic jerks. These are typically, although not always, longer than 100 ms.

Dystonic movements may also be the presentation of a psychogenic movement disorder. Clinical features which support a psychogenic movement disorder are distractibility, inconsistent movement(s), and entrainment, in the case of a tremor. Abrupt onset, association with a trigger (e.g., stressful event), history of psychiatric condition(s), multiple unexplained medical complaints, and la 'belle indifference' may also be present in a psychogenic movement disorder. These may be present in primary dystonia as well, however. Further certain interesting characteristics of a physiologic dystonia can be falsely interpreted as psychogenic despite that they are known features of dystonia: movement specific dystonia (e.g., dystonia of the foot present when walking forward and not backward), presence of a sensory trick and of a null point in case of a dystonic tremor. Moreover, it should be kept in mind that these two

Table 1 Inherited primary dystonia: primary dystonia syndromes and dystonia-plus syndromes

Type	*Epidemiology*	*Age of onset*	*Clinical features*	*Gene/ Chromosome/Protein*
Autosomal dominant primary dystonia				
DYT 1 Dystonia musculorum deformans; Oppenheim's dystonia	Most common primary dystonia; 50% of EO dystonia in non-Jews; 90% in Ashkenazi Jews	Usually childhood Mean age = 12.5 years	Limb onset (typically LE), evolution to generalized or multifocal dystonia	TOR1A/9/Torsin A
DYT 4 Whispering dysphonia	Single large Australian family	13–37 years	Laryngeal and cervical dystonia	Unknown
DYT 6	Mennonite families	Mean age = 18.9 years	Focal or segmental, craniocervical involvement, possible evolution to generalized dystonia	THAP1/8/THAP1
DYT 7	Single German family	Adult	Focal (cervical, laryngeal, limb, blepharospam), postural tremor	Unknown/18/Unknown
DYT 13 Multifocal and segmental dystonia	Single Italian family	Mixed Mean = 15.6 years	Semental dystonia with cranio-cervical, upper extremity dystonia	Unknown/1/Unknown
Autosomal recessive primary dystonia				
DYT 2		Childhood onset	Generalized or segmental	Unknown
DYT 17	Single Lebanese family	Adolescence to early adulthood	Initially cervical dystonia, evolution to segmental or generalized dystonia	Unknown/20/ Unknown
X-linked recessive primary dystonia				
DYT 3 Dystonia-parkinsonism 'Lubag'	Predominantly males from Panay Island in Philippines	4th or 5th decades	Segmental or generalized dystonia with parkinsonism	DYT3/TAF X (gene is multiple transcript system)
Dystonia-plus syndromes				
DYT 5 DRD/ parkinsonism Segawa	F > M	Childhood Mean = 6 years Earlier, often in infancy	Foot dystonia, diurnal fluctuation, +/− parkinsonism, dramatic response to levodopa	(Autosomal Dominant) GH1/14/GTPCH1 (Autosomal Recessive) TH/11/Tyrosine hydroxylase
DYT 11 Myoclonus dystonia		Childhood to adolescence	Myoclonic jerks with variable features of dystonia; very EtOH responsive	SGCE/7/ε-sarcoglycan
DYT 12 Rapid-onset dystonia-parkinsonism	Very rare	From childhood to adulthood	Abrupt onset of dystonia (predominantly of bulbar muscles) and parkinsonism	ATP1A3/19/Na/K-transporting ATPase α-3 chain

EO, early onset; EtOH, ethanol; F, female; LE, lower extremities; M, male.

entities are not mutually exclusive and there may be elaboration in a patient with primary dystonia.

Diagnostic Work-up/Tests

As for any other etiology of dystonia, a detailed family history and detailed medical history, inquiring about past and current use of medications especially dopamine blocking agents (which may have been prescribed for psychosis, depression, anxiety, sleep, or as anti-emetics).

The diagnosis of DYT1 dystonia is made by molecular genetic testing for the only mutation known to cause this condition: the GAG deletion in the TOR1A gene. Such testing is available through some academic laboratories and commercially. Counseling regarding risk to family members and the meaning of a negative test, particularly that it does not mean that the dystonia is not genetic, should be performed in all cases. This should be done by a trained genetics counselor or physician. Physicians are encouraged to refer patients to genetics counselors as there are many implications both for the individual and the family.

Structural imaging of the brain, preferably an MRI, should be considered to exclude secondary etiologies. Testing for Wilson's disease should be performed in all patients presenting with dystonia before the age of 50 years or regardless of the age of the patient, even more so if there are suspicious associated clinical features (liver disease, psychiatric symptoms, dysarthria, etc.). This evaluation should include serum ceruloplasmin (falsely negative in ~5% of cases), ophthalmology consultation with slit lamp exam to assess for Kaiser–Fleisher rings (present in almost all patients with neurological symptoms and/or signs), and a 24-h urine collection for copper may be considered.

A levodopa trial for possible DRD is strongly recommended in early-onset patients, patients with a progressive 'cerebral palsy' phenotype, and those with a family history of dystonia and/or parkinsonism. Even in older patients, this diagnosis should be kept in mind and a therapeutic trial of levodopa should be considered in patients with diurnal fluctuations.

Complementary investigations depend on the clinical findings and are performed when indicated. For example, a metabolic work-up should be performed in a child with dystonia and episodes of metabolic decompensations in order to rule out or in, among other diseases, organic aciduria (e.g., methylmalonic aciduria, proprionic aciduria).

Management

As noted, in patients with suspected DYT1 dystonia as well as in any young patient with dystonia, a levodopa trial should be considered. Patients with DRD will improve dramatically with a low dose of levodopa, usually within a few weeks.

The mainstay of treatment of generalized dystonia not due to DRD (e.g., DYT1 dystonia and non-DYT1 primary dystonia) consists primarily of oral medications, although more recently surgical intervention is being started earlier. Anticholinergic medications, especially trihexyphenidyl, benzodiazepines, and lioresal are effective in treating dystonia. Double-blind studies are limited, however, with trihexyphenidyl constituting the best studied. In the pediatric population trihexyphenidyl may be well tolerated, even at high doses. The primary trihexyphenidyl trial used doses up to 30 mg/day, although higher doses are frequently used in children. In adults, the side effect profile may limit the dose and cause intolerable side effects before any benefit occurs. The dose of anticholinergic agents are titrated up until efficacy or until undesirable side effects occur, typically short-term memory loss, sedation, confusion, hallucinations, dry mouth, urinary retention, and constipation. While the peripheral anticholinergic side effects may improve with the addition of a peripheral procholinergic such as pyridostigmine, if cognitive side effects are primary, then the medication usually is decreased or discontinued.

Benzodiazepines, and especially clonazepam, are used in the treatment of dystonia, typically in combination with trihexyphenidyl, and with or without lioresal. The doses are increased gradually until efficacy is achieved. The principal side effect is drowsiness, although behavioral changes may also be prominent. Lioresal is also frequently used in the treatment of DYT1 dystonia, often in combination with trihexyphenidyl with or without clonazepam. The doses are increased until efficacy is obtained, undesirable side effects appear or the maximum recommended doses are achieved. The main side effects of this medication are sedation, confusion and drowsiness. If baclofen is not tolerated or ineffective, the dose should be tapered as sudden discontinuation can cause severe reactions, including seizures. If oral baclofen is effective but side effects are limiting the dosage used, it is possible to administer baclofen intrathecally, although this is usually reserved for patients with mixed spasticity and dystonia, as occurs in cerebral palsy. However, this mode of treatment is seldom used for primary dystonia, because patients with DYT1 dystonia respond so well to deep brain stimulation (DBS) of the globus pallidus interna.

Botulinum toxin injections are the treatment of choice for most focal dystonia. In the case of generalized dystonia, botulinum toxin may be used in certain problematic muscles if oral medications fail or produce a suboptimal response.

DBS is a relatively new treatment modality for movement disorders, and it is debated how early in the course of disease individuals should receive DBS. For dystonia, DBS electrodes are implanted in the globus pallidus internal segment bilaterally, and programming of the continuous electrical stimulation of these structures is done to optimize the response. DBS is been used in different type of movement disorders including Parkinson's disease, dystonia, tremor, and more recently tics (Tourette's syndrome). The region implanted and stimulated is different from one disease to another. Because of the possible serious although infrequent (1–2%) side effects (infection, stroke, intracranial hemorrhage, including fatal hemorrhage), this treatment modality is usually reserved for patients who failed medical therapy. DBS has been shown to be very effective in patients suffering from DYT1 dystonia, although a recent study suggests that the response for primary dystonia is excellent even among non-DYT1 individuals.

Supportive treatment is also of importance, including physiotherapy, exercises programs, psychological support for the patient and family. Genetic counseling is also suggested. The later is often challenging because of the low penetrance of this condition. Even though the risk of carrying the mutated gene is 50% for the patient's relatives (parents, siblings, offsprings), as much as 60–70% of

carriers will not develop the condition. In rare instances, a de novo mutation will be responsible of a patient's disease and in this particular case, only the patient's offsprings are at risk to carry the mutated gene and to possibly develop the disease. The variable expressivity of this disease adds further complexity to the genetic counseling; an asymptomatic patient may have a child with severe generalized dystonia and a patient with symptomatic generalized dystonia may have a completely asymptomatic child carrying the mutated gene. In the same line of thought, genetic testing for asymptomatic individuals with a family history of DYT1 dystonia remains a difficult dilemma because there is no presymptomatic treatment available. It is well accepted that genetic testing of an asymptomatic adult individual can be performed after a counseling session, but genetic testing for an asymptomatic child (younger than 18 years) is not recommended. Finally, prenatal diagnostic testing and preimplantation diagnostic testing is available.

Prognosis

DYT1 dystonia has a different evolution depending on the initial affected body part. In most patients presenting with dystonia of a leg, there is typically an evolution to a generalized dystonia over several months to years. On the other hand, in patients presenting with dystonia of an upper extremity, the progression is more variable and only about 50% evolve to a generalized dystonia. The rare patients presenting with dystonia of the neck or cranial muscles have also a variable progression. In general, 60–70% of patients with DYT1 dystonia progress to a generalized or a multifocal dystonia. Approximately 20% of DYT1 dystonia patients remain with a focal dystonia; and these are usually those who presented with writer's cramp. Finally, life expectancy in DYT1 dystonia is normal unless complications occur.

See also: Dystonia; Dystonia in Amish-Mennonite and Mennonite Families; Dystonia, Secondary; Dystonia, Task-specific; Dystonia, Traumatic; Dystonic Storm; DYT2, Autosomal Recessive Generalized Dystonia; DYT4, Autosomal Dominant Type Dystonia or Whispering Dysphonia; DYT5; DYT6, Mixed Phenotype Primary Dystonia; DYT7, Autosomal Dominant Focal Dystonia; DYT11, DYT15, Myoclonus-dystonia; DYT12, Rapid Onset Dystonia-parkinsonism; DYT13, Cranio-Cervical-Brachial.

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www.ncbi.nlm.nih.gov – National Center for Biotechnology Information.
www.wemove.org – Worldwide Education and Awareness for Movement Disorders.

DYT2, Autosomal Recessive Generalized Dystonia

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Glossary

Germinal mosaicism – It is a special form of mosaicism, where some gametes (sperm cells or oocytes) of the same individual carry a specific mutation but the rest do not. The cause is usually a mutation that occurred in an early stem cell that gave rise to all or part of the gonadal tissue. Germinal mosaicism can result in some children who are gene carriers not being affected even for a dominant disease with complete penetrance.

Pseudodominance – When an autosomal recessive condition appears in subsequent

generations, and so therefore appears to follow an autosomal dominant pattern. This usually occurs in inbred populations where there is a high frequency of an autosomal recessive founder mutation.

Definition and History

Since the 1960s there is accumulating evidence that most familial primary generalized dystonias are inherited in an autosomal dominant fashion with decreased penetrance and variable expression.

The occurrence of autosomal recessively inherited primary generalized dystonia has been and still is a matter of debate. The denomination DYT2 is reserved now for those families with suspected autosomal recessive inheritance with primary dystonia syndromes. So far, only a few cases have been described. Unfortunately, follow up data and examination of other first degree relatives, brain imaging, levodopa trial, and exclusion of the now known loci for primary dystonias and other disorders are lacking in many reports. This is important, in view of the history of DYT1, in which an autosomal dominant gene with decreased penetrance and variable expression including very mild 'formes frustres' of the disease, was mistakenly described as autosomal recessive for years.

A comprehensive review by Eldridge of the torsion dystonias from 1970 made the distinction between autosomal recessive and dominant inheritance on the basis of clinical observations in large families. Eldridge proposed that the recessive form would affect patients of Jewish ancestry and affected parents or offspring in Jewish families were explained by pseudodominance. Studies of families in the United Kingdom also supported this hypothesis. However, in the following years, studies from Israel showed that familial cases had affected relatives in other generations and there were too many affected relatives without a significant increase in parental consanguinity to support such autosomal recessive inheritance. Inheritance appeared dominant with decreased penetrance and for the first time, a founder effect was suggested to account for the increase prevalence among Ashkenazi Jews. Linkage analysis assigned DYT1 to chromosome 9q32–q34. The mutated gene (*DYT1*) and the affected protein (torsinA) were identified in 1997. So far, linkage analysis and in some cases gene identification have been described for other primary dystonias, most of them inherited in autosomal dominant fashion (DYT6, DYT7, DYT13). Only one dystonia gene inherited in autosomal recessive fashion has been identified to date, the gene coding for tyrosine hydroxylase that causes dopa-responsive dystonia. However this is a dystonia-plus syndrome rather than primary dystonia, as parkinsonism, hyperreflexia and impaired cognition may be present.

The reported cases in the literature of presumed autosomal recessive primary idiopathic torsion dystonia will be reviewed here. The described cases in Ashkenazi Jews prior to linkage analysis of DYT1 were excluded.

Pathogenesis and Pathophysiology/ Clinical Features and Diagnostic Criteria

Gimenez-Roldan reported in 1976 and 1988 a total of nine cases of childhood onset dystonia, from four families of Spanish Gypsy ancestry. Three of the families had known parental consanguinity and parents and other relatives were unaffected. Most patients had lower limb onset with rapid progression to a wheelchair-bound condition without other neurological features and normal cognition. Almost all patients evolved to have cranial involvement, and many had unintelligible speech by late adolescence. All cases had normal copper studies and unremarkable pneumoencephalograms. One family was however atypical, with predominantly orofacial involvement and postural and action myoclonus of the upper extremities, which while it could represent primary dystonia, most likely had myoclonus-dystonia (see DYT11 and 15 chapters).

A family described by Santangelo in 1934 is often cited as the first report of autosomal recessive inheritance of primary torsion dystonia. Three out of five children from first cousin consanguineous parents of Italian Catholic descent were affected with generalized dystonia in childhood. However, in detail review of Santagelo's cases, the three affected members also had mental retardation, cranial nerve abnormalities, especially oculomotor disturbances including oculogyric crisis, raising the question of another etiology rather than primary dystonia.

A report from Mexico in 1984 describes three out of five affected siblings of unaffected unrelated non-Jewish parents who developed in childhood limb onset dystonia that evolved to generalized dystonia. Despite normal intelligence, central facial paresis, ptosis, supranuclear gaze palsy, and hyperreflexia were present. Liver function tests and CT scan of brain were normal in the affected members. The patients were then lost to follow up. While sometimes cited as consistent with DYT2, the additional features discount the diagnosis of primary dystonia. In another family containing three affected sibs from South Africa, the diagnosis of primary dystonia is questionable in at least one subject who had hemilateral pyramidal signs after bacterial meningoencephalitis as an infant. Other sibling had intermittent blepharospasm and lateral ocular deviation in addition to generalized dystonia. These individuals were

tested only for serum copper and ceruloplasmin levels. There was no known parental consanguinity although the family was part of an isolated inbred community.

The most recent and better documented cases include a Sephardic Jewish kindred from Iran and pair of siblings of Chaldean Babylonian descent from Northern Iraq. Kahn et al. described the three affected children from first cousin parents with normal birth histories and developmental milestones, who had onset of lower limb and trunk dystonia in childhood that spread to involve craniofacial, bulbar, and cervical muscles. They were of normal intelligence and no other neurological manifestations were described. They had a comprehensive work up that included copper and other metabolic studies, cerebral imaging, and genetic testing for DYT1, screening for epsilon-sarcoglycan mutations, spinocerebellar ataxias (SCA) 2,3,6,7; dentatorubral-pallidoluysian atrophy (DRPLA) and mitochondrial point mutations. There was no significant response to alcohol or levodopa.

Moretti et al. described a brother and sister born to consanguineous parents of Chaldean Babylonian Iraqi descent. The dystonia began in the leg and spread to involve all extremities and the trunk years and was unresponsive to levodopa. Copper studies, plasma amino acids and urine organic acids, brain imaging and blood cell lysosomal enzyme panel were normal and they did not posses the DYT1 mutation. Partial response was obtained with baclofen and benzodiazepines.

Differential Diagnosis/Diagnostic Work-up and Tests

Thus in summary, the families who meet the clinical phenotype of primary torsion dystonia include some of the Spanish gypsy families, the Sephardic Iranian and the Chaldean Iraqi sib pairs. Only the latter two families had extensive genetic testing. While the inheritance pattern suggests autosomal recessive disease, dominant inheritance with reduced penetrance, new mutations and germinal mosaicism cannot be excluded. Determining that these conditions are truly autosomal recessive will only be possible when the specific genes have been identified.

The most frequent etiology for dystonia inherited in an autosomal recessive manner is dystonia due to metabolic causes. In these cases, dystonia is not usually the sole feature and other neurologic features are often present. In all cases of childhood onset dystonia, structural etiologies must be ruled out with brain imaging. Detailed birth, developmental history, and physical examination should guide other biochemical studies such as serum amino acids and urine organic acids. All cases suspected to have a primary dystonic disorder should undergo a levodopa trial (and potentially cerebrospinal fluid (CSF) measurements of catecholamine and tetrahydrobiopterin levels) to exclude dopa-responsive dystonia. Genetic testing is available for both GCH1 and tyrosine hydroxylase mutations, although at this time, mutations are not identified in all families. Serum copper, ceruloplasmin levels and neuroophthalmological evaluation to assess for Wilson disease should be performed also in all patients with early onset dystonia of unknown etiology, especially if the pedigree suggests autosomal recessive inheritance. Testing for the GAG deletion of *DYT1* gene is advised even if the pedigree suggests recessive inheritance.

Management/Prognosis

There is ongoing debate on the existence or homogeneity of autosomal recessive primary torsion dystonia, and clearly, more data and larger families in which linkage analysis can be performed are needed. Most primary generalized dystonias are dominantly inherited; it is to date unclear if of the few, when confirmed, recessively inherited primary dystonias represent the same single disease in all reports, phenocopies or other known conditions including dominantly inherited primary dystonias, or rare different conditions.

In view of this confusion, it is prudent to treat these patients as having primary torsion dystonia with the available arsenal of antispasmodic agents, including a levodopa trial, and consideration of oral agents including anticholinergics, lioresal, and benzodiazepines. Chemodenervation and deep brain stimulation surgery may be considered in certain refractory cases.

See also: Basal Ganglia; Dystonia; Dystonia: Animal Models; DYT1; DYT4, Autosomal Dominant Type Dystonia or Whispering Dysphonia; DYT5; DYT11, DYT15, Myoclonus-dystonia; DYT12, Rapid Onset Dystonia-parkinsonism; Ramisectomy; Wilson's Disease.

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http://www.dystonia-foundation.org – Dystonia Medical Research Foundation.

DYT3, X-linked Dystonia-parkinsonism (Lubag)

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Definition and History

X-linked dystonia-parkinsonism (XDP) or 'Lubag' afflicts primarily adult Filipino men, and rarely women. It was first described in the 1970s and is believed to have originated ancestrally in the Philippine island of Panay through a founder mutation some 50 meiotic generations ago (1–2000 years ago). In the local dialect, 'Lubag' describes intermittent twisting or posturing, whereas 'Wa-eg' and 'Sud-sud' refer to sustained postures and shuffling gait respectively.

Pathogenesis/Pathophysiology

Genetics

The gene locus (DYT3) was narrowed to a 350-kb candidate region at Xq13 between markers DXS559 and DXS6673E3′. The segregating XDP haplotype consists of the following allele sizes: 200 at DXS7117; 136 or 138 at DXS6673E3′; 150 at ZNF261; 292 at DXS10017; 140 at DXS10018; 240 at DXS559, and 114 at DXS1124.

In 2003, Nolte and Müller reported that the disease gene in Lubag was a multiple transcript system (MTS) within the XDP critical region, and is composed of several of the 38 known TAF1 (TATA-box binding protein-associated factor 1) exons and an additional 5 of the then-unknown exons that lie 3′ of TAF1 exon 38. They described five disease-specific single-nucleotide changes (DSCs), specifically DSC 1, 2, 3, 10, and 12, as well as a 48-bp deletion within this MTS unique to XDP.

Using genomic sequencing analysis followed by expression analysis of XDP brain tissues, Makino et al. recently reported a disease-specific short interspersed nuclear element, variable number of tandem repeats, and Alu composite (SVA) retrotransposon insertion in an intron of the TAF1 gene, with significantly reduced expression of TAF1 and the dopamine receptor D2 (DDR2) gene in the caudate nucleus of XDP patients.

Whether an abnormal protein gene product results from the mutation in DYT3/TAF1 is unknown. Nolte and Müller hypothesized that the DYT3-specific sequence changes could contribute to the disease by influencing splicing of transcripts. Makino et al. suggested that the SVA retrotransposon insertion into the TAF1 gene may cause XDP by altering expression of TAF1 isoforms (including the neuron-specific TA14–391), possibly through DNA methylation alterations. The decreased expression of the TA14–391 isoform (and possibly other TAF1 isoforms) in XDP brains may result in transcriptional dysregulation of many neuronal genes, including DRD2.

Neuropathology

The earliest neuropathological report in one Lubag patient with dystonia-parkinsonism described neuronal loss and multifocal mosaic pattern of astrocytosis in the caudate and lateral putamen. We later confirmed the

mosaic pattern of striatal gliosis, but further noted that the gliotic patches showed dorsal to ventral, rostral to caudal, and medial to lateral gradients. The caudate was more affected than the putamen, and the caudate head was more affected than the tail. The patchy areas of striatal gliosis were not associated with microglial activation. With synaptic immunostaining, we observed that the patchy areas of gliosis corresponded with the areas of poor synaptophysin staining, suggesting that the patchy gliosis represents synaptic loss rather than neuronal loss.

Goto et al. in 2005 elegantly described their neuropathological findings on 7 XDP patients. Postmortem analyses of the basal ganglia based on striatal compartments (i.e., the striosomes and the matrix compartment) showed that in the XDP neostriatum, the striosomes are severely depleted while the matrix component is relatively spared. Thus, they proposed that the disproportionate involvement of the neostriatum striosomal compartments and their efferent projections may be responsible for dystonia in XDP.

Epidemiology and Risk Factors

More than 500 cases of Lubag have been described in literature. The prevalence is 5.24 out of 100 000 in the Panay Islands, with the highest rate of 18.9 out of 100 000 in the province of Capiz. The prevalence in the Philippine general population is estimated at 0.34 out of 100 000. The male to female ratio is 99:1. The range of age at onset is 12–64 years (mean = 39.48 years). In women, the age of onset is older (mean = 52 years; range = 26–75 years). The time from onset of dystonia to generalization ranges from 1 to 23 years (mean = 3.8 years). A family history is positive in only 94% of cases.

Clinical Features and Diagnostic Criteria

Initial Symptoms

Traditionally, based on clinical history, the presenting symptom was thought to be consistently dystonia. On longitudinal follow-up of our cohort of genetically confirmed XDP carriers, the initial presenting sign is almost universally parkinsonism. Breakdown of rapid alternating limb movements can often be appreciated on careful neurological examination in early symptomatic (or soon to be symptomatic) XDP carriers.

Tremor

Tremor, either at rest or action, can be seen in the early stages or develop later in the disease. An asymmetric limb 3–6 Hz rest tremor can be observed similar to Parkinson's disease (PD). Some patients may also have a coarse, relatively symmetric upper limb or head tremor similar to essential tremor (ET). Thus, Lubag can be misdiagnosed as PD or ET. The tremor can also involve the trunk, craniofacial region (lips, jaw, or mimetic muscles), and larynx.

Parkinsonism

Lubag patients may present predominantly with one or more parkinsonian features, including rest tremor, bradykinesia, rigidity, or postural instability. Shuffling gait, in the absence of lower limb dystonia, can be quite severe. Some patients may remain with pure parkinsonism and no dystonia for many years. In some, the dystonia develops very late in the course, and is usually focal or segmental. Some patients with parkinsonism may be levodopa responsive. The parkinsonism often persists till death, though overshadowed by dystonia.

Dystonia

The dystonia develops focally, most commonly in the jaw, neck, trunk, limbs, eyes, and larynx in that order. Individuals who have dystonia progressing to a segmental or multifocal distribution within the first couple of years usually have a more rapid course. The most characteristic dystonia in male Lubag patients is jaw dystonia, more commonly jaw-opening than jaw-closing dystonia (**Figure 1**). Neck dystonia often develops, with retrocollis being more common than torticollis, laterocollis, or anterocollis. The retrocollis can be severe along with trunk hyperextension (**Figure 2**). Tongue dystonia may develop, manifesting as either involuntary tongue protrusion or limitation in voluntary tongue protrusion (**Figure 3**). Pharyngeal dystonia (with dysphagia) usually affects those with orolingual dystonia, and may lead to significant weight loss, aspiration pneumonia, or early death. Laryngeal dystonia with stridor can also lead

Figure 1 Male Lubag patient presenting with prominent jaw-opening dystonia, as well as cervical dystonia.

Figure 2 Male Lubag patient with severe retrocollis as well as trunk hyperextension dystonia.

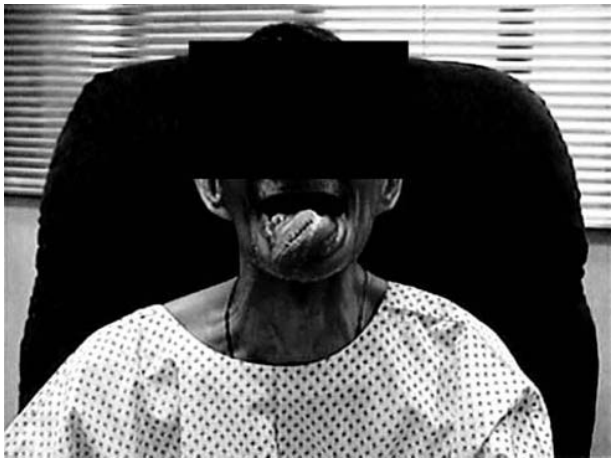

Figure 3 Male Lubag patient with severe tongue protrusion dystonia, drooling, and dysarthria.

to sudden death. Patients may present with vocalizations during inspiration or expiration. Sensory tricks are often observed, particularly those with cervical dystonia, blepharospasm, or jaw dystonia (**Figure 4**).

Other Phenotypes

Lubag can also present with pure tremor (similar to ET), chorea, athetosis, or myoclonus. The chorea usually involves the distal upper limbs with some athetosis. The chorea can also be seen with the generalized phasic dystonic movements. Action myoclonus can be present in the limbs or even the craniofacial region. The myoclonus may appear like a jerky tremor.

Phenotype in Women

Female XDP carriers are mostly asymptomatic. Rarely, women may present with focal dystonia of the neck or limb, which is nonprogressive and nondisabling. The other

Figure 4 Male Lubag patient in **Figure 1** with severe jaw-opening and cervical dystonia showing a 'sensory trick'. His jaw-opening and torticollis are partially and temporarily relieved by touching his chin.

phenotypes in women include chorea, focal tremor, or parkinsonism. The parkinsonism is usually mild, nonprogressive, and nondisabling. Rarely, severe levodopa-responsive parkinsonism can be observed.

Differential Diagnosis

With a clear-cut X-linked recessive pattern of transmission in a symptomatic Filipino adult male with parkinsonism-dystonia, and maternal roots from the Philippine Island of Panay, the diagnosis is almost certainly Lubag or XDP. However, some patients may have an atypical course, or may not have identifiable relatives with similar symptoms, or may have no traceable maternal roots from the Panay Islands. It is the latter set of patients that may be confused with PD, Parkinson's-plus syndrome, ET, or idiopathic dystonia.

Diagnostic Work-up/Tests

Laboratory Testing

No metabolic abnormalities occur in Lubag patients. A serum thyroid stimulating hormone (TSH) level may be reasonable to test for to rule out superimposed hypothyroidism. Serum or urine toxicologic studies are unnecessary since such have been completely normal in XDP patients.

Brain Imaging

We performed brain CT/MRI on 20 symptomatic genetically confirmed Lubag patients with parkinsonism plus varying severity of dystonia. None were deemed to have any significant striatal or brainstem atrophy, while some had age-appropriate generalized atrophy or some incidental ischemic white matter changes or scattered lacunes (due to vascular risk factors). In one patient, increased signal on T2-weighted images was seen at the outer rim of the putamen.

Fluorodeoxyglucose (FDG) positron emission tomography (PET) findings in three male XDP patients with dystonia-parkinsonism consisted of selective reduction in striatal glucose metabolism, but normal $\{^{18}F\}$ fluorodopa uptake, suggesting that the extrapyramidal manifestations are metabolically localized postsynaptically to the striatum. In a separate report, $\{^{18}F\}$ fluorodopa PET in an affected male with dystonia-parkinsonism showed reduced striatal uptake, consistent with presynaptic nigrostriatal involvement. We performed FDG-PET scans on 6 men with genetically confirmed XDP; four were symptomatic (2 had parkinsonism, and 2 had generalized dystonia-parkinsonism). The cranial PET scans showed nonvisualized bilateral putamina in all 4 symptomatic patients, and normal results in the 2 asymptomatic carriers. Brain CT/MRI revealed mild generalized atrophy in 3 of the 4 symptomatic patients, and normal results in 1 of 4. Thus, symptomatic Lubag patients may have putaminal abnormalities on FDG-PET scans even in early or mild disease despite normal brain CT/MRI.

We also performed single-photon emission computed tomography (SPECT) using $\{^{123}I\}\beta$-CIT (measures dopamine transporter density) in a male Lubag patient with generalized dystonia and levodopa-responsive parkinsonism. The SPECT scan showed reduced uptake in the putamen bilaterally similar to PD, but more symmetric and less pronounced.

Fluoropropyl-carbomethoxy-iodophenyl-nortropane (FP-CIT) SPECT scan in another male patient with multifocal dystonia and levodopa-responsive marked parkinsonism showed moderate decrease of putaminal dopamine transporter activity, thus suggesting a presynaptic nigral abnormality. This was further corroborated by evidence of hyperechogenic signals in both substantia nigrae on transcranial parenchymal sonography. The same patient also had on ^{123}I-iodobenzamide (IBZM)-SPECT scan decreased dopamine D2 receptor expression in both striata, suggestive of a dopamine postsynaptic defect.

Thus, by functional imaging, Lubag patients may have postsynaptic striatal involvement, or presynaptic nigrostriatal involvement. The first group may represent the majority of XDP patients with pure dystonia or combined dystonia-parkinsonism from the early stages, that are not levodopa responsive. The second group may represent the rarer patients with pure parkinsonism (with dystonia setting in late in the course), that appear to be more levodopa responsive.

Neurophysiology

We performed electromyography (EMG), somatosensory evoked potential studies, electroencephalography (EEG), blink reflex studies, and brainstem evoked potential studies on 10 symptomatic male Lubag patients with dystonia-parkinsonism. No abnormalities were noted. Surface EMG–EEG polygraphy was also performed. Those with a resting tremor had the same frequency of tremor (3–6 Hz) commonly seen in PD. Rarely, a slow 1–3-Hz distal limb tremor can be observed (myorrhythmia). The action/postural tremor in Lubag patients may range in frequency from 3 to 12 Hz. Two patients with myoclonus presented with brief EMG bursts (50 ms or less) that on back-averaging were time-locked to a premovement EEG surface-positive cortical potential localized to the somatosensory cortex, thus supporting the cortical origin of the myoclonus.

Olfactory Testing

We administered a culturally corrected University of Pennsylvania Smell Identification Test (ccUPSIT) consisting of 25 odor items to 20 symptomatic males with XDP and 20 control subjects matched by sex, age, educational background, smoking history, and geographical origin. The mean ccUPSIT score of Lubag patients (18 ± 3.19) was statistically lower ($p = 0.003$) than controls (20.5 ± 3.02). The small scores did not correlate with phenotype, severity of dystonia, or duration of disease. Nine of 20 Lubag patients (45%) had ccUPSIT scores below the mean, with the lowest score being 11. Our findings suggest that olfactory dysfunction may occur in Lubag patients even early in the disease.

Management

Pharmacologic Treatment of Dystonia

The most common symptom requiring treatment in Lubag patients is dystonia. When the dystonia is focal/segmental, anticholinergic agents (trihexyphenidyl or biperiden) plus benzodiazepines (particularly clonazepem) may be effective. Once the dystonia is multifocal or generalized, even polypharmacy offers only partial relief. In Lubag patients, zolpidem appears to have a robust effect on dystonia (some experience near 100% improvement of dystonia for a few hours) and a modest effect on parkinsonism. The effect may last 6–8 h per 10-mg dose in the first few weeks. Subsequently, the duration becomes progressively shorter, bottoming out at 2–3 h (corresponding to its 2.5 h elimination half-life).

Neuroleptics, particularly haloperidol, are often prescribed because of the relatively cheap cost and easy availability. However, its benefits in more advanced dystonia remains dubious, as it may lead to the extrapyramidal side effects. Risperidone seems less effective than haloperidol in controlling dystonic symptoms. Of the atypical neuroleptics, clozapine has the greatest potential to be effective. However, its use is limited by its potential to cause aplastic anemia. Tetrabenazine can improve dystonia in Lubag. Other drugs with inconsistent effects on in Lubag include gabapentin, topiramate, baclofen, and tizanidine. Botulinum toxin injections have benefited focal dystonia, particularly cervical dystonia, blepharospasm, tongue dystonia, and jaw dystonia. It can, however, worsen swallowing. Muscle afferent blocking injections using ethanol and lidocaine are much cheaper than botulinum toxin, and have been attempted in Lubag patients with cervical dystonia. They only offer very short clinical benefits (1–2 weeks), and are associated with undesirable side effects like severe pain during injections, and muscle fibrosis and contractures with repeated treatment.

Surgical Treatment of Dystonia

We reported the first successful deep brain stimulation (DBS) surgery in Lubag in 2007. The patient had parkinsonism and generalized dystonia, with severe disabling jaw-opening dystonia, drooling, dysphagia, and dysarthria. He only got partial relief with a combination of levodopa, piribedil, trihexyphenidyl, and zolpidem. The patient had a remarkable improvement of his generalized dystonia and parkinsonism after bilateral pallidal DBS, with sustained benefits 4-year post-DBS.

Prognosis

The clinical course in men with Lubag is highly variable. Those with pure parkinsonism with little or no dystonia have the best prognosis; they have nondisabling and slowly or nonprogressive symptoms. Those who develop a combination of parkinsonism and segmental dystonia in the orobuccolingual and cervical distribution early in the course (first year or two) have the worst prognosis. Such patients develop multifocal or generalized symptoms from the second to fifth years, become bedridden quite rapidly, and die prematurely from aspiration pneumonia, laryngeal stridor, or intercurrent infections resulting from being bedridden. Symptomatic women usually have a benign nonprogressive course with mild symptoms.

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See also: Dystonia; DYT1; DYT2, Autosomal Recessive Generalized Dystonia; DYT4, Autosomal Dominant Type Dystonia or Whispering Dysphonia; DYT5; DYT6, Mixed Phenotype Primary Dystonia; DYT7, Autosomal Dominant Focal Dystonia; DYT11, DYT15, Myoclonus-dystonia; DYT12, Rapid Onset Dystonia-parkinsonism; DYT13, Cranio-Cervical-Brachial.

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DYT4, Autosomal Dominant Type Dystonia or Whispering Dysphonia

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Glossary

Dystonia – Cocontraction of agonist and antagonist muscles resulting in abnormal postures or repetitive movements.

Spasmodic dysphonia – A focal form of dystonia, associated with involuntary spasms of the vocal cords causing interruptions of speech and affecting the voice quality. It may be 'ab'ductor, with cords pulling outward, which often results in a breathy, whispery voice, 'ad'ductor, whereby the cords pull in causing breaks and a more staccato speech, or mixed abductor and adductor.

Definition and History

A large Australian family was described in 1985 by Parker et al. and subsequently by Ahmad et al. Twenty definitely affected family members through five generations were reported. Whispering dysphonia, frequently misdiagnosed as psychogenic in nature was the presenting feature in many members, acquiring the name 'hereditary whispering dysphonia'. In addition to dystonia, which is generalized in many cases, there was life threatening dysphagia in two, and early onset progressive dementia and behavioral disorders were also present in some members. A pair of siblings with indistinguishable phenotype from their other relatives had laboratory and clinical systemic evidence of Wilson's disease; however, linkage analysis excluded the Wilson's disease locus in other family members. The loci for DYT1, DYT6, and DYT7 were also excluded in these patients.

Pathogenesis and Pathophysiology

Because parent child transmission was noted in many members in five generations (although in 17 out of 20 cases, it was maternal), and there was male to male transmission, this suggested autosomal dominant inheritance with high penetrance. As mentioned above, in 1999, linkage analysis excluded the known loci of DYT1 ('early-onset dystonia'), DYT6 ('intermediate onset dystonia'), and DYT7 ('adult-onset dystonia'). Unfortunately, no other similar families have been described to date with similar phenotype, and specific genotype information is lacking. The pathophysiology of this type of generalized dystonia is unknown, but dysfunction of the basal ganglia or their pathways is suspected, as in other primary dystonias. Evidence of dysfunction of copper metabolism in two affected members may explain the disease in those two individuals, but normal biochemical status despite penicillamine therapy in the other relatives makes this explanation uncertain. The rostro-caudal spread of symptoms and prominent bulbar features is also suggestive of rapid-onset-dystonia-parkinsonism (RDP, DYT12). No reports suggest that testing for this condition was ever performed.

Clinical Features and Diagnostic Criteria

The Australian family described was of non-Jewish English origin and had no known consanguinity. Age of onset ranged between late childhood and early adulthood with most patients expressing the disease in their twenties. In all but three patients, dystonia affected speech first. Out of the three patients who did not have speech onset, two had torticollis and one obligate carrier had questionable foot and axial dystonia. Most living patients at the time of the report had mild focal or segmental dystonia.

In the original description of this family, choreiform involuntary movements are described in the older generations, and there was a consideration of an atypical Westphal variant of Huntington's disease. Sustained involuntary postures suggestive of torsion dystonia were more evident in the younger generation.

One case described at length in Parker et al. had onset of dystonia as transient torticollis and spasmodic dysphonia. In addition, he had low IQ and reported deviancy. His mother, who died young at an age of 43 of pneumonia, was thought to have Huntington's disease because of choreiform movements heralded by whispering dysphonia since early adulthood and early progressive dementia with features of aggression and mood disorders that lead to several suicide attempts. Another relative who died prior to the introduction of neuroleptic agents is also described with early onset dementia, no audible speech, and 'champing' movements of the jaw. Her daughter also developed a mood disorder followed by chorea and progressive dementia in her forties, but she received antipsychotic therapy.

Interestingly, a pair of siblings presented with hemolytic anemia, persistently abnormal liver function tests, and thinning of bones. Biochemical testing and liver biopsy confirmed Wilson's disease. Ataxia, labile mood, and severe dystonia followed the systemic manifestations including severe dysarthria and a sardonic smile. Other affected relatives did not have biochemical evidence of copper metabolism dysfunction.

Differential Diagnosis and Diagnostic Work-up/Tests

As with the other forms of dystonia, especially when presenting with craniobulbar and psychiatric symptoms and in view of the sibling pair mentioned earlier, Wilson's disease must be ruled out with appropriate biochemical and pathologic studies.

Presence of early-onset progressive dementia and mood and behavioral disorders is highly unusual for other primary dystonic disorders. However, it is relatively common for some neurodegenerative conditions such as Huntington's disease or panthotenase-kinase associated neurodegeneration (PKAN). Magnetic resonance imaging will show structural etiologies and iron accumulation. Genetic testing with appropriate counseling for Huntington's disease in individuals with dystonia, mood disorders, and cognitive decline may be considered.

There is no confirmatory test for this particular and rare condition. No specific imaging abnormalities were reported.

Management/Prognosis

Penicillamine therapy provided only minimal improvement in the siblings with documented Wilson's disease. Dopaminergic as well as chelation therapy was ineffective in other affected family members. One patient who was bedridden with generalized dystonia had marked improvement following stereotactic thalamotomy, but within a few years, her symptoms of leg and neck dystonia returned.

The prognosis in many of the reported subjects was of relatively rapid progression at onset followed by stabilization, with the exception of the affected members with progressive rapid dementia or severe dysphagia.

This family represents the first evidence for the now known locus heterogeneity for autosomal dominant inherited idiopathic torsion dystonia. However, the presence of two members with documented Wilson's disease and other members with progressive early-onset dementia and severe behavioral abnormalities may suggest neurodegeneration or an alternative etiology rather than a primary dystonia syndrome.

See also: Dystonia; DYT1; DYT5; DYT6, Mixed Phenotype Primary Dystonia; DYT7, Autosomal Dominant Focal Dystonia; DYT11, DYT15, Myoclonus-dystonia; DYT13, Cranio-Cervical-Brachial; Huntington's Disease; Spasmodic Dysphonia: Focal Laryngeal Dystonia.

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Relevant Websites

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DYT5

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Glossary

Diurnal fluctuation – Improvement in the morning after sleep and deterioration at night.

Drug-induced dyskinesias – Hyperkinetic abnormal movement disorder as a side effect of medication(s).

Dyskinesia – Hyperkinetic abnormal movement disorder classically characterized by choreic movements, although the term can comprise the range of hyperkinesias including tics, dystonia, myoclonus, chorea, and tremor.
Dystonia – Dystonia is characterized by sustained twisting and posturing movements. Contractions of agonist and antagonist muscles cause these involuntary repetitive movements or abnormal postures.
Generalized dystonia – Dystonia involving both legs (or one leg and the trunk) and at least one other body region.
HUGO (Human Genome Organization) – An international organization of scientists promoting international collaboration within the Human Genome Project.

Definition and History

Dystonia is a syndrome characterized by sustained muscle contractions, producing twisting and repetitive movements or abnormal postures. The movements tend to be directional in nature. Dystonia can be classified as primary or secondary. In primary dystonias, dystonia is the only neurologic feature (except tremor, which may also be present). There is no laboratory or imaging data to suggest an acquired or degenerative cause, there is no sustained response to levodopa, and there is no history implicating an environmental, structural, or pharmacologic cause. An example of primary dystonia is DYT1 or Oppenheim dystonia. Secondary dystonias, on the other hand, are characterized by neurologic features in addition to dystonia and/or by the presence of a secondary etiology (acquired forms of dystonia). Dystonia related to metabolic disorders, heredodegenerative diseases, mitochondrial disorders, and toxic environmental exposures often show abnormalities of the basal ganglia on neuroimaging. However, patients with some secondary dystonias have normal neuroimaging. In this latter category are several rare disorders termed 'dystonia-plus' syndromes, which are caused by genetic defects that result in dystonia in association with another movement disorder. The dystonia-plus syndromes include dopa-responsive dystonia (DYT5), myoclonus-dystonia (DYT11) and rapid-onset dystonia and parkinsonism (DYT12).

DYT5 dystonia is classified in the dystonia-plus category, as it may be associated not only with dystonia and tremor but also with parkinsonism, spasticity, and hyperreflexia. It is commonly known as dopa-responsive dystonia because of its very dramatic response to low-dose levodopa. The condition was first described by Segawa in 1970, who reported about several girls with childhood onset dystonia with diurnal fluctuations and good response to levodopa, and hence is known as Segawa's disease. While most DYT5 dystonia is autosomal dominant (AD) GTP cyclohydrolase 1 deficient dopa-responsive dystonia (DYT5a), rarer autosomal recessive (AR) forms have also been identified (DYT5b). The HUGO designation DYT14 was given to a form of dopa-responsive-dystonia (DRD), which is actually due to DYT5, therefore DYT14 is no longer used, and DYT14 dystonia should be considered DYT5.

Pathogenesis/Pathophysiology

DYT5 is usually inherited in an AD fashion, and caused by mutations of the *GCH1* gene (DYT5a) encoding for the GCH1 enzyme (GTP cyclohydroxylase 1). GCH1 catalyses the first and rate-limiting step in the synthesis of tetrahydrobiopterin (BH4). BH4 is an essential cofactor for the enzymes phenylalanine hydroxylase and tyrosine hydroxylase (TH), which convert phenylalanine to tyrosine and tyrosine to levodopa, respectively. TH is the rate-limiting step in the synthesis of dopamine. It is important to note that, GCH1 activity is reduced in peripheral cells in GCH1 mutation carriers without disease, and the correlation between GCH1 activity and development of dystonia and/or parkinsonism is poorly understood. Because the penetrance is markedly increased in girls and women (3–4:1 compared to men and boys), it is assumed that activity may be modulated by gender specific factors, although this has not been definitively demonstrated. BH4 is also a cofactor for the aromatic amino acid tryptophan hydroxylase (which is responsible for the conversion from tryptophan to serotonin), as well as nitric oxide (NO) synthase, although the role of serotonin and NO in the DRD phenotype is not clear.

No nigral cell loss is demonstrated in brains of DYT5 patients, and no Lewy bodies are detected, however, neurochemical analysis shows striatal dopamine reduction which is thought to be due to both decreased TH activity from low BH4 as well as to loss of striatal TH protein, possibly by lack of regulation of BH4 on TH.

AR forms of dopa-responsive-dystonia (DYT5b) also exist, although these are rare. TH deficiency is inherited in an AR manner. TH is the enzyme catalyzing the first and rate limiting step in the synthesis of catecholamines (dopamine, norepinephrine, and epinephrine). It is responsible for the conversion of tyrosine into dopa, the precursor of dopamine.

Epidemiology/Risk Factors

The prevalence of DYT5a mutation is ~0.5 individuals per million in England and Japan. It has been described in

diverse ethnic groups, and no strong founder mutation is reported. Spontaneous mutations may be common, while AD mutations of the *GCH1* gene have an incomplete sex-related penetrance. Penetrance is increased in girls and women compared to boys and men, giving a female to male ratio of ~3–4:1.

Clinical Features and Diagnostic Criteria

DYT5a: GCH1 Dopa-Responsive Dystonia

GCH1 typically presents in childhood from age 1 to 12 (mean age is ~6 years). Children often develop early toe walking, and may have flat feet. Leg dystonia (equinovarus posture) causes gait difficulties and a tendency to fall. The hallmark of this disease is the diurnal fluctuation. Patients are typically better after sleep in the morning, and their symptoms are worse at night. If they are not treated, they experience a gradual progression of their dystonia, and this can lead patients to be wheelchair bound until treatment with levodopa is initiated. The dystonia typically remains more severe in the lower extremities, although trunk and arms (and less often, cervical muscles) may become involved. With progression, the diurnal fluctuation becomes less prominent. Patients may have brisk deep tendon reflexes in the lower extremities, ankle clonus and striatal toe (i.e., dystonic extension of the big toe). Unlike TH deficiency (DYT5b), cognition is normal. Some patients develop parkinsonism in addition to the dystonia, with tremor (either postural or rest) and sometimes postural instability. Dramatic and sustained response to low doses of levodopa is characteristic. It is important to note that these patients do not usually develop long-term motor fluctuations which occur in young-onset parkinsonism, although dose-dependent dyskinesias which improve with lower doses may occur.

DYT5a can also present in older patients; they may develop parkinsonism in isolation or with mild dystonia, for example, writer's cramp. Rarely DRD can present in adult patients with a focal dystonia (e.g., oromandibular, cervical, etc.).

There is a wide intra and interfamilial variability in the clinical presentation. For example, within the same family, one member can have a typical DRD presentation with spastic and dystonic gait, while another may present with adult-onset parkinsonism responding dramatically to levodopa.

DYT5b: TH Deficiency

AR TH deficiency is a rare disease with a wide range of clinical presentation, from mild to severe. At the milder end of the spectrum, TH deficiency presents as dopa-responsive dystonia, possibly with diurnal variation. Patients at the other end of the spectrum have severe disease and present with infantile parkinsonism poorly responsive to levodopa, oculogyric crises, truncal hypotonia with appendicular hypertonia, severe global developmental delay, cognitive impairment, and ptosis.

Differential Diagnosis

DYT5 or DRD is usually due to AD GCH1 deficiency (DYT5a) and rarely due to AR TH deficiency (DYT5b). Compared to DYT5a, DYT5b is typically more severe and is not more common in females. Cerebrospinal fluid (CSF) pterins (biopterin and neopterin) are useful to differentiate these two conditions (see 'diagnostic work-up/tests' section below for more details).

AD sepiaterin reductase (SR) deficient DRD (very rare) is an early-onset disorder which may present similarly to DRD (see **Table 1**).

Allelic disorders of DYT5a are worth mentioning in the differential diagnosis, even if the clinical presentation is somewhat different. Patients with AR GCH1 deficiency typically present in the first 6 months of life with severe neurological dysfunction (seizures, developmental delay, mental retardation, truncal hypotonia, appendicular hypertonia, involuntary movements) and a BH4 dependent hyperphenylalanemia. The treatment of this condition includes BH4 as well as neurotransmitter replacement. Dystonia with motor delay is an intermediate disease between the AD and AR forms of GCH1 deficiency. The patients reported with this phenotype were compound heterozygotes. These patients present with motor delay, truncal hypotonia, and limb dystonia progressing to generalized dystonia without hyperphenylalanemia.

Other causes of dystonia are also important in the differential diagnosis, including primary dystonias, and especially DYT1 or dystonia musculorum deformans. Secondary causes of dystonia may also be considered, including early onset parkinsonism. Early in the presentation of PARK2, for example, dystonia may be the prominent feature. Although with PARK2, the onset is usually slightly older (see **Table 1**). Other syndromes with dystonia and parkinsonism include the rare, rapid-onset dystonia parkinsonism or DYT12, a condition differentiated from DYT5 by the abrupt onset of symptoms, but mainly by the absence or suboptimal response to levodopa, and the Westphal variant of Huntington disease. Additional secondary causes of dystonia include acquired (e.g., hypoxic–ischemic encephalopathy, dyskinetic cerebral palsy, kernicterus as well as basal ganglia stroke, hemorrhage, tumor, etc.) and inherited causes (e.g., Wilson's disease, organic acidurias, pantothenate kinase associated neurodegeneration (PKAN), Lesch Nyhan, etc.).

Another group of diagnoses to consider is the group of diseases causing gait disorders in the pediatric population such as spastic diplegia and hereditary spastic paraparesis. Spastic diplegia is a form of cerebral palsy occurring

Table 1 Differential diagnosis of dystonia responding to levodopa

	GCH1 (DYT5a)	*TH (DYT5b)*	*DYT1*	*PARK2 (Parkin)*[a]	*SR*
Inheritance	AD, reduced penetrance	AR	AD, reduced penetrance	AR[b]	AR
Gene	Heterozygous mutations in *GCH1* in many	Heterozygous mutations in *TH* (11p15)	Heterozygous GAG deletion in *DYT1*	Homozygous or compound heterozygous *parkin* mutations	Homozygous or compound heterozygous *SPR* gene mutations
Testing	Screening for *GCH1* in select laboratories	Sequencing/CSF	Commercially available	Screening for some *parkin* mutations in select laboratories	Commercially available molecular testing (sequencing)
Age of onset	6 years (infancy to 70s)	First decade	13 years (4–60s)	Adolescence (7–50s)	First decade
Initial presentation	Leg > arm or trunk action dystonia, gait dystonic, and often spastic with toe walking	Gait disturbance attributable to dystonia in leg, flexion-inversion of foot, cognitive impairment	Arm or leg action dystonia, occasionally trunk or neck	Foot/leg > hand/arm dystonia, rest tremor, akinesia/rigidity	Motor delay, truncal hypotonia and appendicular hypertonia, cognitive delay, oculogyric crises +/− bulbar involvement, dystonia, +/− parkinsonism, +/− chorea,
Diurnal fluctuation	Common	Yes	Rare	May occur but usually not dramatic	Yes
Bradykinesia	Yes (maybe mild)	Yes	No	Yes	Some patients
Postural instability	Yes	Variable	No	Yes	Some patients
Initial levodopa response	Excellent (low dose)	Variable, some nonresponsive, some complete	Inconsistent, and usually not dramatic	Excellent and low to moderate dose	Yes, may be incomplete
Long-term	Sustained (infrequent dyskinesias)			Dyskinesias often prominent, motor fluctuations	
CSF					
HVA	⇓	⇓	Normal	⇓	⇓
Biopterin	⇓	Normal	Normal	⇓	⇑
Neopterin	⇓⇓	Normal	Normal	Normal	
Others					⇑ Sepiapterin ⇓ 5-HIAA
F-DOPA PET	Normal		Normal	Abnormal	
Prognosis	Sustained excellent response, near-complete resolution in most	Generalization	Progression, then stabilization	Slow to moderate progression	Good response to levodopa and serotonin, although cognitive or motor limitations persist

[a]PINK1- and DJ-1, also cause early onset parkinsonism and may also present with dystonia – see these sections.
[b]The role of heterozygous *parkin* mutations is debated, although most likely such mutations are disease causing.
GCH1 = GTP cyclohydrolase 1; 5-HIAA: 5-hydroxyindoleacetic acid; SR: Sepiapterin reductase; TH = tyrosine hydroxylase; HVA = homovanillic acid; AD = autosomal dominant; AR = autosomal recessive.

typically in expremature infants. The imaging correlate is periventricular leukomalacia. The history of prematurity and complicated perinatal history, together with the typical toe walking gait with or without motor delay and the abnormal imaging help to differentiate this condition from DRD. Further, while there may be a delayed onset of movement disorders in cerebral palsy (CP), it does not worsen as untreated DRD does. Hereditary spastic paraparesis is differentiated mainly by the quality of the gait; spastic with circumduction instead of dystonic with posturing of the foot or feet. Moreover, patients with spastic paraparesis do not have the typical diurnal fluctuation present in DRD patients. When there is any doubt regarding the diagnosis, a trial of levodopa should be performed to confirm the presence or absence of DRD, a treatable disease.

Finally, as with other causes of dystonia, a psychogenic movement disorder remains in the differential diagnosis. However, many individuals with DRD have been mistakenly labeled psychogenic and not treated with L-dopa, and the diagnosis of DRD should be seriously entertained in patients with possible DRD.

Diagnostic Work-up/Tests

It is critical to take a careful family history for all forms of movement disorders in all patients. Detailed past and current medication history should also be ascertained to eliminate the possibility of a tardive syndrome (e.g., tardive dyskinesia secondary to neuroleptics or antiemetics).

Brain imaging is usually performed in order to eliminate other causes of dystonia. It is also useful to differentiate DYT5 from periventricular leukomalacia, which can present with spastic diplegia. In DYT5, the brain imaging is normal. SPECT and PET imaging may help distinguish DRD from early-onset PD (see **Table 1**).

Investigations for Wilson's disease are usually undertaken because it is a treatable disease: serum ceruloplasmin, ophthalmologic evaluation for Kayser–Fleischer rings, and 24 h urine collection for copper. Wilson's disease typically presents with liver dysfunction in the prepubertal child; the neuropsychiatric presentation is more typical of adolescent and adult patients. Other investigations for the secondary causes of dystonia (e.g., metabolic work-up including urine organic acids, uric acid, etc.) should be performed for patients where the diagnosis is unclear and if a specific condition is suspected (e.g., if there are episodic decompensations suggesting a diagnosis of organic aciduria such as methylmalonic aciduria, or if there are symptoms such as automutilation, suggesting a diagnosis of Lesch Nyhan, etc.).

CSF studies, and more specifically the CSF pterins (biopterin and neopterin) and catecholamine metabolites, may be helpful in the diagnosis of DRD. However, these investigations are available in only a few laboratories, and may be difficult to obtain. CSF homovanillic acid (HVA) is reduced in GCH1 and TH deficiency. CSF biopterin and neopterin are both reduced in GCH1 deficiency, but are normal in TH deficiency. In PARK2 (young onset parkinsonism due to mutations in the *parkin* gene), biopterin is reduced and neopterin is normal (see **Table 1**). As samples must be collected in special tubes, contacting the laboratory is imperative prior to performing the lumbar puncture.

Molecular genetic testing for *GCH1* gene mutations can be performed as it is available on a clinical basis for suspected symptomatic patients. Even in an asymptomatic individual at risk for this disease (e.g., a family member of a known case of DYT5), it is reasonable to consider molecular genetic testing. However, even if a mutation in the *GCH1* gene is identified, the individual will not necessarily develop the disease as it is only partially penetrant. Moreover, there is no way to predict which patients with the mutated gene will develop the disease and which patients will not. Further, mutation sequencing does not identify all individuals with DRD (the range is from 20 to 80%) although when screening for deletions and screening of promoter sequences is performed, the likelihood of identifying a mutation is increased.

Abnormal peripheral activity of liver phenylalanine hydroxylase demonstrated by the phenylalanine loading test has also been suggested to screen for DRD, but both false-positives and false-negative findings have been reported. Measurement of GCH1 enzyme activity in cultured fibroblasts may eventually help with diagnosis, but at this time it remains limited to a few labs.

Because of the potential false negatives with gene testing and phenylalanine loading, the diagnosis of DRD can be most reliably made by the dramatic and sustained reversal of symptoms with an empiric trial of low dose levodopa.

Management

The mainstay of treatment is with low-dose levodopa (combined with a decarboxylase inhibitor, either carbidopa or benserazide). The suggested initial doses are of $\leq$25 mg per day levodopa in children and 50 mg per day in adults. The adult initial dose can be increased by 50 mg every few days, until there is a dramatic response or up to 300–600 mg. The pediatric dose needs to be increased by smaller increments. While most patients will have a response to 300 mg of levodopa, infrequent patients respond better at higher doses. Some patients will experience early dyskinesias which subside with a dose reduction. The effective doses used to treat these patients are typically low, and patients will not develop long-term motor fluctuations such as wearing-off and dose-failures. Of note, all patients respond to levodopa, even if the treatment is delayed, although these patients may require higher dose and take longer to achieve benefit.

Prognosis

GCH1-deficient DRD, if appropriately diagnosed and treated, has a very good prognosis. In fact, these patients respond extremely well to low doses of levodopa; their response is sustained, and they do not develop motor fluctuations over time. The association between DRD and psychiatric features has not been well-established, although concerns about comorbid depression and anxiety have been raised, as BH4 is also a cofactor for the synthesis of serotonin from tryptophan.

In contrast to the excellent response to L-dopa in GCH1 deficient DRD, patients with TH deficiency may have a worse phenotype. Patients with the milder form typically respond well to levodopa. At the other end of the spectrum is the severe form of the disease with significant neurological dysfunction resulting in important impairments and for some patients in a reduced life expectancy. These children do not respond well to levodopa and may even not respond at all. Some of these patients will develop side effects of the levodopa therapy (e.g., gastrointestinal side effects and motor fluctuations, including dyskinesias).

See also: Basal Ganglia; Dopa-decarboxylase Inhibitors; Dystonia; DYT1; Fahn–Marsden Rating Scale; Geste Antagonistique; Levodopa.

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www.wemove.org – Worldwide Education and Awareness for Movement Disorders.

DYT6, Mixed Phenotype Primary Dystonia

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Glossary

Mixed phenotype – DYT6 was described as mixed, as it shared features with DYT1, early onset dystonia, particularly arm involvement, and early onset, as well as with adult onset dystonia and the prominent cranial and cervical involvement, which is infrequently seen in DYT1.

Primary dystonia – Dystonia is characterized by sustained patterned involuntary cocontractions of agonist and antagonist muscles resulting in abnormal postures and repetitive movements. Primary (torsion) dystonia is defined when dystonia is the only abnormality present, with the exception of tremor, and no known metabolic, structural, or toxic etiology is identified.

Definition and History

Since the 1960s, it has been demonstrated that most familial primary generalized dystonia primary torsion dystonia (PTD) is inherited in an autosomal dominant fashion with decreased penetrance and variable expression. Until the recent discovery of the DYT6 gene, only one gene for primary dystonia was known, DYT1, and only four loci for primary dystonia were mapped, including DYT7 and DYT13.

Almasy et al. mapped the DYT6 gene for PTD to chromosome 8p21–q22 in two apparently unrelated Amish-Mennonite families (M and C) who shared a haplotype of marker alleles across a 40 cM linked region. The identical haplotypes segregating with PTD suggested a common ancestor. Fifteen affected Amish-Mennonite family members were reported, and the dystonia was characterized by a relatively early but broad age of onset (mean 18 years, SD 10.9, range 5–38 years). The body regions first affected included the cranial muscles, neck, arm, and rarely the leg; almost all had some degree of progression of dystonia to other body regions, but this varied widely. In 2006, five additional members from the original families were characterized and contributed to the knowledge of the phenotype. In addition, three other multiplex Amish-Mennonite families were identified and tested for the known DYT6 haplotype and for recombination events. One of the three new families (Family R) carried the shared haplotype, whereas the region was excluded in the two other families, suggesting genetic heterogeneity for PTD in the Amish-Mennonites. Genotyping of additional markers in the DYT6-linked families revealed recombinations that placed the gene in a 23 cM pericentromeric region between markers D8S2317 and D8S2323 on chromosome 8.

In 2009, based on the Amish-Mennonite families (M, C, and R), Fuchs et al. reported that a mutation in the *THAP1* gene is responsible for DYT6 dystonia. They also showed that mutations in DYT6 are responsible for mixed phenotype dystonia in non-Amish Mennonite families.

Pathogenesis and Pathophysiology

DYT6 is inherited in an autosomal dominant manner with reduced penetrance and variable expressivity. The penetrance is estimated to be approximately 60%. While DYT6 is more common in women, it appears that the penetrance does not depend on gender.

In the three families of Amish-Mennonite origin, M, C, and R, a 5bp insertion/3bp deletion mutation resulting in premature termination of the THAP1 protein was discovered. In addition, the same mutation and disease haplotype was identified in additional family with more remote Amish-Mennonite ancestry supporting that this mutation is a founder mutation in this population. In addition, a different mutation, an exon 2 missense mutation was also identified in a German family without Amish-Mennonite ancestry. This suggests that *THAP1* plays a role in PTD families of diverse origins and is responsible for a portion of PTD in beyond those of Amish-Mennonite background.

The role of THAP1 in causing dystonia is not clear. THAP1 is a member of the recently described family of cellular factors sharing a highly conserved atypical zinc finger THAP domain. Through its DNA binding domain, THAP1 regulates endothelial cell proliferation. Analysis of the three-dimensional structure of the THAP domain from human THAP1 showed four Zn-binding residues participating in zinc finger formation, as well as a number of critical residues for DNA binding. Both the frameshift mutation in families M, C, and R, as well as the missense mutation in family Cr are likely to be sufficient to abolish the DNA binding activity of THAP1. The loss of DNA binding should cause transcriptional dysregulation, which is believed to affect downstream targets.

THAP1 has also been described to function as a nuclear proapoptotic factor, and in vivo, it interacts with prostate apoptosis response 4 protein (Par-4). Par-4 has been associated with programmed cell death in prostate cancer and neurodegenerative diseases, including Parkinson's disease. Par-4 may modulate also dopamine D2 receptor signaling. Several lines of evidence suggest that dystonia is associated with altered dopamine neurotransmission, and as such, THAP1 may also cause dystonia via dopaminergic dysfunction. However, in two cases treated with carbidopa/levodopa, there was no improvement of dystonia.

[18F]-Fluorodeoxyglucose PET studies are able to separate DYT1 subjects from DYT6 by network patterns. While both DYT1 and DYT6 manifesting carriers showed bilateral increases in the superior frontal gyrus, the precuneus and the inferior parietal cortex compared with nonmanifesting carriers, DYT6 carriers, irrespective of the presence of dystonia, had a decreased putaminal metabolism and temporal hypermetabolism. This is in contrast to the significant metabolic increases in the cerebellum seen in DYT1 carriers.

Clinical Features and Diagnostic Criteria

In the initial families described with DYT6 dystonia, the mean age of onset was 16.1 years (SD 10.0, range 5–38). In more than half, PTD began before age 16 years. Dystonia was most likely to start in an arm (46%); in 27%, first symptoms involved cranial muscles (larynx, tongue, facial muscles) and 22.7% had the onset in the neck. Unlike DYT1, the leg was rarely affected first (4%). Almost all had some degree of progression to other body regions, but final distribution varied widely. Two had focal dystonia,

eight had segmental dystonia, and 12 had generalized or multifocal dystonia involvement that included the leg. Despite the fact that half had leg involvement, only two required an assistive aid for mobility. Most had brachial dystonia (19/22), and in more than half (13/22) speech was affected. In most, the greatest disability derived from dystonia of the neck and cranial muscles. Speech difficulties were prominent. A greater percentage of affected individuals were female (68% vs. 32% male), and the age of onset did not vary by gender (female: mean 15.4 ± 9.0, male mean age onset 17.7 ± 12.33).

Recent discovery that DYT6 accounts for PTD in families other than those of Amish-Mennonite descent and that other mutations in addition to that seen in families M, C, and R cause dystonia, raises the question as to whether the phenotypic spectrum may be broader than previously realized. While there are only three exons in the *THAP1* gene, genotypic heterogeneity will make screening for *THAP1* mutations more arduous. Additional studies that evaluate similar familial or sporadic cases, as well as adult onset focal/segmental cases, will further determine the phenotypic spectrum associated with *THAP1* mutations.

Differential Diagnosis

The differential diagnosis for DYT6 dystonia includes inherited dystonia with prominent cranio-cervical involvement (DYT13, DYT7), as well as other forms of PTD with limb involvement (e.g., DYT1) and sporadic cervical dystonia. Secondary causes of dystonia are less likely, since this condition presents with isolated dystonia (with or without dystonic tremor, typically of the head); however, as it is a highly treatable disorder, Wilson disease should always be considered. If cervical dystonia is the sole feature, structural lesions that may result in head postures may also be considered. As with all other forms of early-onset dystonia, the dystonia-plus condition, dopa-responsive dystonia should also be kept in the differential.

In comparison with a group of Amish-Mennonites who did not show linkage to the region on DYT6, Amish-Mennonites harboring the DYT6 gene had earlier age of onset (16.1 vs. 46.9 years), and the dystonia was both less likely to be of focal distribution and unlikely to begin in the cervical muscles.

As previously noted, the prominence of cranio-cervical symptoms and high prevalence of speech abnormalities in DYT6 families differentiates this genetic form of dystonia from the characteristic prominent leg involvement and gait abnormalities of DYT1.

The DYT6 phenotype shares features to the Italian family members with dystonia mapped to the DYT13 locus on chromosome 1p. The age of onset is early (mean age 15.6, range 5–43) but also has a wide range, similar to DYT6. Similar to DYT6, the body regions first affected in DYT13 included the neck, cranial muscles, and arm. Few individuals had leg involvement and the disability from leg dystonia was mild. From the only 11 individuals described to date with DYT13, there appears to be less laryngeal involvement than in DYT6.

Diagnostic Workup/Tests

First, as it is the case for other types of dystonia, a careful and detailed history and examination should be performed to determine whether the dystonia is primary. This includes a careful medication history, including current and past exposure to neuroleptics and antiemetics to elucidate medication induced tardive dystonia. Because of the prominent oromandibular dystonia, as well as retrocollis in some cases, the phenotype may be similar to tardive dystonia. Further, a careful family history should be obtained. As this is an autosomal dominant disorder with reduced penetrance, in theory, apparently sporadic cases may harbor DYT6 mutations.

Since the DYT6 gene was only recently elucidated, no commercial testing for DYT6 exists at this time. However, it will likely not be long before such testing is available. Two caveats are important: (1) like DYT1, there is incomplete penetrance and variable expression, and hence, not all gene carriers will develop dystonia, and when they do, they may develop very mild dystonia or severely limiting dystonia. (2) Unlike DYT1, there are multiple mutations that are likely to account for DYT6 dystonia. This is more akin to DYT5 dystonia where a genetic test may be 'negative' yet the patient may harbor an identified mutation (which may be a deletion or a promoter sequence mutation). Genetic counseling, including discussing the ramifications of these two important issues, is strongly recommended.

For cases of suspected DYT6 dystonia, MRI of the brain should be considered. It is also prudent to consider the diagnosis of Wilson disease, a treatable neurodegenerative disease in patients presenting before the age of 50 years. The evaluation for Wilson includes serum ceruloplasmin and slit lamp examination and may include 24 h urine collection for copper. According to the patient's presentation, other secondary causes should be evaluated. In the presence of an isolated abnormal posture of the head (without dystonic tremor), one should consider MRI of the cervical spine to evaluate for a structural lesion of the spine or of the spinal cord. In addition, a levodopa trial should be considered in all individuals presenting solely with dystonia in which a genetic diagnosis is not known.

Management/Prognosis

Among the original three Amish-Mennonite families, fourteen of the 22 family members received treatment for

dystonia, including botulinum toxin for blepharospasm, spasmodic dysphonia, and cervical dystonia, with improvement. Those patients who had been tried on carbidopa/levodopa had mild benefit at best. Best oral medication responses were reported to trihexyphenidyl, lioresal, and clonazepam. Dopamine depleters and blockers, and carbamazapine were also tried, but without clear benefit.

The preferential treatment for a focal dystonia in the cranio-cervical region and brachial regions is botulinum toxin injections. When the dystonia involves multiple or other body parts or generalized, treatment options include anticholinergics (e.g., trihexiphenidyl), benzodiazepines (e.g., clonazepam), lioresal, or injections of botulinum toxin in the most affected muscle groups. None of the original Amish-Mennonite DYT6 family members has had deep brain stimulation surgery (DBS) yet, and the role of DBS, including stimulator settings, needs to be determined.

See also: Dystonia; DYT1; DYT2, Autosomal Recessive Generalized Dystonia; DYT4, Autosomal Dominant Type Dystonia or Whispering Dysphonia; DYT5; DYT7, Autosomal Dominant Focal Dystonia; DYT11, DYT15, Myoclonus-dystonia; DYT12, Rapid Onset Dystonia-parkinsonism; DYT13, Cranio-Cervical-Brachial; Tardive Syndromes; Wilson's Disease.

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DYT7, Autosomal Dominant Focal Dystonia

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Glossary

Blepharospasm – A form of focal dystonia that involves involuntary and sustained contractions of the muscles around the eyes.

Cervical dystonia – Also known as spasmodic torticollis, is the most common form of focal dystonia. It is characterized by abnormal movements or postures of the neck and head.

Dystonia – Cocontraction of agonist and antagonist muscles resulting in abnormal twisting and posturing movements.

Spasmodic dysphonia – A focal form of dystonia that involves involuntary spasms of the vocal cords which may cause interruptions of speech and affect the voice quality.

Definition and History

Focal adult-onset dystonia usually presents in the form of cervical dystonia, blepharospasm, spasmodic dysphonia, other cranial dystonia, writer's cramp, or a combination of the above. Cervical dystonia is the most common. There is usually little spread to other sites. Focal dystonia is much more prevalent than generalized dystonia, which usually starts in childhood.

While adult-onset focal dystonia had originally been thought to be primarily a sporadic condition, family studies support a genetic contribution. The incidence of dystonia in first-degree relatives of patients with focal dystonia is higher than that expected from population studies and several families have been identified showing apparent autosomal dominant inheritance, including a monozygotic twin pair.

Despite this, no genes for adult-onset focal dystonia have been elucidated. In 1996, a large German family with seven definitely affected and six possibly affected members plus three obligate carriers showed significant linkage to chromosome 18p, this region was termed DYT7. Autosomal dominant inheritance was inferred based on observations of affected members in successive generations, roughly equal sex distribution and male-to-male transmission. All definitely affected patients had adult-onset focal dystonia, most in the form of spasmodic torticollis or cervical dystonia, one with both cervical dystonia and spasmodic dysphonia and two patients had additional Meige syndrome and writer's cramp in addition to cervical dystonia. Several possibly affected individuals had postural hand tremor. The dystonic symptoms had remained focal over many years of disease duration in all patients. Linkage analysis to the DYT1 locus was excluded. This was the first linkage study of a primary dystonia gene with the most common form of dystonia, adult-onset focal dystonia.

Investigation of apparently sporadic patients with this type of dystonia from the same geographic region of Northwest Germany (Emsland) showed also linkage to the 18p locus, suggesting a common ancestor and low penetrance of the gene. The study also suggested that DYT7 is the predominant cause of focal adult-onset dystonia in this area of Germany and the location was further narrowed within 18p. The following year, genotyping of 18 families with similar phenotype from Central Europe, revealed that 15 of them shared the chromosome 18p haplotype, but 3 did not, suggesting both that DYT7 mutations are common even outside of the Emsland region in Germany and that there is locus heterogeneity for adult-onset focal torsion dystonia. There are also reports of focal dystonia associated to the 18p locus of non-German origin but it usually not found in non-German population. However, controversy exists in respect to how common this mutation actually is, as analysis of 85 patients with focal and segmental dystonia from Northern Germany did not reveal any evidence for linkage disequilibrium at the markers tested on chromosome 18p, including those previously identified in the initial proband family.

Genetic heterogeneity is thought to underlie the etiology of other large families with adult-onset focal dystonia who do not posses the 18p mutation.

Pathogenesis and Pathophysiology

The pathogenesis of DYT7 adult-onset focal dystonia is not known. Large deletions of the short arm of chromosome 18 may infrequently present with focal adult-onset dystonia among other neurological features. In a description of three patients with large 18p deletions, focal and segmental dystonia developed in mid to late adolescence, in addition to developmental delay and mental retardation. It is possible that the dystonia in these patients may have been caused by haploinsufficiency. As the gene has not yet been identified, the molecular substrate underlying the dystonia is unknown. No specific pathological changes have been associated with adult-onset focal dystonia in autopsy series.

Clinical Features/Diagnostic Criteria

Clinical features of DYT7 are not clearly distinguished from other forms of adult-onset focal dystonia of unknown genetic etiology. As noted, DYT7 dystonia is predominantly cervical, although associated writer's cramp, segmental cranial dystonia, and isolated spasmodic dysphonia were also reported. About a fourth of patients with cervical dystonia have postural hand tremor resembling essential tremor, and the prominent hand tremor is noted in DYT7 dystonia as well.

There is a remarkably narrow range of age of onset for various forms of dystonia. While DYT1 generalized dystonia usually begins in the late first and second decades of life, most patients with cervical dystonia or spasmodic dysphonia have their onset in the fourth or fifth decade, and this age of onset holds for DYT7 dystonia as well.

Differential Diagnosis/Diagnostic Work-up and Tests

When approaching a patient with suspected focal dystonia, it is important to rule out other conditions that mimic dystonia (pseudodystonia), that is, to make sure that the patient has, in fact, dystonia. Features unique to dystonia may help in the diagnosis, such as task specificity or the presence of a sensory trick or *geste antagoniste*. Some conditions that can cause pseudodystonia are atlanto-axial subluxation, posterior fossa tumors, Arnold–Chiari malformations, trochlear nerve palsy, stiff-person syndrome and, in children, Sandifer syndrome and congenital torticollis. Psychogenic movement disorders may also mimic dystonia.

An important step in the evaluation of the patient with dystonia is to evaluate for secondary etiologies. In primary dystonias, dystonia is the only neurological manifestation (except tremor). In the dystonia-plus syndromes, dystonia is present associated with parkinsonism. Secondary dystonias are common, usually due to toxin, drug exposure, or structural brain disease. Dystonia may also be a symptom of heredodegenerative diseases such as Wilson's disease – the only one that is potentially preventable – neuroferritinopathies, Fahr's disease, lysosomal storage disorders such as Niemann–Pick disease type C, amino and organic acidurias, mitochondrial disorders, other inborn errors of metabolism, trinucleotide repeat disorders like Huntington's disease or spinocerebellar ataxia type 3 (Machado–Joseph

disease), and parkinsonian syndromes like in idiopathic Parkinson's disease, multiple system atrophy or corticobasalganglionic degeneration.

Careful medication review with special focus on current or prior exposure to neuroleptic agents or antiemetics should be performed. Brain imaging, preferably magnetic resonance imaging, is recommended in all patients with hemidystonia to rule out structural disease. Copper studies to rule out Wilson's disease are recommended in all children and young adults presenting with dystonia. Although yield is low, a levodopa trial may be performed to assess for dopa-responsive-dystonia (DRD), as isolated cervical dystonia with DRD has been reported. Genetic testing for the DYT1 mutation is recommended for patients younger than 26 with limb-onset dystonia. While DYT1 positive individuals presenting with late-onset craniocervical dystonia have been described, the yield of a positive genetic result in these cases is low. There is some overlap with DYT6 dystonia, as some individuals affected with DYT6 may have adult-onset dystonia, although many have limb involvement. Commercial testing for DYT6 dystonia is not yet available; however, it is anticipated that it will be in the near future. As the DYT7 gene has not been elucidated, there is no commercially available testing for the DYT7 dystonia.

Management/Prognosis

Botulinum toxin injections are the treatment of choice for most forms of focal dystonia. The side effects are minimal and the duration of benefit is 3–4 months. Side effects range from discomfort at the side of the injection to excessive muscle weakness that, depending on location, may cause transient ptosis or dysphagia. Medications such as anticholinergic agents, baclofen, and benzodiazepines can be used but their use is limited by side effects, especially, in the adult population. Pallidal deep brain stimulation is a safe and effective treatment of primary generalized and segmental dystonia, including cervical dystonia; however, it is still reserved for patients with severe medication refractory symptoms.

See also: Basal Ganglia; Blepharospasm; Cervical Dystonia; Dystonia; Dystonia, Task-specific; Dystonia: Animal Models; DYT1; DYT4, Autosomal Dominant Type Dystonia or Whispering Dysphonia; DYT5; DYT11, DYT15, Myoclonus-dystonia; DYT12, Rapid Onset Dystonia-parkinsonism; Fahn–Marsden Rating Scale; Generalized Primary Torsion Dystonia; Geste Antagonistique; Spasmodic Dysphonia: Focal Laryngeal Dystonia.

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DYT8, Paroxysmal Non-kinesiogenic Dyskinesia-PNKD

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Historical Background

Since the initial description of Mount and Reback, in 1940, quite a few families were reported with an autosomal dominant inheritance with a fairly similar clinical description between families.

Definition and Characteristics of an Attack

Paroxysmal nonkinesigenic dyskinesia (PNKD) is characterized by attacks of dyskinesia, which are frequently precipitated by alcohol, caffeine, stress, or fatigue. In contrast,

paroxysmal kinesigenic dyskinesias are typically triggered by sudden movements, as the name suggests.

Also, patients with PNKD have longer (10 min to 6 h) and less frequent attacks (1–3 per day) compared with the kinesigenic variant. The dyskinesia may be of any form but often tend to be more dystonic or choreic in nature. More males than females are affected (1.4:1) for sporadic cases, and onset is usually in childhood with a tendency for the attacks to diminish with age.

A detailed report of typical clinical features of a large English family with 18 affected members was provided by Jarman et al. In all cases, onset age was very early, in the second year of life and even earlier in some. Witnessed attacks consisted of generalized choreoathetosis in two individuals. Attacks started in one limb or one side and progressed to become generalized. In one case there was associated dysarthria during an attack. Coffee, alcohol, anger and excitement, hunger, and sleep deprivation were general precipitants as well as cold and exercise in two individuals. The attack duration varied from 10 min to 12 h; however, the majority of attacks lasted between 30 and 180 min. All adults reported a decline in attack duration and frequency with age. One 85-year-old member now experienced only one mild attack a year. All affected cases reported remarkable response to sleep with 5–10 min of sleep being sufficient to abort an attack while some found drinking cold fluids or vigorous exercise could abort an attack in an early phase. There was some diurnal fluctuation with a tendency to having more attacks in the afternoon or evening compared with the morning. Recently, Bruno et al. have made similar observations in 14 kindreds with classic PNKD.

Interictal Findings

Generally, PNKD cases have no detectable abnormalities between attacks, although there has been one report of patient with PNKD who also had some interictal dystonia. There has also been a family with PNKD with additional myokimia. However, these reports date back to the pre-molecular area (see below).

Investigational Findings

With regard to investigations, routine tests as well as EEGs and brain imaging in the idiopathic cases are normal. Pathological examination at autopsy in two cases revealed no significant abnormalities.

Linkage and Genes

In the mid-1990s, two groups of researchers separately linked families with PNKD to chromosome 2q. Fouad et al. also showed tight linkage between PNKD and microsatellite markers on distal 2q (2q31–q36) in a five-generation Italian family with 20 affected members. Fink et al., who performed a genome-wide search in a large American kindred of Polish descent with 28 affected members, have also mapped PNKD to chromosome 2q33–q35. The smallest region of overlap of the candidate intervals identified by these two groups placed the PNKD locus in a 6-cM interval. In a six-generation British family, Jarman and coworkers subsequently narrowed the candidate region down to a 4-cM interval. A German family, originally described by Przuntek and Monninger as a classic example of Mount and Reback-PNKD, and other typical PNKD families (one from North American of German descent as well as a Japanese family), were also found to link to the same genetic location designated FPD1 (familial paroxysmal dyskinesia type 1).

In 2004, the gene responsible for PNKD was discovered to be the *myofibrillogenesis regulator 1 (MR1)* gene. The gene (PNKD1/DYT8) contains 10 exons and has a transcript length of 3110 bps and a translation length of 385 residues. The reported single-nucleotide mutations caused substitution of valine for alanine in residue 7 and residue 9. The same mutations were found in a family originally reported by Raskind et al. and in a 15-year-old Serbian boy with PNKD1 described by Djarmati *et al.*

There is also suggestion of genetic heterogeneity, after Spacey et al., by genome-wide linkage analysis, identified a candidate locus, termed PNKD2 (DYT20) on chromosome 2q31 in a large family with PNKD. Onset was between teenage-life and mid-adult life. Episodes lasted for about 5 min and occurred daily to monthly. Some had associated migraines. Molecular studies revealed a parametric LOD score of 2.03 and a multipoint nonparametric LOD score of 7.0. Haplotype analysis delineated a 10-cM interval between markers D2S2188 and D2S364. Mutations in the *MR1* gene as well as the *GAD1* gene were excluded by molecular analysis. The gene underlying PNKD2 remains to be identified. However, all the families with the typical PNKD phenotype segregate with the *MR1* gene.

Pathophysiology

MR-1 encodes an enzyme in a stress response pathway. The identified mutations cause changes in the N-terminal region of two MR-1 isoforms. The MR-1L isoform is specifically expressed in brain and is localized to the cell membrane whereas the MR-1S isoform is ubiquitously expressed and shows diffuse cytoplasmic and nuclear localization.

Bioinformatic analysis revealed that the *MR-1* gene is homologous to the *hydroxyacylglutathione hydrolase (HAGH)* gene. HAGH plays a role in a pathway to detoxify methylglyoxal, a compound present in coffee and alcoholic beverages and produced as a by-product of oxidative stress.

This demonstrates a possible mechanism whereby alcohol, coffee, and stress are linked in and trigger attacks in PNKD.

Diagnostic Principles

Detailed history, family history, and clinical characterization of the type of paroxysmal dyskinesia. Exclusion of secondary causes of paroxysmal dyskinesias (demyelination, vasculopathy, infectious disease (HIV, CMV), cerebral and peripheral trauma, neurodegenerative disease, hormonal and metabolic dysfunction (diabetes mellitus, hyperthyroidism, hypoparathyroidism, pseudohypoparathyroidism), neoplasm, Chiari malformation, cervical syringomyelia, and cerebral palsy). In primary paroxysmal disorders, ictal and interictal EEG and sleep-EEGs are usually normal or show transient epileptic discharges.

Therapeutic Principles

Most importantly, triggering factors like caffeine, alcohol, or stress should be clarified and avoided or reduced. If treatment is required, the drug of first choice is clonazepam. In a study of 49 genetically proven *MR-1* gene mutation carriers, a favorable reponse was noted by 97% of those who had tried benzodiazepines. The response to antiepileptic treatment is, however, limited; although there may be an initial response, this is usually lost over the years. Haloperidol, gabapentin, and acetazolamide, as well as L-dopa may also bring some benefit. The prognosis is overall good as the attack frequency may tend to decrease with age.

See also: DYT9, Paroxysmal Dyskinesia with Spasticity; DYT10, Paroxysmal Kinesiogenic Dyskinesia-PKD; Paroxysmal Exertion-induced Dyskinesia; Paroxysmal Movement Disorders.

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DYT9, Paroxysmal Dyskinesia with Spasticity

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Definition and Characteristics

In 1996, Auburger et al. reported a large German family in which affected members had choreo-dystonic attacks of toes, legs, and arms induced by alcohol, fatigue, and exercise. A total of 18 affected and 11 unaffected members over four generations were clinically assessed (for pedigree see **Figure 1**). Inheritance was in an autosomal dominant pattern. Onset age was between age 2 and 15, but usually before age 6. Episodes lasted approximately 20 min and occurred twice daily to twice yearly.

In addition to involuntary movements, some affected members showed a rather complex phenotype with marked spastic paraparesis and other clinical features, including paresthesias periorally and of the lower limbs, double vision, and headache. During attacks, patients exhibited imbalance and dysarthria; however, there were no clear cerebellar signs. Examination was normal between attacks, except in five patients who had spastic paraplegia with pyramidal signs and increased latencies on electrophysiological assessment. One patient was cognitively impaired, whereas the remaining subjects were neuropsychologically normal. EEGs excluded epileptic activity. Neuroimaging using 31P NMR spectroscopy for assessment of pH in the cerebellum revealed values in the upper normal range. The condition was reported under the heading 'choreoathetosis/spasticity (CSE).'

Thus, clinically, they did not fit in with the main, well-described subtypes of paroxysmal dyskinesias, according to Demirkiran and Jankovic's classification. However, based on the triggering factors, there was overlap with the nonkinesigenic variant (PNKD, paroxysmal nonkinesigenic dyskinesia due to mutations in the MR-1 gene on chromosome 2q33–35), which is typically triggered by coffee or alcohol intake. There was also overlap with paroxysmal exercise-induced dyskinesia (PED). PED is a genetically heterogeneous syndrome. Recently, for some families, as well as in some sporadic cases, gene mutations in the *GLUT1* gene have been demonstrated by Weber et al. and Schneider et al. Notably, in some of the genetically proven *GLUT1* gene mutation carriers, PED was accompanied by epilepsy, migraine including hemiplegic migraine, mild developmental delay, and reduced cerebral spinal fluid (CSF) glucose levels.

Auburger et al., in their original report, also discussed the similarities with one of the episodic ataxia syndromes (episodic ataxia type 1, defined by the presence of additional myokymia due to mutations in the potassium channel gene *KCNA1* on chromosome 12p) and excluded linkage to that area.

Prevalence

Only limited data are available and, so far, the disease is reported only in a single large pedigree from Germany.

Linkage and Genes

Linkage to chromosome 12p (*KCNA* gene associated with episodic ataxia type 1) was excluded. However, linkage to chromosome 1p21–13.8 where a cluster of related potassium channel genes is located, could be demonstrated. Genotyping of 18 affected and 11 unaffected family members with 28 microsatellites over a region of 45 cM showed linkage with a LOD score of 7.2 at a recombination fraction $\theta = 0$ to D1S451/421/447/GGAT4C11. Crossing-over events in nine patients and four unaffected offspring suggested a probable assignment of the gene to a

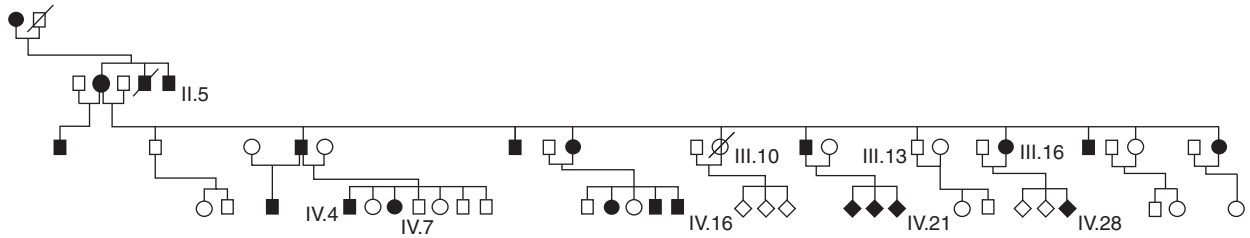

Figure 1 Pedigree with paroxysmal choreoathetosis/spasticity in four generations and 22 affected individuals. Affected individuals are shown as black symbols. Reproduced from Auburger G, Ratzlaff T, Lunkes A, et al. (1996) A gene for autosomal dominant paroxysmal choreoathetosis/spasticity (CSE) maps to the vicinity of a potassium channel gene cluster on chromosome 1p, probably within 2 cM between D1S443 and D1S197. *Genomics* 31: 90–94.

region of 2 cM between D1S443 and D1S197. The condition was allocated to the DYT9 locus.

Interestingly, the locus is in proximity to the gene locus of *GLUT1* (*SLC2A1)* associated with PED (chromosome 1p35-p31.3). Mutations in this gene can present with a spectrum of severity ranging from very severe (labeled as 'classic *GLUT1* deficiency syndrome') to mild (pure PED, which occurs episodicallys only). The severe syndrome of 'GLUT1 deficiency,' as recognized by paediatricians, is characterized by delayed development with microcephaly, drug-resistant seizures, ataxia, spasticity, hypoglycorrhachia, and decreased erythrocyte glucose uptake. Atypical forms of GLUT1 deficiency syndrome have a milder phenotype or late-onset, without seizures or presence of intermittent ataxia or dyskinesias triggered by exercise or coffee. The phenotype of the choreoathetosis/spasticity syndrome described by Auburger et al. is well compatible with the GLUT1 phenotype and mutations in the *GLUT1* gene remain to be excluded or confirmed.

Pathophysiology and Therapeutic Principles

The original family by Auburger et al. responded to acetazolamide and phenytoin; however, the response was variable.

To date, the exact gene underlying the choreoathetosis/spasticity syndrome (DYT9) is unknown. If it were to be due to mutations in the *GLUT1* gene, this may have implications for treatment. *GLUT1* encodes the GLUT1 transporter responsible for glucose entry into the brain. It has been found that the defect in this transporter can be bypassed by a ketogenic diet or a less restrictive modified Atkins diet. Oral medication which has been reported to produce benefit in PED includes gabapentin, clonazepam, levodopa, and acetazolamide.

Patients with *GLUT1* gene mutations were found to have reduced or borderline CSF glucose levels. There are no reports about CSF levels in the original CSE family.

Diagnostic Principles

Diagnostic principles include detailed history of the patient, family history, and clinical characterization of the type of paroxysmal dyskinesia. These exclude secondary causes of paroxysmal dyskinesias (demyelination, vasculopathy, infectious disease (HIV, CMV), cerebral and peripheral trauma, neurodegenerative disease, hormonal and metabolic dysfunction (diabetes mellitus, hyperthyroidism, hypoparathyroidism, pseudohypoparathyroidism), neoplasm, Chiari malformation, cervical syringomyelia, and cerebral palsy). In primary paroxysmal disorders, ictal and interictal EEG and sleep-EEGs are usually normal or show transient epileptic discharges.

See also: DYT8, Paroxysmal Non-kinesiogenic Dyskinesia-PNKD; DYT10, Paroxysmal Kinesiogenic Dyskinesia-PKD; Paroxysmal Exertion-induced Dyskinesia; Paroxysmal Movement Disorders.

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DYT10, Paroxysmal Kinesiogenic Dyskinesia-PKD

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Glossary

Centimorgan (cM) – A measure of distance of genes on a chromosome determined by the frequency with which recombination occurs between them. Two gene loci are one centimorgan apart if recombination occurs in 1% of meioses.
Choreoathetosis/spasticity (CSE) – The combination of choreic and athetotic involuntary movements and pyramidal involvement causing spasticity.
Cerebrospinal fluid (CSF) – The clear fluid within the subarachnoid space and the ventricular system around and inside the brain.
Electroencephalogram (EEG) – The recording of electrical activity of neurons and a diagnostic tool for example in the context of epilepsy.
Glucose transporter gene (*GLUT1* gene) – The gene encoding for a membrane protein that transports glucose across the membrane. Different subtypes of GLUT transporters have been identified. The GLUT1 transporter, in particular, is expressed at highest levels in erythrocytes as well as in the endothelial cells of barrier tissues inlcuding the blood–brain barrier.
Myofibrillogenesis regulator 1 gene (*MR-1* gene) – The gene associated with paroxysmal nonkinesigenic dyskinesia (PNKD).
Nuclear magnetic resonance (NMR) – A tool used to study molecular physics, crystals, and noncrystalline materials through NMR spectroscopy. NMR is also routinely used in advanced medical imaging techniques, such as in magnetic resonance imaging (MRI).
Paroxysmal exercise-induced dyskinesia (PED) – A form of episodic movement disorder where attacks are triggered by prolonged physical exercise.

Historical Background and Synonyms

Paroxysmal kinesigenic dyskinesia (PKD) were first described by Gowers in 1901 as attacks of an 'unusual character' that occur after sudden movement. In contrary to epileptic seizures, consciousness was not lost and movements were tonic without clonic component. However, despite this observation, the condition was classified as 'extrapyramidal epilepsy,' 'striatal epilepsy,' 'tonic seizures,' 'tonic motor attacks,' and 'reflex epilepsy.'

The first detailed description of clinical features was presented by Kertesz in a seminal review of 31 cases from the literature and 10 new cases, including one autopsied. Brain pathology was found normal except for a slight loss of neurons of the nucleus coeruleus.

Clinical Characteristics of PKD

In addition to a number of single case reports, there are two studies reviewing clinical features in larger cohorts. One of these is by Houser et al. (26 patients with PKD), and the other by Bruno et al., who reviewed features of 121 affected individuals with a presumptive diagnosis of idiopathic PKD and referred for genetic studies. On this basis, the latter authors also proposed new diagnostic criteria.

In view of the classification by Demirkiran and Jankovic, PKD episodes are by definition triggered by sudden movements, for example, getting up quickly to answer the door bell or the telephone; and the attacks are typically brief lasting seconds. Many patients (70–80% of patients) note an abnormal sensation prior to the movement ('aura') like numbness or 'pins and needles' in the affected limb or the epigastric region.

The clinical manifestation of the attack is most commonly with dystonia. There may also be chorea, ballismus, or a combination of these. Typically, attacks affect limbs on one side, although attacks can also be generalized. About one third of patients develop speech disturbance (dysarthria or anarthria), which may be due to the involvement of the face. There is usually no loss of consciousness (in 98%) and no 'postictal' confusion or drowsiness.

Most attacks (88–100%) are very brief, lasting only seconds. In the series by Houser et al., attacks lasted less than 2 min in 88% and between 30 and 60 s in two-thirds of patients. Similarly, in the study by Bruno et al., attacks were shorter than 1 min in 95% of patients. Longer lasting PKD-like attacks should thus make the clinician suspicious of a secondary cause including the possibility of a psychogenic paroxysmal movement disorder.

PKD attacks are frequent. Most patients have 1–20 attacks per day, while some may also have more than 20 attacks per day. The frequency of PKD episodes usually peaks in puberty with up to 30–100 attacks and then becomes less after age 20, and may even completely remit after age 30.

The age of onset in PKD varies between 6 months and 33 years, but onset is usually in teenage life between 7 and 15 years. Among the primary form, 65–72% of PKD

patients have a family history of a similar disorder with autosomal dominant inheritance. Pentrance was complete in more than half of the cases. There appears to be a higher prevalence in males (4:1 even up to 8:1) in the sporadic form but not in familial cases.

Diagnostic Criteria

Criteria as proposed by Bruno et al.:

- Identified kinesigenic trigger for the attacks
- Short duration of attacks (<1 min)
- No loss of consciousness
- Onset age 1–20 years, if no family history
- Control of attacks with phenytoin or carbamazepine
- Normal neurological examination; exclusion of other causes

Genetic Linkage of PKD

A genetic breakthrough of this disorder was achieved with the recognition of similarities between PKD and paroxysmal movements noted in the context of the syndrome labeled 'ICCA' because of the presence of *infantile convulsions and paroxysmal choreo-athetosis*. The ICCA syndrome had been mapped to a 10 cM interval of the pericentromere region on chromosome 16. Subsequently, a number of families with pure PKD were also linked to the same area.

Since then, idiopathic PKD cases have also been linked to the pericentromic region of chromosome 16 (spanning a 24 cM segment between D16S3131 and D16S408). However, despite various attempts and detailed analysis by Kikuchi et al. of 157 genes in this area, no mutations could yet be identified that are shared by unrelated families. Recently, nonsynonymous substitutions affecting the SCNN1G and *ITGAL* gene, which were segregated with disease in two families, have been proposed by Kikuchi et al. to play a role.

There is also evidence of genetic heterogeneity for PKD. One independent locus maps to chromosome 16 (EKD2/DYT19) as described by Valente et al. and there are also cases where linkage to chromosome 16 was excluded by Spacey et al. suggesting existence of a third locus elsewhere.

There is also overlap with the syndrome of rolandic epilepsy, paroxysmal exercise-induced dyskinesia, and writer's cramp (RE-PED-WC). In RE-PED-WC syndrome, there is a strong relation between symptom expression and age: both seizures and paroxysmal dystonia peaked in childhood. The onset of writer's cramp also was in childhood but did not cease with age. However, unlike typical PKD inheritance was autosomal recessive. Genome-wide linkage analysis identified a critical region spanning 6 cM on chromosome 16. In fact, the region of the ICCA syndrome entirely included this 6-cM-wide critical RE-PED-WC region. However, it remains unknown whether these conditions are caused by mutations of the same gene or two different genes.

Pathophysiological Mechanisms of PKD

Two studies recently investigated patients with idiopathic PKD, using transcranial magnetic stimulation. One of the studies assessed a proportion of patients on and off treatment. Here, Mir et al. found a reduced short intracortical inhibition, a reduced early phase of transcallosal inhibition, and a reduced first phase of spinal reciprocal inhibition. The abnormalities in transcallosal inhibition could be normalized by carbamazepine, while the other parameters did not change with treatment. Other measures like the cortical silent period, the startle response, and the second and third phases of reciprocal inhibition were normal. The authors concluded that the abnormalities of the cortical and spinal inhibitory system may be useful parameters to differentiate PKD from primary dystonia and epilepsy. In the other study, Kang et al. found normal measures for thresholds, intracortical facilitation, and silent period. In contrast to Mir et al., they found also normal short intracortical inhibition. Functional imaging studies like SPECT scans demonstrated an altered perfusion of the basal ganglia contralaterally to the affected side or bilaterally.

Diagnostic Principles

Detailed history, family history, and clinical characterization of the type of paroxysmal dyskinesia to exclude secondary causes of paroxysmal dyskinesias (demyelination, vasculopathy, infectious disease (HIV, CMV), cerebral and peripheral trauma, neurodegenerative disease, hormonal and metabolic dysfunction (diabetes mellitus, hyperthyroidism, hypoparathyroidism, pseudohypoparathyroidism), neoplasm, Chiari malformation, cervical syringomyelia, cerebral palsy). In primary paroxysmal disorders, ictal and interictal EEG and sleep-EEGs are usually normal or transient epileptic discharges.

Treatment and Prognosis of PKD

PKD attacks usually respond well to anticonvulsants: Carbamazepine is the drug of choice and 86% of patients studied by Bruno et al. responded well to either carbamazepine or phenytoin. The dose of phenytoin required to control PKD in children is comparable to the dose used for epileptic seizures. In adults, a lower dosage is sufficient and Houser et al. suggested for adults doses of

5 mg kg^{-1} per day of phenytoin or 7–15 mg kg^{-1} per day of carbamazepine.

An alternative or adjunct to carbamazepine in the treatment of PKD may be acetazolamide, especially when the condition is due to demyelinating lesions. Other drug options include hydantoin, topiramate, or barbiturates. Benzodiazepines were reported beneficial in patients with HIV-associated PKD.

The prognosis is generally good, as attack frequency decreases with age and patients have a normal life expectancy. However, if undiagnosed, this disorder can be very distressing and can affect life quality. During pregnancy, 50% of affected women may note improvement.

See also: DYT8, Paroxysmal Non-kinesiogenic Dyskinesia-PNKD; DYT9, Paroxysmal Dyskinesia with Spasticity; Paroxysmal Exertion-induced Dyskinesia; Paroxysmal Movement Disorders.

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DYT11, DYT15, Myoclonus-dystonia

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Glossary

Dystonia-plus – The term dystonia-plus refers to conditions in which dystonia is one of only two neurological conditions present, the other being myoclonus or parkinsonism, in the absence of neurodegeneration. This term applies to three conditions: myoclonus-dystonia, dopa-responsive dystonia, and rapid-onset dystonia-parkinsonism.
Myoclonus – Brief, rapid involuntary and random muscle jerk produced by muscle contraction. Myoclonus can also result from brief lapses in muscle contraction.

Definition and History

The nosology of myoclonus-dystonia is often confusing because in the historical record it has been variously described as 'hereditary essential myoclonus,' 'myoclonic-dystonia,' 'dystonia-myoclonus,' and most recently, myoclonus-dystonia. Some confusion arises as most but not all of the cases falling into this disorder category are actually myoclonus-dystonia. It was suggested that when myoclonus is part of primary dystonia, such as DYT1 it should be termed 'myoclonic dystonia' to distinguish it from the characteristic syndrome of myoclonus-dystonia.

Myoclonus-dystonia is characterized by a combination of rapid, brief muscle contractions (myoclonus) and/or

sustained twisting, and repetitive movements that result in abnormal postures (dystonia). While most reports on myoclonic dystonia are indeed referencing this condition, as noted above, myoclonic dystonia may also refer to primary dystonia, such as DYT1 dystonia, where there is myoclonus superimposed on the dystonia (discussed by Obeso et al.), but the myoclonus is not the prominent feature in the individual or the family, if it is familial.

Davidenkow first described in 1926 the association of truncal and neck dystonia with tic-like hyperkinesis of neck and facial muscles in a pair of siblings and labeled it 'hereditary myoclonic dystonia.' Quinn and Marsden described an additional six patients from four families of childhood onset 'myoclonic dystonia' inherited as an autosomal dominant trait with variable penetrance. Exquisite response to alcohol with potential for alcohol dependence and premenstrual worsening in female patients were also mentioned. In 1988, a study in one family in upstate New York by Kurlan et al. described eight affected family members with dystonia and/or myoclonus of onset around age 12. Dystonia manifested predominantly as writer's cramp and myoclonus was irregular, most commonly generalized and responsive to alcohol. Because of the early onset with absence of marked progression to generalized dystonia, the absence of gait impairment, and the electrophysiological evidence of subcortical myoclonus, they differentiated this entity from idiopathic torsion dystonia. Additional descriptions confirmed the same observation and the entity was further separated from hereditary benign chorea and hereditary essential myoclonus, although recently some cases originally described as hereditary essential myoclonus have been relabeled as myoclonus-dystonia. The description of a very large family in Sweden in 1990 helped confirm this condition as a separate entity and provided important data on its wide spectrum of clinical manifestations. Exhaustive genomic screens using two large families excluded major parts of the genome and linkage analysis in a German family excluded the DYT1 locus and the 13 subunits of the $GABA_A$ receptor. In 1999, Nygaard et al. mapped a locus for myoclonus-dystonia to the 7q21–q31 region and in 2001 the first mutations in the ε-sarcoglycan gene were identified. The locus was designated DYT11. In 2002, linkage analysis in a large Canadian family revealed a novel locus on the short arm of chromosome 18p11. In this family, the clinical characteristics were identical to those due to mutations in the *SGCE* gene. The locus was designated DYT15. Two additional families have been now potentially linked to this region, but the gene has not been identified yet.

Pathogenesis and Pathophysiology

The myoclonus-dystonia syndrome has been attributed to mutations in the ε-sarcoglycan gene (*SGCE*, DYT11) mapped to 7q21 and more recently to a novel locus in chromosome 18p11 (DYT15). The *SGCE* gene is composed of 12 exons that span 71 kb. Exon 10 is alternatively spliced and is missing in the majority of transcripts. Several different mutations have been described; the most common appears to be a nonsense mutation in exon 3 (304C > T, R102X), although missense mutations, insertions, deletions, and substitutions have been described. Novel mutations continue to be described including de novo mutations. The R102X mutation does not have a common allele and it does not appear to represent a common founder mutation. Most of the mutations lead to loss of function as a result of frameshift and protein truncation before the transmembrane domain. Missense mutations produce proteins that are not correctly localized to the plasma membrane and are degraded by the proteasome. Large exonic deletions in patients in which direct sequencing through polymerized chain reaction (PCR) did not reveal mutations in the *SGCE* gene have been described with similar phenotype as patients with point mutations. However, deletions extending beyond the *SGCE* gene have been associated with dysmorphism and other features.

The pattern of inheritance is autosomal dominant with decreased penetrance and variable expression. The reduced penetrance in the expression of the disease is thought to result from maternal imprinting, with most of manifesting offspring inheriting the affected gene from their father.

There is evidence of genetic heterogeneity, and the majority of patients with the clinical syndrome remains negative for *SGCE* mutations, although as mentioned before, large deletions may be overlooked if just direct sequencing without screening for changes in exon copy number is performed. *SGCE* mutation-positive cases and mutation-negative cases are phenotypically very similar, except that positive family history, truncal myoclonus and axial dystonia are more frequent in the mutation-positive cases.

The syndrome had been also associated in the past to mutations in the D2 receptor and also to an 18-bp deletion on the gene encoding for TorsinA (DYT1) However, in both cases, mutations were also found in the SCGE gene.

The pathophysiology of myoclonus-dystonia currently remains elusive. Some electrophysiological studies suggest a generator within the basal ganglia as both pallidal and thalamic stimulation ameliorates the symptoms. In addition, a preliminary functional MRI study in a single *SCGE*-related myoclonus-dystonia patient showed specific activation within the thalamus and dentate nucleus.

The *SGCE* KO mouse model showed myoclonus, deficits in motor coordination, balance and learning, and psychiatric alterations consistent with anxiety and depression, as well as compulsive checking behavior, demonstrating that the diverse symptoms in DYT11 myoclonus-dystonia syndrome are indeed the effects of a single gene mutation

involving *SCGE* gene. ε-Sarcoglycan is a major constituent of the dystrophin–glycoprotein complex in striated muscle. Mutations in α, β, γ, and δ-sarcoglycan cause different recessive limb girdle muscular dystrophies and they are primarily expressed in muscle. In contrast, ε-sarcoglycan is found in midbrain monoaminergic neurons, cerebellar Purkinje cells, and other brain regions. The pathophysiological relation of mutated ε-sarcoglycan to the development of the myoclonus-dystonia is not known.

Clinical Features and Diagnostic Criteria

The clinical spectrum is wide with marked variation even within members of the same family. Classically, the disease onset is on the first or second decades of life, although onset in early infancy has been described as well as onset in the sixth decade. Myoclonus is usually the first manifestation, ranging from mild distal segmental myoclonus in the arms that could be mistaken with tremor, to generalized violent jerks involving the entire body. The myoclonus is most prominent and frequent in the axial musculature. Dystonia commonly follows and tends to remain focal or segmental and affect the cranial–cervical musculature and the arms in the form of writer's cramp more often than the legs or trunk. In rare cases, it may be the presenting and only symptom. Both dystonia and myoclonus can markedly worsen with action, and myoclonus can be exacerbated by stress, sudden noise, touch, and caffeine. Mild parkinsonian features of reduced arm swing, postural instability, and rest tremor have also been reported in a few mutation positive individuals. Lastly, growth retardation, mild developmental delay, and facial dysmorphism have been described in patients with large deletions of the 7q21 locus; however, the deletions also included contiguous genes in those myoclonus-dystonia patients.

Exquisite alcohol sensitivity in many affected individuals is a classic feature of this condition. It was first noticed by Daube and Peters in 1966 and it has been widely documented. The effect of alcohol appears to be a palliative one, rather than a result of the mutated gene expression. Forty-four percent of manifesting carriers of the DYT11 locus in a study of three families prior to the identification of the gene met criteria for alcohol dependence, versus 12.8% of nonmanifesting carriers, while the rates of alcohol dependence between carriers and noncarriers did not differ. A larger cohort of patients with documented ε-sarcoglycan mutations showed similar results.

Independently from alcohol, psychiatric comorbidities such as obsessive–compulsive disorder and depression have been described associated with this syndrome.

By definition, in myoclonus-dystonia there is an absence of seizures, dementia, ataxia, or other neurological deficits, in order to distinguish it from the myoclonic epilepsies and other progressive ataxic syndromes. Routine electroencephalograms and somatosensory evoked potentials are normal in these patients and electroencephalogram (EEG) jerk-locked back averaging does not detect a premyoclonic cortical potential pointing towards a subcortical origin of the myoclonus in myoclonus-dystonia. However recent reports have demonstrated that there may be both seizures and EEG abnormalities in some cases with *SGCE* mutations.

Differential Diagnosis

When assessing a patient with myoclonus, it is imperative to consider that myoclonus, as a symptom, may arise from different brain regions (cortex, subcortical region, or brainstem), spinal cord and even peripheral nerves, and therefore has many different etiologies. Cortical myoclonus usually involves the distal hand or less commonly the foot. It is usually stimulus-sensitive, and may be rhythmic or arrhythmic. Reticular reflex myoclonus (brainstem myoclonus) is usually severe, causing generalized flexor jerks of the proximal upper and lower limbs and trunk. It is usually arrythmic and may be stimulus-sensitive. Spinal segmental myoclonus, typically involves one or two adjacent segments of the cervical or thoracic cord, is typically rhythmic, and may be stimulus-sensitive. Propriospinal myoclonus is rare, often involving the thoracic cord, and is characterized by a visible delay between jerks stimulated by reflexes.

Myoclonus can occur as a natural physiologic phenomenon (hiccups, hypnic jerks) and as part of the epileptic phenotype (epileptic myoclonus, like in juvenile myoclonic epilepsy (JME). It can also occur in a large number of disorders in the company of seizures and progressive neurologic deterioration, the so-called progressive myoclonic epilepsies like Lafora disease, myoclonic epilepsy with ragged red fibers (MERRF) or Unverricht–Lundborg disease, or in conditions like dendatorubralpallidoluysian atrophy (DRPLA) or the juvenile form of Huntington's disease (Westphal variant). Symptomatic myoclonus may arise from hypoxic–ischemic injuries, as part of myoclonic dementias such as Alzheimer's disease or Creutzfeldt–Jakob disease (CJD), as a side effect of certain drugs and withdrawal from opioids and alcohol. Lastly, myoclonus may appear in isolation without apparent external cause and without associated neurodegeneration, called essential myoclonus. The myoclonus of myoclonus-dystonia belongs to this latter type.

When dystonia and not myoclonus is the presenting or prominent symptom, other primary dystonic disorders and secondary dystonias need to be ruled out, including structural disease, Wilson's disease, especially when family history is missing or the pattern of inheritance is not clear for an autosomal dominant condition.

Diagnostic Work-Up/Tests

The work-up of the patient with suspected myoclonus-dystonia should be individualized based on the onset, age of the patient and the presence of other neurologic disturbances, like seizures or other neurologic deficits such as pyramidal signs, extrapyramidal signs, or cognitive impairment. Direct sequencing of the ε-sarcoglycan gene with screening for changes in exon copy number to additionally look for deletions can be performed although a negative result will not rule out myoclonus-dystonia, due to its genetic heterogeneity. Such testing should be performed together with a genetic counselor, if possible, as the explanation of the transmission pattern and its meaning in subsequent generations is complex. Particularly, it should be noted that while there is maternal imprinting and most gene carrying children of mothers with myoclonus-dystonia do not develop disease, the imprint is incomplete, and approximately 5–10% may develop symptoms.

The work-up should include a detailed review of medication use, as some medications may cause myoclonus. Further, careful assessment of alcohol intake to look both for a beneficial effect on the myoclonus and myoclonus resulting from alcohol withdrawal should also be performed. Routine laboratory studies to consider include: complete blood count (CBC), biochemistry panel, ammonia, liver function tests including copper biochemical studies and thyroid function tests. All patients should undergo brain imaging; magnetic resonance imaging is preferred when feasible. Serum ceruloplasmin and ophthalmologic examination for Kayser Fleischer rings should be considered.

Electrophysiological studies are of key importance in the evaluation of a patient with myoclonus. EEG is readily available and should be routinely obtained in any patient with myoclonus to rule out seizures and to evaluate different patterns and background, like periodic synchronous discharges such as in CJD and generalized periodic epileptiform discharges like in subacute sclerosing panencephalitis (SSPE). Electromyogram (EMG) is readily available and useful in defining the duration of the jerks (myoclonus is typically <100 ms) and in differentiating peripheral myoclonus from other muscle contractions like fasciculations and myokymia. EEG–EMG back averaging is a specialized test not readily available but it represents the most useful tool for confirming time-lock between the myoclonic jerks and the EEG signal and can definitively differentiate cortical from subcortical myoclonus.

Genetic testing is commercially available for some of the progressive myoclonic epilepsies like Lafora disease and Unverricht–Lundborg disease, as well as MERRF and JME, neurodegenerative conditions such as Huntington's disease and primary dystonias like DYT1.

Management/Prognosis

The condition usually follows a benign course compatible with normal life span. Spontaneous remission of dystonia in childhood or adolescence has been described and progression to worsening dystonia and myoclonus is rare but also reported.

Counseling regarding the negative long-term effects of alcohol should be considered in alcohol-responsive cases. As parents may not be affected (if the disease was transmitted through the grandmother) and may not be aware of the short term alleviation of symptoms with alcohol, they should be counseled that affected teenagers may start abusing alcohol to dampen the symptoms.

The treatment of myoclonus and dystonia is symptomatic and should be reserved for those patients in whom there is functional impairment. Response to medications targeted to treat myoclonus, in particular, benzodiazepines, sodium oxybate (γ-hydroxybutyric acid), valproic acid, levetiracetam, and L-5-H-triptophan has been reported; as has response of the dystonia to anticholinergic medications, although historically results have been far less than satisfactory for the treatment of myoclonus. Most patients with myoclonus require treatment with more than one drug and individual susceptibility to side effects varies considerably from patient to patient. Negative myoclonus is historically difficult to treat. Deep brain stimulation of the ventral intermediate thalamic nucleus and globus pallidus pars interna has been shown to alleviate both myoclonus and dystonia in mutation-positive selected individuals. Levodopa may be helpful in selected individuals.

See also: Cervical Dystonia; Deep Brain stimulation; Drug-induced Movement Disorders; Dystonia; Dystonia: Animal Models; DYT1; DYT4, Autosomal Dominant Type Dystonia or Whispering Dysphonia; DYT5; DYT6, Mixed Phenotype Primary Dystonia; DYT12, Rapid Onset Dystonia-parkinsonism; DYT13, Cranio-Cervical-Brachial; Huntington's Disease; Myoclonus; Myoclonus, Epileptic; Myoclonus-Dystonia/Essential Myoclonus; Obsessive-Compulsive Disorder; Wilson's Disease.

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Relevant Websites

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http://www.dystonia-foundation.org – Dystonia Medical Research Foundation.

DYT12, Rapid Onset Dystonia-parkinsonism

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Glossary

Haploinsufficiency – Lower production of a protein as a result of a mutated gene, which in turn causes an abnormal phenotype.

Definition and History

Rapid onset dystonia parkinsonism (RDP, DYT12) is a rare movement disorder of autosomal dominant inheritance with incomplete penetrance and variable expression. It was first described in 1993 in a large Midwestern family in which the affected members had rapid development of both dystonia and parkinsonism over hours or days with some progression over the following days or weeks and a subsequent stable course. The symptoms were unresponsive or minimally responsive to levodopa and other dopaminergic therapies. A second unrelated Midwestern family had a very similar presentation which was published in 1997. The first case in a European family was described in Ireland in 1999. Since then, several sporadic cases in different countries as well as other familiar cases have been described.

Linkage analysis to an 8 cM region on chromosome 19q13 was demonstrated in 1999 in the two initial Midwestern families, confirmed in the Irish and in a Polish kindred but not in a German family and later refined to a 5.9 cM minimal interval in 2004. Missense mutations in the *ATP1A3* gene which codes for the α3 subunit of the Na^+/K^+-ATPase pump were identified in 2004 in patients with the previously described familial and sporadic cases.

Pathogenesis and Pathophysiology

The relation between the Na^+/K^+-ATPase pump dysfunction and the development of symptoms is not well understood. Voltage-gated sodium channels are essential for the initiation and propagation of action potentials in neuronal cells. The transmembrane sodium gradient is maintained by the activity of the Na^+/K^+-ATPase pump, which belongs to the P-type ATPase group. Its α subunit has a catalytic function and there are three isoforms expressed in the nervous system: α1, α2, and α3, with α3 being expressed exclusively in neurons. Mutations in the α2 subunit have been associated with familial hemiplegic migraine type II and epilepsy. The missense mutations described in RDP patients result in a loss of activity or loss of folding stability of the protein, or both. Hence, in RDP, there is haploinsufficiency with reduced activity and expression of α3. An inability to keep up with a high demand for ion transport activity after stressful events probably underlies the development of dystonia and parkinsonian symptoms. Given the

heterogeneity of presentation and the reduced penetrance, it is assumed that additional genetic and/or environmental factors influence expression.

Clinical Features and Diagnostic Criteria

The classic presentation is of abrupt onset of asymmetric dystonia and parkinsonism over hours or a few days to weeks, with more involvement of bulbar and upper extremity muscles than of leg (rostro–caudal gradient). Bradykinesia and postural instability are the primary features of the parkinsonism. RDP usually begins in late childhood or early adulthood, with a range in age of onset from 4 to 55 years. Physical stressors, including fever, infection, excessive exercise, childbirth, or alcohol binges, or psychological stressors, have been reported as triggers. Digoxin may also be a trigger. After a few days or weeks of progression, a stable course with minimal improvement may follow over many years. Additional episodes with worsening of the case and then further plateau of function may be observed. There is minimal response to levodopa, dopamine agonists, and other antispasmodic agents.

Some individuals develop mild antecedent symptoms prior to the sentinel development of dystonia-parkinsonism. These include mild brachial dystonia or limb cramping, or parkinsonism.

The phenotype is variable even within the same family, and no consistent clinical differences have been observed between patients bearing different mutations. Some patients from the different families reported mild limb dystonia and cramping, sometimes in the form of writer's cramp, also transient dysarthria and retrocollis prior to the development of the abrupt severe symptoms.

Reports of a slowly progressive course as well as of fluctuating daily symptoms coinciding with periods of fatigue and exhaustion, similar to other channelopathies such as the episodic ataxias exist.

Parkinsonism was demonstrated in most patients by facial hypomimia with open mouth postures and drooling, severe bradykinesia, variable degrees of rigidity, and shuffling gait with postural instability without tremor. Sardonic smile, facial grimacing, dysarthria, dysphagia, truncal, and asymmetric predominately upper limb dystonia with painful spasms were the most common dystonic manifestations. The cranial features are reminiscent of Wilson disease.

A few patients had transient oculogyric crises at the time of onset, reminiscent of von Economo's disease, and seizures at onset were described in three mutation-positive individuals. Hyperreflexia with flexor plantar responses was common. Clinical depression at the onset of symptoms, probably reactive, responsive to antidepressant therapy was also frequently described. In addition, other psychiatric comorbidities including social phobia and generalized anxiety disorder were described in the Irish kindred.

Table 1 Diagnostic criteria for RDP[a]

Main criteria	Rapid development of dystonia with features of parkinsonism over minutes to days
	Rostro-caudal gradient of involvement
	Prominent bulbar findings
	Minimal or no response to levodopa or dopaminergic agents
Additional criteria	Minimal or no tremor at onset
	Occasional mild focal limb dystonia before onset
	Identifiable trigger at onset
	Rare second 'onsets' or abrupt worsening later in life
	Stabilization of symptoms within 1 month
	Minimal improvement overall (except for mild gait improvement)
	Low levels of HVA in CSF

[a]Adapted from Brashear et al. (2007).

In all patients with *ATP1A3* mutations, the clinical manifestations were limited to the central nervous system. However, in the latest family described in which the DYT12 locus was excluded, several family members had renal disease in adulthood.

Diagnostic criteria and a severity scale were published at the same time in the second kindred's description and were recently revised. These are summarized in **Table 1**.

Most patients and some asymptomatic carriers had low CSF levels of the dopamine metabolite, homovanillic acid (HVA), without relation to the disease severity or duration. However, based on normal results of [^{11}C]β-CFT PET imaging of RDP patients, this observation was not accounted for by a decrease in the number of presynaptic dopaminergic cells and dopamine reuptake sites. Magnetic resonance imaging is normal. The first and only pathologic study to date detailed the absence of pathologic changes in the brain of a patient with RDP.

Differential Diagnosis

RDP needs to be differentiated from other childhood, adolescence, and young adult onset of primary and secondary dystonias. The primary dystonias include DYT1, DYT6, and DYT13. DYT1 is an early onset primary dystonia which often presents insidiously in a limb (frequently the legs) and usually progresses in a caudal-to-rostral pattern, although it may remain focal in the limb, classically the arm. Involvement of cranial and cervical muscles, while it may be present, is less common. Interestingly, predominant bulbar and upper extremity involvement is a feature of DYT6 and DYT13 dystonia. However, to date most DYT6 patients are of

Amish-Mennonite origin, and DYT13 is limited to a single Italian family.

Dystonia-plus syndromes (dopa-responsive-dystonia and myoclonus-dystonia) need to be included in the differential diagnosis of RDP. Dopa-responsive-dystonia (DRD, DYT5, Segawa's disease), most commonly associated with mutations in the GTP cyclohydrolase I (*GCH1*) and less frequently to mutations in the tyrosine hydroxylase gene (*TH*), appears early in childhood and affects legs and trunk more than the arms although cervical muscles may be involved. It has classic diurnal fluctuations, worsening at the end of the day. In addition, parkinsonian features have been described in some patients. However, contrary to RDP, it responds dramatically and consistently to levodopa at low doses. Myoclonus-dystonia (MD), an autosomal dominant disorder associated with mutations in epsilon-sarcoglican (*SGCE*), is characterized by myoclonic jerks mainly involving the arms and axial muscles in combination with dystonia. It also develops often during childhood or early adolescence. Contrary to the other dystonic syndromes, myoclonus is often the predominant feature, with 'lightning jerks' that frequently are responsive to alcohol.

The combination of parkinsonism and dystonia is not exclusive of RPD. About 40–60% of patients with Wilson disease have neurological dysfunction as initial clinical manifestation. Although most commonly presenting with tremor, the dysarthria, dysphonia, parkinsonism, and dystonia are frequent manifestations, and hence the possibility of Wilson disease should be taken into consideration. As noted, the sardonic facial expression in RDP is very reminiscent of that in Wilson disease. Levodopa-induced and levodopa-responsive dystonia are the common features of idiopathic Parkinson's disease and a common presenting symptom of young-onset Parkinson's disease. However, the dystonia tends to affect the limbs and not the bulbar muscles; the onset is gradual with subsequent progression, and the patients respond well to levodopa. Young-onset Huntington disease (Westphal variant) is an important diagnostic consideration, especially in the presence of an autosomal dominant pedigree, as these patients are characterized by an akinetic-rigid syndrome with dystonia. Severe intellectual decline, frequent seizures, and myoclonus are also present and are distinct features.

Diagnostic Work-up/Tests

RDP should be considered as a diagnostic possibility in cases of levodopa unresponsive parkinsonism and in cases of atypical presentations of parkinsonism and dystonia with predominately bulbar and upper extremity symptoms even in the absence of family history, as de novo mutations have been described.

As mentioned above, more common causes of primary and secondary dystonia and early-onset parkinsonism should be excluded. Screening for Wilson disease is paramount as this is a treatable degenerative disorder. Brain imaging is recommended to exclude a structural lesion. Genetic testing for DYT1 dystonia, parkin mutations, and Huntington disease may be considered with proper genetic counseling. A levodopa trial to evaluate for DRD is recommended, and a trial with dopamine agonist or levodopa for levodopa-responsive parkinsonism should be considered. At this point, measurement of CSF HVA levels is not indicated, and it is a nonspecific finding. Genetic testing is now available and can be considered in the setting of proper counseling. As noted, not all cases of RDP have identifiable mutations.

Management/Prognosis

There is minimal or no response to dopaminergic agents, and only a few patients respond to other antispasmodic agents. There is only one case reported of an RDP patient undergoing deep brain stimulation, and no benefit was observed with bilateral GPi DBS. In a handful of patients, selective botulinum toxin injections in the limbs were helpful.

Unfortunately, from the reports of the published cases, the symptoms rarely improve significantly after the primary onset, although there is documentation of mild improvement, especially in the leg symptoms, in a few patients. The bulbar and arm symptoms do not tend to improve at all with time. Supportive therapy is recommended: this includes treatment and monitoring for dysphagia, physical therapy to prevent contractures, and treatment of psychiatric features, if present. Genetic counseling is also recommended.

The utility of decreasing physical stress has not been demonstrated, however because infections and other stressors may be the triggers, it has been postulated that careful treatment of insipient infections could be beneficial, and alcohol, psychologic stress, and excessive exercise, should be avoided when possible.

See also: Dystonia; DYT1; DYT5; DYT6, Mixed Phenotype Primary Dystonia; DYT11, DYT15, Myoclonus-dystonia; DYT13, Cranio-Cervical-Brachial; Painful Limbs Moving Extremities (PLME); Spasmodic Dysphonia: Focal Laryngeal Dystonia.

Further Reading

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DYT13, Cranio-Cervical-Brachial

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Glossary

Dystonia – Disorder characterized by involuntary movements and postures which are usually directional in nature.
Focal dystonia – Dystonia involving only one body region.
Generalized dystonia – Dystonia involving both the legs and at least one other body region, or one leg and the trunk.
Geste antagoniste – Specific sensory modality (e.g., light touch) used by a patient suffering from dystonia to lessen the abnormal posture or repetitive movements (also called sensory trick).

Null point – Position in which a dystonic tremor diminishes.
Primary dystonia – Isolated dystonia (absence of other movement disorder except tremor) and no secondary cause or structural abnormality.

Definition and History

Dystonia is an involuntary hyperkinetic movement disorder characterized by simultaneous contraction of agonist and antagonist muscles leading to abnormal postures or movements. Dystonia is classified as primary when it is the only movement disorder (except tremor), and there is no secondary etiology, and as secondary when it is associated with other movement disorders or if it is due to inherited and/or degenerative disorder or an etiology or structural lesion is demonstrated. Primary dystonia can be further classified according to the age of onset: early (age of onset less than 26 years, typically DYT1), late (age of onset greater than 26 years), and mixed early and late onset. DYT13 is one of the two forms with a mixed age of onset (the other being DYT6). PYT13 is characterized by segmental upper body dystonia with myoclonic-like jerks of the neck and shoulders. It was first described in 1997 in a large non-Jewish Italian family. The locus for this disorder was identified in 2001, but the gene has not yet been elucidated.

Pathogenesis/Pathophysiology

DYT13 is inherited in an autosomal dominant fashion with reduced penetrance (58%). It is caused by a mutation in a yet unknown gene at the locus 1p36.32–p36.13. One of the candidate genes is the *cvHsp* gene, which is a member of the heat-shock protein family. The protein is present in the brain (striatum, substantia nigra, and amygdala) and other tissues. It is interesting to note that it bears similarity to torsinA, the abnormal protein in DYT1, which is also a member of the heat-shock protein family.

Epidemiology/Risk Factors

DYT13 is a rare form of primary torsion dystonia. Only 11 cases have been reported so far, and all were members of a large non-Jewish Italian family. No risk factor has been identified at this point.

Clinical Features and Diagnostic Criteria

DYT13 has a very variable age of onset: it typically presents in adolescence (mean age 15.6 years), but the range is from 5 to 43 years. The dystonia classically starts in the cranio-cervical region (neck, face, larynx, and pharynx), and less commonly in the upper extremities. The patients described with DYT13 did not have any other movement disorder other than dystonia, with the exception of prominent jerky (Myoclonic - like) neck and shoulder movements and tremor in some. Compared to the patients with DYT6, the other form of mixed onset primary torsion dystonia, there seems to be less laryngeal involvement. The progression is typically slow, with most patients, being relatively mild and able to perform their daily activities. Of the 11 cases described, generalization occurred in only two, and in both the cases, the dystonia remained relatively mild and the patients remained ambulatory, despite the fact that they had a more diffuse involvement. This is in contrast to DYT1 where severe generalized dystonia may lead affected individuals to be wheelchair bound.

Differential Diagnosis

The differential diagnosis includes sporadic cervical dystonia, inherited dystonia with prominent cranio-cervical involvement (DYT4, DYT6, DYT7) as well as other forms of primary torsion dystonia (e.g., DYT1). Secondary causes of dystonia are less likely since this condition presents with isolated dystonia (with or without dystonic tremor, typically of the head), however, as it is a highly treatable disorder, Wilson disease should be considered. Structural lesions which may result in head postures may also be considered. As with all other forms of early onset dystonia, the dystonia-plus condition, dopa-responsive dystonia should also be kept in the differential.

In case of a dystonic tremor of the head, the differential diagnosis should also include essential tremor (in this condition, when a tremor of the head is present, there is also a tremor of the upper extremities) and head titubation (which is usually accompanied by other cerebellar features). Occasionally, Parkinson's disease may have a head tremor, but other features of the disease, such as rest tremor, rigidity, bradykinesia are present, and the tremor typically involves mainly the chin.

To differentiate a dystonic tremor from another type of tremor, a few characteristics can be very useful to the clinician: first, the dystonic tremor is typically irregular in amplitude and rhythm, there is typically an accompanying abnormal posture, a null point may be present, and a geste antagoniste is typically used by the patient to stop the tremor or improve the abnormal posture

Diagnostic Work-up/Tests

First, as it is the case for other types of dystonia, a careful and detailed family history should be performed. As this is an autosomal dominant disorder with reduced penetrance, in

theory, apparently sporadic cases may have this condition. However, such cases will not be identified until the gene is elucidated. Second, a medication history should be obtained, including current and past exposure to neuroleptics and antiemetics to elucidate medication induced tardive dystonia.

There is no specific test for DYT13, and when the diagnosis of DYT13 is suspected, it is because a primary dystonia involving the cervical and cranial muscles is present. The work-up is accordingly. MRI of the brain should be considered. It is also prudent to consider the diagnosis of Wilson disease, a treatable neurodegenerative disease in patients presenting before the age of 50 years. Evaluation for Wilson disease includes serum ceruloplasmin and slit lamp examination, and may include 24 h urine collection for copper. According to the patient's presentation, other secondary causes should be evaluated. In the presence of an isolated abnormal posture of the head (without dystonic tremor), one should consider MRI of the cervical spine to evaluate for a structural lesion of the spine or of the spinal cord.

Genetic testing for the DYT1 GAG deletion may be considered in: (1) young patients (less than 26 years), (2) if there is a positive family history of early-onset dystonia, and (3) in patients with evolution to generalized dystonia. A trial of L-dopa may be considered as an empiric diagnostic test for DYT5 (GTPCH1 deficiency), a treatable cause of dystonia. This is more likely if there is diurnal fluctuation, spasticity, parkinsonism, or a family history of dystonia or parkinsonism, however, cases with isolated cervical or brachial dystonia have been reported.

Once other causes have been eliminated and when the diagnosis of DYT13 is still suspected, there is unfortunately no clinical genetic testing available for this condition at this point of time.

Management

The preferential treatment for a focal dystonia in the cranio-cervical region and brachial regions is botulinum toxin injections. When the dystonia involves multiple other body parts or is generalized, treatment options include: anticholinergics (e.g., trihexiphenidyl), benzodiazepines (e.g., clonazepam), baclofen, or injections of botulinum toxin in the most affected muscle groups. Of note, a 1 month trial of levodopa/benserazide was performed in two of the affected patients without success. None of the reported patients have been treated with deep brain stimulation to our knowledge.

Prognosis

This form of primary torsion dystonia typically has a slow but definite progression to other body region(s). Only two of the 11 reported patients evolved to generalized dystonia. In all patients, including the patients with generalized dystonia, the prognosis was good with no impairment of daily activities.

See also: Cervical Dystonia; Dystonia; DYT1; DYT4, Autosomal Dominant Type Dystonia or Whispering Dysphonia; DYT5; DYT6, Mixed Phenotype Primary Dystonia; DYT7, Autosomal Dominant Focal Dystonia; Wilson's Disease.

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E

Electroencephalography (EEG)

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Glossary

Electroencephalogram (EEG) – A recording of electrical activity produced spontaneously by neurons in the brain, commonly used in the diagnosis and management of seizure disorders.
Seizure – Paroxysmal abnormal electrical activity produced by nerve cells in the central nervous system. These discharges may result in overt clinical symptoms or signs which may be experienced by the patient or observed by others.
Status epilepticus – A state of prolonged seizure activity or multiple seizures without a return to baseline.

Definition and History

Electroencephalography (EEG) is a technique used in the diagnosis and management of different forms of epilepsy and some movement disorders. EEG measures the electrical activity of the brain as a function of voltage potentials between different regions on the scalp. The electrical activity recorded is a summation of the activity of a large number of neurons in the cerebral cortex immediately beneath the skull. This registration provides useful information on both the normal activity of the brain in different states (e.g., sleep and wakefulness) and abnormal activities resulting from a variety of disease processes.

EEG has its origins in the long history of electrophysiology experimentation. However, the person generally credited with the first application of EEG to human subjects is Hans Berger (1873–1941), a German neuropsychiatrist, who began recording EEG from people in 1924. The use of EEG has increased significantly in recent decades, as technology has improved and new applications have been discovered.

Methods

The most routinely encountered method of EEG recording begins with the placement of recording electrodes (metal discs) at standardized anatomic locations on the scalp. The exact number and placement of electrodes can vary depending on the purposes of recording. Typically, all major regions of the brain will be covered to some extent. A conducting gel solution is used to reduce electrical resistance at the skin. The electrical signals acquired by the electrodes are then fed through an amplifier and filtered so that frequencies only within the usual bands, generated by cortical activity, are displayed. In the past, electrical signals were recorded on a continuously moving strip of paper by a pen that deviated up or down according to the changes in the voltage. Current EEG equipment allows the digitization of the analog EEG signals recorded by the electrodes, and therefore, they can be displayed and modified by a computer. In special cases, typically for localizing the epileptogenic cortex for the purpose of surgical resection, electrodes may be surgically placed inside the skull. They may be placed directly on the surface of the brain or stereotactically implanted within the brain in order to reach deep-lying brain structures. This enables much greater precision in the localization and characterization of electrographic abnormalities. Similar surface recordings may also be done during brain surgery to remove epileptic cortex, tumors, or other abnormal tissue.

EEG is sometimes necessary for the evaluation of the paroxysmal episodes of chorea or dystonia (paroxysmal dyskinesias). As these disorders are sometimes considered an interface between epilepsy and movement disorders, a search for a deep cortical or subcortical epileptic focus may require extra surface electrodes (double-density montages) or cortically placed electrodes.

The recorded electrical activity is routinely viewed as a series of continuous horizontal lines representing voltage differences between pairs of electrodes (**Figure 1**). Deviations of these lines, up or down, reflect changes in the

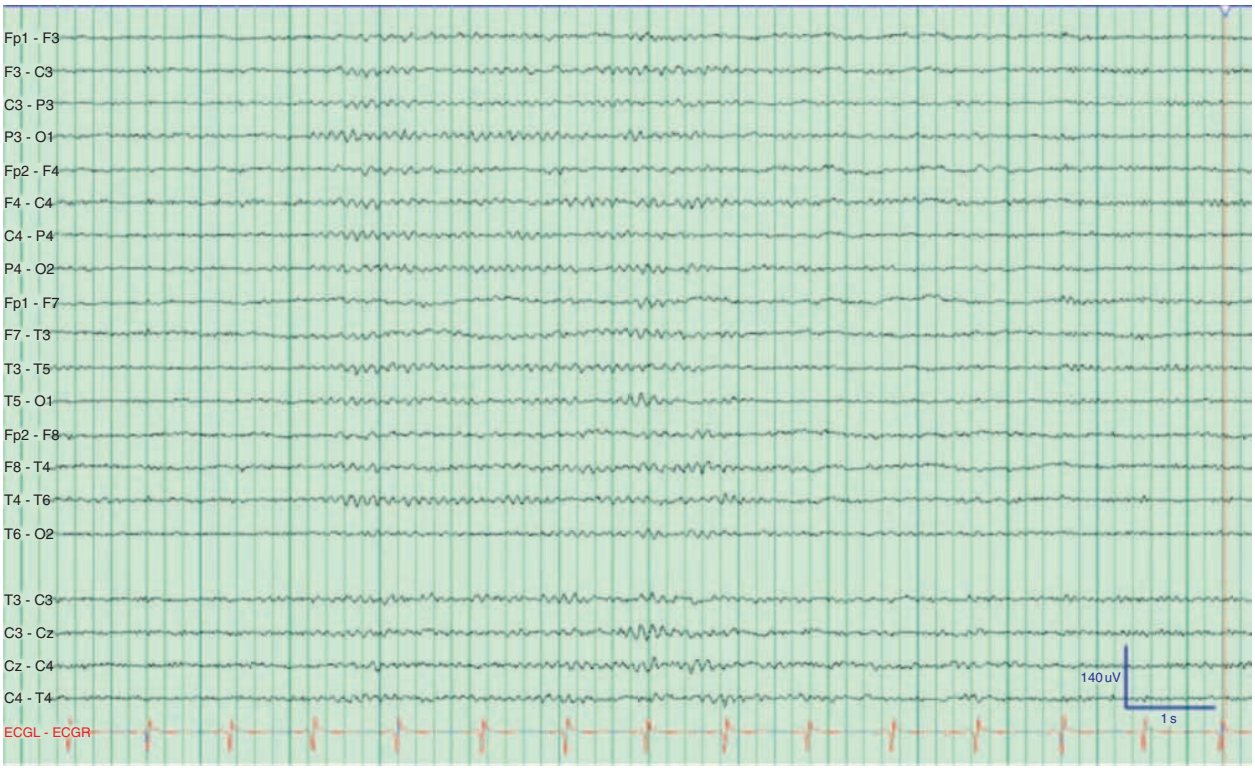

Figure 1 A snapshot of a normal EEG recording. Each vertical line represents 1 s. Each horizontal line represents the potential difference between two interconnected scalp electrodes. The letters refer to the brain region (Fp = frontopolar, F = frontal, C = central, P = parietal, O = occipital). Odd numbered electrodes are placed on the left side of the head and even numbers on the right. An ECG (cardiac) tracing is at bottom in red.

summated membrane potentials of large populations of cortical neurons. Rearrangement of the groupings of paired electrodes into different 'montages' allows an improved spatial analysis of the signals, and thus for an increased diagnostic efficacy. The actual amplitude or strength of a given signal may be measured, to a certain extent, by measuring the voltage between a single electrode and a relatively electrically neutral reference point such as the mastoid, or with the average of all electrical activity.

EEG interpretation is generally performed by neurologists, often with specialized training, by visual analysis. The complexity of EEG signals has precluded automatic, solely computerized EEG reading. Computerized EEG analysis has proved useful, however, in certain specialized situations such as long-term EEG monitoring in critically ill patients with strokes, brain trauma, and other life-threatening conditions.

Interpretation

The interpretation of the electroencephalogram rests on the differentiation between abnormal and normal electrical activity. The brain generates a continuous stream of activity that varies between wakefulness and the different stages of sleep, as well as with the level of alertness and environmental stimuli. These rhythms, generated or influenced by specific regions of the brain such as the thalamus, are the electrical representation of the normal function of the cerebral cortex. Well-established parameters for these findings are age specific. For example, a healthy adult in a state of wakefulness is expected to have a characteristic rhythm over the parietooccipital regions of the brain, consisting of monomorphic alpha (~8–13 Hz) waveforms. Other rhythms are normally seen over other parts of the brain. Changes in these basic patterns may suggest an underlying abnormality.

The types of abnormalities seen on EEG vary dramatically, and may include changes or loss of normal rhythms or the emergence of various abnormal rhythms. Abnormalities are analyzed in terms of their spatial location, waveform morphology, and rhythmicity, as well as their evolution over time. Although many different subtypes exist, there are only a few broad morphologic categories into which most abnormalities may be grouped:

1. decrease or increase of the underlying frequency;
2. decrease or increase in voltage/amplitude;
3. morphologically distinct activity.

These are further characterized by location (focal versus diffuse patterns), and more specifically, by their specific morphology and evolution.

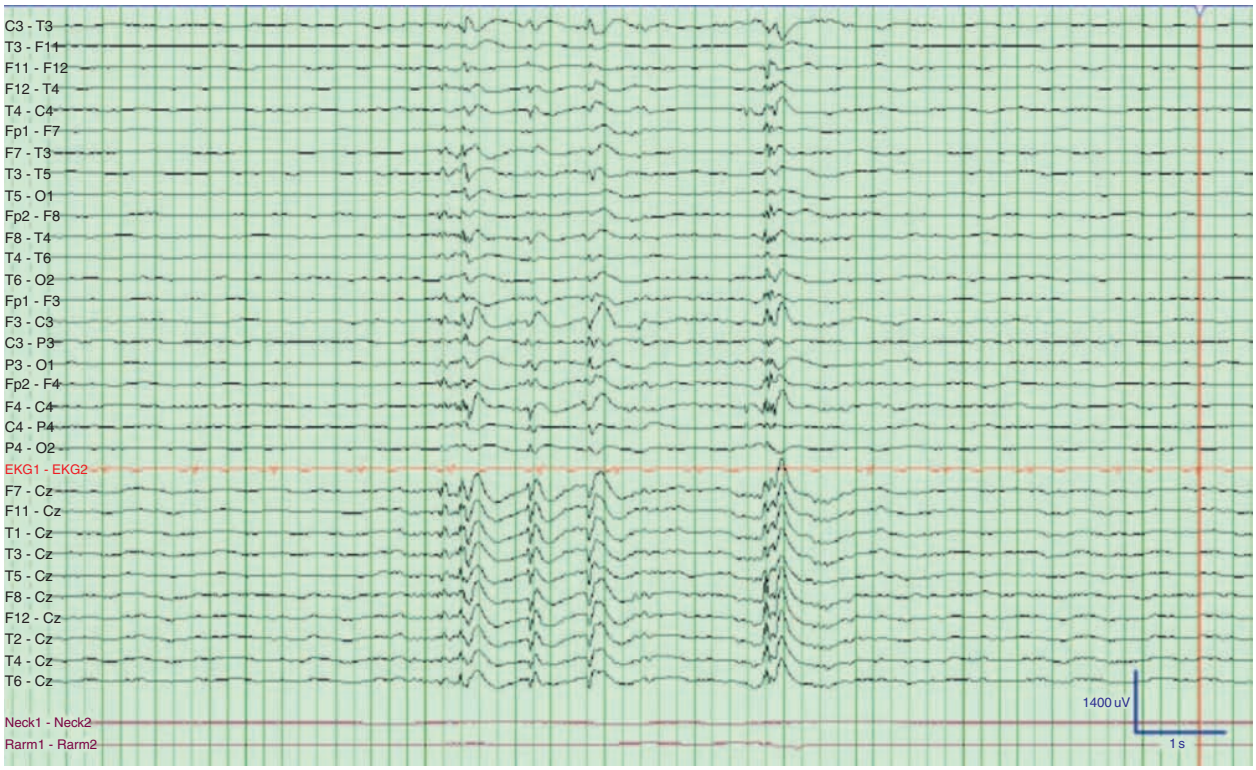

Figure 2 Abnormal epileptiform discharges are seen in the form of bursts of spike and slow wave activity.

The slowing of background rhythms may be seen in a wide variety of conditions, including metabolic abnormalities, medication effects, and postictal states. The EEG in patients with epilepsy characteristically shows interictal, sharply configured, and paroxysmal discharges called spikes, sharp waves, or epileptiform activity, a result of the hyperexcitability of these neuronal circuits (**Figure 2**). Sustained epileptiform discharges that evolve rhythmically are characteristic of seizures themselves. A normal interictal EEG, however, does not rule out a diagnosis of epilepsy.

Applications

In the evaluation of some movement disorders, EEG is a useful adjunctive tool when used in combination with the clinical history, physical examination, and other supportive data. When a clinical diagnosis of epilepsy is suspected, a routine EEG (~45 min) can often help confirm the diagnosis. In some cases, more information may be gleaned from a prolonged EEG that includes drowsiness and sleep, that is, states that often bring about abnormal activities that are absent in the awake state. Admission to a hospital for prolonged and continuous video EEG monitoring is useful in a variety of situations where diagnosis and management are difficult. The availability of ambulatory EEG devices has also extended the ability of the clinician to diagnose epilepsy.

EEG is also frequently used in the acute setting when serious and life-threatening conditions such as status epilepticus are of concern, particularly, as several studies have shown that subclinical status epilepticus tends to be underdiagnosed. In this setting, prolonged EEG monitoring may be the only objective way to ascertain if the seizure activity is ongoing and if the treatment is effective. Finally, the EEG is increasingly part of the physiologic monitoring performed in critical care units, to monitor ongoing cerebral activity and help identify and quantify serious conditions such as increased intracranial pressure or cerebral ischemia.

The standard EEG is invariably unchanged during abnormal movements related to movement disorders. For example, the intermittent movements of paroxysmal dyskinesia are often difficult to differentiate clinically from frontal lobe seizures. The EEG shows no changes during the dyskinesias. On the other hand, unless completely obscured by movement and muscle artifact, the EEG almost always shows abnormal activity during such seizures. Similarly, tics cause no EEG changes, whereas myoclonic seizures are invariably accompanied by diffuse spike/wave discharges.

See also: Cortical Myoclonus; Epilepsia Partialis Continua; Juvenile Myoclonic Epilepsy; Magnetoencephalography (MEG); Myoclonic Epilepsy with Ragged Red Fibers (MERRF); Myoclonus, Epileptic.

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http://www.aesnet.org/ – American Epilepsy Society.

Electromyography (EMG)

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Glossary

Amplitude cancellation – The reduction in signal amplitude due to the summation of overlapping positive and negative phases of concurrent muscle fiber potentials.
Electromyogram (EMG) – A recording of the field potentials generated by the currents that underlie muscle fiber action potentials.
Field potential – The potential difference (voltage) between two locations caused by the currents associated with the muscle fiber action potentials.
Interference EMG – The signal obtained by the superimposition of many muscle fiber potentials.
Motor unit – A motor neuron, its axon, and the muscle fibers it innervates.
Rectification – A processed EMG recording in which the negative phases of the muscle fiber potentials are either eliminated (half-wave rectification) or converted to an absolute value (full-wave rectification).

Electromyography (EMG) is the technique used to record the electrical signals generated by muscle (myo) fibers in response to activation by the nervous system. The recording obtained with this technique is known as an electromyogram. The first report of the technique was published in 1849 when the German physiologist Emil de Bois-Reymond (1818–1896) demonstrated the existence of electrical currents in nerves and muscle.

The electrical signals measured with EMG correspond to the field potentials associated with the currents that underlie muscle fiber action potentials. The field potentials are recorded with electrodes that are either attached to the skin over the muscle or inserted into the muscle. Because the electrodes remain in the same location during a muscle contraction, they detect the field potentials as the action potentials propagate along the muscle fibers from the neuromuscular junctions to the ends of the fibers.

A typical electromyogram obtained during a muscle contraction comprises the summed field potentials due to the activation of many muscle fibers. The number of muscle fibers activated during a muscle contraction depends on the intensity of the contraction and is related to the number of motor neurons that are recruited for the task. A motor neuron and the few hundred muscle fibers it innervates are known as a motor unit and the nervous system controls muscle force by varying the amount of motor unit activity. Because there is usually a high fidelity between the generation of an action potential by a motor neuron and its subsequent appearance as muscle fiber action potentials, EMG recordings provide information about the activation of muscle by the nervous system.

Depending on the geometry and location of the electrodes, an electromyogram can range from a recording of the muscle fiber potentials belonging to a single motor unit through to those produced by many motor units (**Figure 1**). The most common approach used in EMG is to attach a pair of electrodes to the skin, connect the electrodes to a differential amplifier, and record the field potentials as the action potentials propagate along many muscle fibers. The subsequent recording, which is known as a surface EMG, comprises waveforms with varying numbers of positive and negative phases that result from the field potentials approaching, passing under, and then traveling away from the electrodes. Because the electromyogram comprises the sum of these waveforms, the field potential associated with each action potential is distorted by the summation of the overlapping positive and negative phases and the composite signal is referred to as an interference EMG.

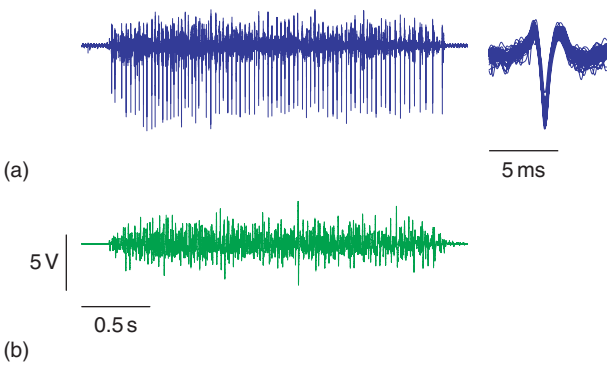

Figure 1 EMG recordings obtained during a voluntary contraction of the tibialis anterior muscle. (a) An intramuscular electrode detected a signal that was dominated by the field potentials associated with the activation of a single motor unit. The potentials for the single motor unit are superimposed to the right of the trace. (b) A surface recording of an interference EMG that comprised the summed potentials of many motor units.

A controversial issue in the interpretation of the electromyogram is to determine the information it provides about the output from the spinal cord. Because the electrodes record field potentials generated by muscle fiber action potentials, the structure of the interference EMG is also influenced by the properties of the muscle fibers and the characteristics of the recording configuration in addition to the activation of the motor units by the nervous system. One of the key properties of the interference EMG, which has been known for almost 100 years (Adrian, 1925), is that summation of the overlapping positive and negative phases of concurrent field potentials reduces the absolute amplitude of the signal. This effect is known as amplitude cancellation. The reduction in signal amplitude due to cancellation from the summation process increases progressively with contraction force and reaches a value of about 70% during a maximal contraction. Although EMG amplitude during a submaximal contraction provides a reasonable estimate of muscle force when normalized to the value recorded during a maximal contraction, the waveform associated with each motor unit is altered by cancellation. As a consequence, it is usually difficult to identify the waveforms generated by single motor units in an interference EMG. Technical advances with multiple-electrode systems, however, have enhanced the ability to decompose the interference EMG into its constituent motor unit waveforms.

Several measurements can be used to characterize the interference EMG. In general, these include quantifying its amplitude and estimating its spectral properties. Both assessments begin by band-pass filtering the recording in the range of 10–800 Hz to attenuate the contributions from sources other than the muscle of interest. Although filtering can reduce the contributions by movement artifacts and signals generated by radiofrequency sources, it does not alter contributions from neighboring muscles, which are referred to as cross talk. To estimate EMG amplitude, the filtered signal is rectified to obtain the absolute values and averages are calculated over specified intervals. EMG amplitude is reported in volts or as a percentage of the value obtained during a reference contraction. The standards advocated by the International Society of Electrophysiology and Kinesiology for reporting EMG data can be found at www.isek-online.org/standards_emg.asp. Note that rectification does not prevent amplitude cancellation because cancellation occurs before the signal is rectified.

Many investigators determine the spectral content of the electromyogram. Due to the significant influence of the shape of the recorded field potentials on the distribution of power in the density spectrum, changes in the shapes of the potentials, such as those that can occur during fatiguing contractions, cause the distribution to shift. Aside from the influence of such global effects on the activated muscle fibers, however, a spectral analysis provides limited information about the motor units that are activated during a contraction. The factors that also influence the frequency spectrum include: (1) distortion of the field potentials by the summation of overlapping positive and negative phases; (2) the distribution of the rates at which the motor neurons discharge action potentials; (3) the amount of correlation in the discharge times of the activated motor units to the frequency spectrum; (4) the anatomical properties of the muscle fibers (e.g., length, angle of inclination to the surface, and location of the neuromuscular junctions); (5) the distance between the activated muscle fibers and recording electrodes; and (6) rectification. Due to the multiple factors that can influence the frequency spectrum, a spectral analysis of the electromyogram does not provide information about such properties as the upper limit of recruitment, the types of motor units recruited during a contraction, or the fiber type proportions of a muscle.

Nonetheless, the electromyogram does provide useful information about the timing of muscle activation and, when normalized, an estimate of the force exerted by the muscle. These features are useful for applications that range from the control of prosthetic devices to the assessment of strategies used by the nervous system to perform various tasks.

Acknowledgments

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See also: Event-Related Potentials: Slow Potentials; Neurogenic Muscle Weakness, Ataxia, and Retinitis Pigmentosa (NARP).

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Encephalitis Lethargica and Postencephalitic Parkinsonism

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Glossary

Ataxia – Incoordination and unsteadiness due to the brain's failure to regulate the body's posture, strength, and direction of limb movements.
Athetosis – Involuntary writhing movements particularly of the arms and hands.
Bradykinesia – Slowed ability to start and continue movements, and impaired ability to adjust the body's position.
Festination – A gait marked by an involuntary hurrying in walking.
Hypomimia – Masked-like facial expression.
Ptosis – An abnormally low position (drooping) of the upper eyelid.
Somnolence – Sleepiness, the state of feeling drowsy, ready to fall asleep.

Encephalitis Lethargica

Definition and History

Discovery

During the winter of 1916–1917, in the midst of World War I (WWI), a small number of patients developed a previously unknown acute infectious disease. Constantin von Economo in Austria, Cruchet in France, Hall in England, and others described a prodromal phase with symptoms of an upper respiratory infection, followed by profound lethargy and somnolence, usually associated with ocular and bulbar palsies and often with extrapyramidal manifestations, including a state resembling Parkinson's disease. Somnolence was distinctive in that, if awakened, patients were lucid and could readily answer questions and follow commands, but if left to themselves, they immediately returned to sleep (**Figure 1**). On 17 April 1917, at a meeting of the Vienna Society for Psychiatry and Neurology, von Economo presented his findings on

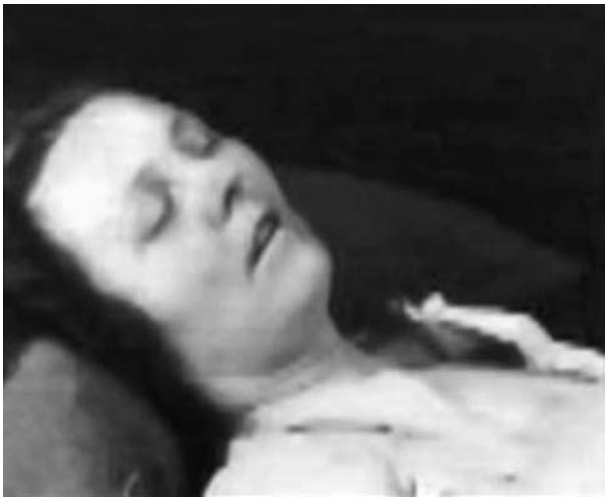

Figure 1 Somnolent female EL patient.

this new disease, which he named, encepha litis lethargica (EL). Subsequently, cases of EL were recognized throughout the world.

Epidemic

By 1920, EL had become a world epidemic spreading first through Europe and then overseas to North America. During this time, EL was reported under various names, including epidemic encephalitis, von Economo's disease, and the popular 'sleeping or sleepy sickness.' The available data indicate that the highest number of cases occurred in 1920 and again in 1924. Conservatively, there were 1 000 000 cases worldwide with a possible mortality of 50% during the epidemic period, with tapering rates after 1930. Since 1940, sporadic reports have continued to appear, suggesting that an EL epidemic might recur 1 day. One such 2004 report from England described 20 cases that seemed 'remarkably similar' to the acute cases described in the years of the epidemic. However, the absence of a pathognomonic sign associated with EL makes diagnosis problematic, and it is questionable whether the post 1940 phenotype is the same as that seen during the epidemic period.

Pathogenesis/Pathophysiology

Etiology

At the time of the EL epidemic, various toxicologic, bacterial, or viral causes were suspected. EL was suggested to relate to the Spanish influenza epidemic. Yet, epidemiological data failed to support a direct association of the two diseases. Furthermore, the improved understanding of influenza, brought by the isolation of its virus in 1934, rendered the notion of direct connections between influenza and EL largely untenable. Other studies that linked viral or bacterial infection to EL were later criticized for methodological weakness.

Modern efforts to identify influenza RNA segments in the brains of EL victims have not been successful, again casting additional doubt on the influenza hypothesis. However, these results are inconclusive, because very few brains are available and it is unknown whether RNA fragments survive for 80 years in nonrefrigerated formalin fixation. A recent English study that identified 20 putative new EL cases reported that 11 had preceding pharyngitis. The study suggested that the EL phenotype might be a secondary autoimmunity to Group A *Streptococcus* infection, that is, a PANDA (pediatric autoimmune neuropsychiatric disorders associated with *Streptococcus* infections) analogous to Sydenham's chorea.

Pathology

Postmortem study of patients who died during the acute phase of EL revealed findings that were later recognized as typical of viral encephalitis. The gross inspection of a fresh brain revealed congestion of meningeal and cerebral capillaries, causing the brain (**Figure 2**) to be reddish in cross-section. The microscopic examination of formalin-fixed sections showed perivascular lymphocytic and plasma cell infiltration, endothelial proliferation, and acute degenerative changes in neurons, including swelling, eccentric nuclei, chromatolysis, neuronphagia, and some glial reactions. The midbrain, particularly the substantia nigra, the pontine tegmetum, and the basal ganglia showed the most marked changes, but there was considerable variation from patient to patient. In cases coming to autopsy in the chronic phase (cf. below), there was a severe loss of neurons in the substantia nigra, more severe than that typically seen in idiopathic Parkinson's disease. This lesion of the substantia nigra was somewhat perplexing at the time, because the existence of the dopaminergic nigrostriatal system was then unknown and it was not until several decades later that the substantia nigra was recognized as the primary site of pathology in Parkinson's disease. Neurofibrillary tangles were prominent in surviving neurons, but in contrast to Parkinson's disease, Lewy bodies were absent.

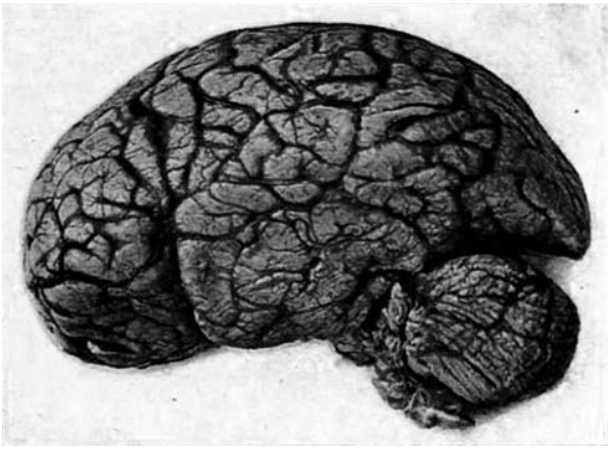

Figure 2 Left brain hemisphere of morbid EL case.

Epidemiology/Risk Factors

Transmission

There was no strong evidence suggesting that EL was contagious. Clinicians speculated that transmission was possibly through nonsymptomatic carriers or the air, because the 1919–1920 Italian and Austrian epidemics were only a week apart, which is consistent with strong winds across the Alps.

Risk factors

It was speculated that the conditions found during WWI, such as concentrated human populations and general hardship, predisposed a person to acquire EL. It has also been suggested that Jews had a higher incidence of EL.

Others suggested the correlation of physical or emotional trauma with the beginning of the acute or chronic phases. With the epidemic occurrence of influenza during the same time period, some clinicians thought that acquiring influenza could increase a person's risk of developing EL. Finally, some clinicians believed that multiple different pathogens could act as symbiotic partners with those of EL.

Clinical Features and Diagnostic Criteria

Prodromal stage

Many cases of EL were preceded by a typical 'grippe-like' prodromal stage of general discomfort, lassitude, seediness, shivering, headache, vertigo, vomiting, a slight fever, and mild pharyngitis. This stage was almost always short, often lasting only 1–2 days.

Disease stage

The gamut of signs and symptoms associated with the acute phase of the disease was wide, but several typical syndromes were identified: somnolent–ophthalmoplegic (somnolence, ocular movement disorders); parkinsonism with bradykinesia, rigidity, festination, spasticity, and tremor; psychiatric with no somatic symptoms; cerebellar with ataxic gait and speech; and hyperkinetic presentation with chorea, athetosis, seizures, and restlessness. Because the signs and symptoms varied between individuals, could change rapidly within any single individual, and could sometimes be very transient, some clinicians of the period did not consider these categories particularly useful. The variations in the manifestations of the disease were presumed to have resulted from the variation in the locus of the infection within the CNS.

Those who survived the initial disease state gradually recovered over several weeks to a year. However, they were typically afflicted with a persistent fatigue or inertia and were said to have 'neurasthernia.' Many had significant personality changes, and a broad variety of behavioral disorders (particularly in children) and bizarre compulsions and tics. The pejorative term, 'Apache,' was used to characterize these children, referring to the wild behavior attributed to Apache Indians.

In at least a third of the survivors, as the lethargy subsided, signs of parkinsonism developed with tremor, rigidity, bradykinesia, festinating gait, stooped posture, scoliosis, masked faces, hypophonic and tachyphemic speech, pallilalia, drooling, and seborrhea: this phase of the disease was termed postencephalitic parkinsonism (PEP). The Parkinsonian syndrome was distinctive because of features not typical of Parkinson's disease such as bizarre postural abnormalities, oculogyric crises, and ocular palsies, including ptosis, diplopia, and paralysis of upward gaze.

Oculogyric crises were a particular associated feature of PEP. In a typical crisis, the patient abruptly lapsed into a rigid state with the head and eyes deviated upward and to one side as if the patient were intently staring at the ceiling. These attacks lasted a few minutes to many hours and then suddenly stopped.

Follow-up studies documented that the majority of EL survivors developed sequalae, PEP being the most prominent. Some observers stated that if one included mild degrees of facial hypomimia, all survivors had PEP to some degree. In children, behavioral problems were also frequent. Some patients who had not experienced a clinically apparent acute phase of illness developed typical PEP insidiously. The long-term clinical course of EL was marked by periods of improvement interspersed with evidence of progression. In the 1920s, patients with PEP were more numerous than those with idiopathic Parkinson's disease. They formed a distinct population cohort that accounted for two thirds or more of the Parkinsonian patients seen in hospitals and clinics at that time. With the decline in the incidence of PEP after the epidemic, the proportion of Parkinsonian patients classified as PEP also declined to about a half during the 1950s compared with that in the period 1931–1942. By the early 1960s, the proportion was ~10%. By 1970, only rare elderly long-term survivors remained.

Severe disability and behavioral disorders led to institutional care for many of the chronic phase patients in the years of the epidemic. Groups of survivors could still be found in the 1960s in chronic care facilities, some specialized for their care such as the Highlands Hospital in England. PEP patients examined in the 1960s, four decades after the epidemic, appeared to have been stable for many years and showed few signs of continuing progression. One cluster of long-term survivors was popularized by Oliver Sacks in his 1973 book, *Awakenings*, and in the 1990 movie by the same name.

Differential Diagnosis

At the time of the epidemic, diagnosis in the acute phase was typically suggested by signs and symptoms of a generalized disturbance of the CNS, combined with disturbed sleep rhythm, usually lethargy and somnolence, ocular disturbances, diplopia, and bulbar palsies, unreactive pupils, and acute behavioral disturbances. However, diagnosis, especially of the nonsomnolent types, was often based on the exclusion of other neurological conditions. One monograph of EL from the period stated: 'And while no other disease, perhaps, presents so many difficulties in diagnosis as does this protean complex. . .that while it usually offers very close resemblance to one or another condition, careful and painstaking study and comparison will reveal either some incongruity, some essential

symptom lacking or a superabundance of elements, thus offering a definite aid or conclusive basis for differential diagnosis.' Since EL lacked any definitive sign, it is possible and perhaps likely that it was substantially overdiagnosed. The subsequent development of PEP is probably the best diagnostic sign. However, in children, seizures and the rapid development of antisocial behavior in the absence of traumatic brain damage were the most reliable diagnostic signs.

In patients in the chronic phase with PEP, the major differential diagnosis was that of Parkinson's disease. The relative youth of the PEP patients was an important point of distinction. However, as the affected PEP cohort aged through the 1940s and 1950s, the distinction occasionally presented more difficulty. Useful points of differentiation included tremor characteristics, because PEP patients rarely had the pill-rolling alternation characteristic of the idiopathic disease. Moreover, PEP featured prominent sleep disturbances, respiratory anomalies such as hyperpnea and respiratory tics, various dysarthrias, palilalia, and echolalia, and choreiforrn, dystonic, and athetotic movements. Psychiatric disturbances and personality changes were also common. Finally, the occurrence of ocuolgyric crises served as the most widely accepted sign of the PEP disorder.

Arteriosclerotoic parkinsonism was distinguished by the advanced age of the patients and the prominence of lower extremity involvement with gait apraxia. Wilson's disease presenting as juvenile parkinsonism and the rigid form of Huntington's disease could have readily been confused with PEP. The finding of the Kayser–Fleischer ring in the former and a positive family history in the latter would have suggested the correct diagnosis.

Several similar morbid entities unknown in the epidemic time have since been recognized, notably, progressive supranuclear palsy (PSP), multiple system atrophy (MSA), striatonigral degeneration (SND), and corticobasal degeneration (CBG). PSP, first identified by Richardson in 1964, may have been misdiagnosed as PEP during the epidemic period. However, the disturbance in ocular motility in PSP differed from PEP and the characteristic supranuclear palsy of PSP was never described in PEP. The combination of cerebellar signs with a primarily bradykinetic Parkinsonian syndrome, typical of MSA, was within the clinical spectrum of PEP, but the relentless progression of disability was not typical of PEP. Likewise, it is possible that some cases of familial spinocerebellar degenerations were included in reported series of PEP.

Diagnostic Work-Up/Test

Spinal fluid lymphocytosis sometimes occurred with increased protein levels, although rarely above 100 mg ml^{-1}. At the time of the epidemic, the value of determining the CSF sugar concentration was emphasized to exclude tubercular meningitis. Abnormal colloidal gold curves, similar to those observed in acute polio and neurosyphilis, were also reported. The significance of those curves is not clear, but many years later, oligoclonal bands in CSF were reported in contemporary cases of EL. There were no laboratory aids in the diagnosis of the chronic phase of PEP. CT and MRI scanning were not yet available. Pneumoencephalography was rarely performed.

Management

During the epidemic period, many different treatments for EL were utilized. In New York, a large-scale effort supervised by the Matheson Commission was devoted to developing vaccines to treat the disease, using the herpes simplex virus and *Streptococcus viridans* independently. The herpes vaccine was reported, by the Commission, to be an effective treatment, yet researchers have since disputed this claim. In relation to the focal infection theory of the time, oral infections were thought to be a precursor to EL, and patients were often prescribed to have some or all of their teeth extracted. In most cases, the management of EL patients during the epidemic period was primarily supportive. No specific therapy has emerged from recent experiences with the sporadic cases that have been reported. The possibility that some cases represent autoimmune disorders has suggested immunosuppressive therapy, and some recent cases have responded well to treatment with methylprednisolone.

The treatment of the chronic phase during and following the epidemic of the early twentieth century relied primarily on the then treatment of Parkinson's disease, Belladonna alkaloids. These anticholinergic agents were moderately effective in reducing parkinsonism and greatly reduced the frequency of oculogyric crises. High doses were often used and care was needed because of the antimuscarinic side effects, including xerostomia, blurred vision, constipation, hyperthermia, and delirium ('the Belladonna jag'). The Belladonna preparations were later superseded by synthetic anticholinergic agents such as trihexyphenidyl and benztropine. When levodopa therapy was introduced in the 1960s, there were few long-term survivors of EL. Levodopa was effective in suppressing symptoms in PEP patients, but the drug's efficacy was compromised by the side effects, including choreiform dyskinesias and a reappearance of behavioral disorders, psychoses, and compulsive tics that had been quiescent for many years. Insufficient experience with stereotaxic basal ganglia surgery such as thalamotomy in PEP patients does not permit any conclusions.

See also: Alzheimer's Disease and Parkinsonism; Basal Ganglia; Basal Ganglia, Functional Organization; Bradykinesia; Chorea; Fahn–Marsden Rating Scale; Gait Disturbances in Parkinsonism; Glucocerebrosidase Gene Mutations and Parkinsonism; Juvenile Parkinsonism;

Levodopa; MPTP; Neurofibrillary Tangles; Parkinson, James; Parkinson's Disease: Definition, Diagnosis, and Management; Substantia Nigra.

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Epilepsia Partialis Continua

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Glossary

Focal seizure – A seizure beginning locally in a specific part of the brain.
Clonic movement – Repetitive, rhythmic, jerking motions seen during some seizures; clonic activity is diffuse during a tonic–conic seizure, but may be restricted to a limb or to the face during a focal seizure.
Electrocorticography – An EEG recorded directly from the surface of the brain.
Rasmussen's encephalitis – A progressive, unilateral inflammatory disorder often associated with continuous focal motor seizures.

Definition and History

Epilepsia partialis continua (EPC) is a form of partial status epilepticus most commonly consisting of prolonged focal motor seizures affecting the motor strip of one hemisphere, and with a clinical correlate which tends to be localized to one motor region or side of the body. It was known in the past as Kojevnikov syndrome as he was the first to describe and document the syndrome in 1894. His patients suffered from very prolonged (up to 5 years) focal motor jerks, which Kojevnikov believed were secondary to injury of the motor strip. Other Russian physicians of the time observed similar phenomenon and linked it to encephalitis occurring in Siberia in the spring–summer cycle. Beginning in the 1950s, Rasmussen and colleagues described numerous cases of focal motor status epilepticus related to a rare, progressive, localized encephalitis. The continuous jerking movements of such seizures share some features with nonictal myoclonus or tics. Myoclonus, however, usually migrates from place to place on the body, and tics include more complex movements involving several muscle groups. In addition, unlike EPC, tics can usually be voluntarily suppressed for a time.

Pathogenesis/Pathophysiology

EPC is caused by focal injury to the cortex. The numerous possible etiologies for such injuries include inflammatory and infectious lesions, anoxia and ischemia, vascular lesions, metabolic abnormalities, and neoplastic or paraneoplastic lesions. EPC has been found to result from both cortical and subcortical sources based on both human and animal

studies. The pathophysiology is somewhat variable based on the cause. For instance, in Rasmussen's encephalitis, a common cause of EPC, pathologic analysis reveals evidence of acute and chronic inflammation with cytotoxic T cells which damage local neurons, resulting in abnormalities of normal neuronal communication and development of epileptic pathways.

Epidemiology/Risk Factors

The exact prevalence of EPC has not been clearly determined. A study in Great Britain estimated prevalence at less than one per million. There is increased incidence in certain disease states. In some studies, up to 50% of patients with Rasmussen's encephalitis will develop EPC. EPC has been reported in numerous diseases. Though not an exhaustive list, some of the other associated diseases include other forms of measles and other viral encephalitides, developmental malformations such as cortical dysplasia and migration abnormalities, mitochondrial diseases, cerebrovascular disease, neoplastic and paraneoplastic processes, metabolic abnormalities, multiple sclerosis, Alper's syndrome, Creutzfeldt–Jakob disease, human immunodeficiency virus (HIV), and progressive multifocal leukoencephalopathy.

Clinical Features and Diagnostic Criteria

EPC is characterized by continuous, repetitive clonic activity limited to a focal muscle segment or body region. This can be exquisitely focal (e.g., in the thumb) or can involve multiple muscle groups, and can even migrate over time. Though EPC is generally unilateral, cases of bilateral partial motor seizure status epilepticus have been reported, though it is not clear if these should be included under the description of EPC. In extreme cases, EPC can continue for a very prolonged period of time (up to years). Consciousness is typically maintained. The twitching varies in frequency but is typically once to twice per second. It continues during sleep. Focal of weakness or sensory abnormalities may be present. EPC is frequently accompanied by other types of seizures including 'Jacksonian' seizures (which move from place to place on the body) and tonic–clonic seizures. As EPC is a result of an underlying inciting process, other symptoms can often be present and are highly variable depending on the specific disease state.

Differential Diagnosis

The differential diagnosis for prolonged focal motor seizures is broad and can vary depending on whether clinical presentation, electroencephalographic record, or both are used in the diagnosis. The list includes nonepileptic myoclonus, sleep myoclonus, chorea, tremors, dystonias, hemifacial spasm, tics, sleep disorders, myoclonus with various types of generalized epilepsies, (e.g., juvenile mycoclonic epilepsy), and myoclonic status epilepticus.

Diagnostic Workup/Tests

Electroencephalography (EEG) may be useful in the diagnosis and management of EPC. However, it should be noted that EEG may be completely normal in a significant proportion of EPC, and thus a normal EEG does not necessarily rule out the diagnosis. It has been reported that in some cases of EPC with normal surface electrode recordings, abnormalities have been demonstrated using electrocorticography, indicating a deep or very focal source. In those cases that do show EEG correlates, there is no specific pathognomonic electrographic pattern that emerges, and there is wide variance in the numbers of clinically affected patients who demonstrate EEG changes. Abnormalities may include irregular sharp and spike waves, particularly over the motor cortex, and periodic lateralized epileptiform discharges (PLEDs). A full neurologic history and exam along with extensive diagnostic workup is generally indicated, and may include imaging with magnetic resonance (MR), single photon emission computed tomography (SPECT), positron emission tomography (PET), spinal fluid analysis, brain biopsy, or laboratory analysis for inherited or acquired forms of metabolic or hereditary abnormalities.

Management

Identification and treatment of the underlying is the primary goal. Medical treatment varies greatly depending on the diagnosis. Medical management of the seizure disorder itself is a somewhat controversial topic in recent years as there is a question as to whether aggressive treatment of partial motor seizures is effective and beneficial. The primary medications include valproate, ethosuximide, and piracetam for the myoclonic seizure activity. Carbamazepine may be effective in some cases, and benzodiazepines have also been reported as useful.

Prognosis

The prognosis of EPC depends largely on the inciting etiology. Often, EPC due to metabolic abnormalities or medication effect may resolve with removal of the agent. EPC secondary to focal lesions such as stroke or tumor may gradually resolve over time with surgical resection or medical management (and healing of the region). EPC due to infectious/inflammatory etiologies such as Rasmussen's encephalitis tends to have a more prolonged course, and are more refractory to treatment with antiepileptic medications. Rasmussen's encephalitis causes

progressive neurologic decline in the affected hemisphere, and hemispherectomy may be considered in refractory cases.

See also: Cortical Myoclonus; Electroencephalography (EEG); Juvenile Myoclonic Epilepsy; Magnetoencephalography (MEG); Myoclonus, Epileptic.

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Essential Tremor: Animal Models

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Glossary

Essential tremor (ET) – A clinical diagnosis based on the presence of bilateral upper extremity appendicular tremor without other neurological signs.
$GABA_A$ receptor – One of two (A and B subtypes) ligand-gated ion channels that bind the 'inhibitory' neurotransmitter γ-aminobutyric acid (GABA). $GABA_A$ receptors harbor allosteric binding sites for benzodiazepines, ethanol, and several other small molecules.
Harmaline – A β-carboline found in plants. In mammals, harmaline produces a tremor by activating inferior olivary neurons and their climbing fiber projections to cerebellar Purkinje cells.
Penitrem A – A tremorgenic mycotoxin that is toxic to cerebellar Purkinje cells.
Tremor – An abnormal repetitive and rhythmic movement of any part of the body.

What is Essential Tremor?

Definition and Clinical Features

To this day, essential tremor (ET) remains a clinical diagnosis. ET is an action tremor with both postural and kinetic components. ET exhibits clinical heterogeneity in terms of anatomical distribution, the relative intensity of its postural and kinetic components, and concomitant neurological features. The NIH Collaborative Genetic Criteria and the Consensus Statement of the Movement Disorder Society (MDS) have been used for the diagnosis of ET in subjects entering clinical trials. The NIH Collaborative Genetic Criteria includes the categories of 'definite, probable, possible, and unrateable' ET. The Consensus Statement of the MDS defines 'classic ET' as a bilateral, largely postural or kinetic tremor involving the hands and forearms. Exclusion criteria for 'classic ET' include the presence of abnormal neurological signs, particularly dystonia.

The differential diagnosis of ET is broad since an appendicular action tremor may be a manifestation of numerous metabolic, structural, nutritional, and infectious disorders of the central nervous system (CNS). For example, action tremors may appear after an ischemic stroke or in the setting of hyperthyroidism. In addition, action tremors are side effects of many prescription drugs, particularly those used to treat psychiatric and neurological disorders. Well-known culprits include lithium and valproic acid.

In contrast to traditional views, ET is much more than isolated action tremor of the arms. In fact, the clinical spectrum of ET includes nonmotor and additional motor features. Nonmotor features may include mild cognitive decline, olfactory deficits, and sensorineural hearing impairment. In addition to head, voice, and leg tremor, many subjects with ET also exhibit mild gait ataxia. ET is probably a disorder with important etiological, pathological, and clinical heterogeneity, with action tremor of the arms as a common feature.

Epidemiology

ET is a common movement disorder with prevalence estimates ranging from 0.5% to 5%. Prevalence increases with age. ET appears to affect all racial and ethnic groups.

Neurophysiology

The frequency of ET is between 4 and 12 Hz. ET is an action tremor with postural and kinetic components. In general, tremor frequency decreases with age. Mechanical loads exert minimal effect on ET frequency, which distinguishes ET from enhanced physiological tremor. Multiple lines of experimental evidence suggest that ET is produced by a central nonlinear oscillator.

Genetics

Reported positive family history in subjects with ET has varied widely in published reports (17–100%). Population-based family and twin studies have provided stronger support for the idea that genetic factors contribute to the etiopathogenesis of ET. Genetic linkage studies have identified susceptibility loci on 3q13 and 2p24.1. A recent genome-wide association study using a sample of 452 Icelandic ET cases and 14 394 population controls identified two markers (rs9652490 and rs11856808) in intron 3 of *LINGO1* on 15q24.3 which showed significant association with ET. The encoded protein, LINGO1, exerts regulatory effects on neuronal survival, axon regeneration, and oligodendrocyte maturation.

Postmortem pathology

The neural pathology of ET has received much less attention than other common age-related neurological disorders such as Parkinson and Alzheimer diseases. Recent work has consistently identified cerebellar cortical pathology in ET. Important findings have included Purkinje cell loss, cerebellar cortical sclerosis with proliferation of Bergmann glia, and 'torpedoes.' Torpedoes are rounded swellings of Purkinje cells axons that appear to represent the misaccumulation of disorganized neurofilaments and other organelles including mitochondria. Another important site of pathology may be the locus ceruleus. In this regard, it is important to note that the locus ceruleus sends a dense noradrenergic projection to cerebellar cortex.

Treatment

A subcommittee of the American Academy of Neurology published practice parameters for ET. Based on Class A evidence, propranolol and primidone have proven efficacy in the treatment of limb tremor in ET. Alprazolam, atenolol, gabapentin, sotalol, and topiramate may also be effective in reducing limb tremor (Class B evidence).

Pathophysiology

Positron emission tomography (PET), functional magnetic resonance imaging, magnetic resonance spectroscopy, and clinical-pathological correlative studies point to olivocerebellar pathways as critical to the pathophysiology of ET. ET may be eliminated by ipsilateral cerebellar or contralateral pontine ischemic strokes and PET studies have documented increased cerebellar blood flow in subjects with ET. Indicative of neuronal damage, magnetic resonance spectroscopy documented reduced cerebellar *N*-acetylaspartate levels in subjects with ET.

Criteria for Judging Animal Models of ET

Animal models of human diseases may be judged by several criteria. In the case of movement disorders, animal models are oftentimes criticized because they do not visually mimic the human condition. With the partial exception of primates, the geometry and biomechanical properties of animal limbs show significant differences from humans. As such, animal models, particularly rodents, cannot replicate or mimic the kinematics of ET or any other movement disorder.

One criteria of an animal model is reliability. Simply put, does the model provide consistent results? Validity is another way of judging animal models. Validity comes in three flavors: face, etiological, and predictive. In the context of ET models, face validity means that the model exhibits a motor syndrome that resembles the human condition. Etiological validity indicates that the model derives from the same cause as the human condition. In general, knockin mouse models of neurogenetic disorders have etiological validity. Finally, a model that can be used to predict a key feature of the disorder, such as response to therapeutic intervention, has predictive validity.

As is the case for Parkinson and Alzheimer diseases, ET is probably a syndrome derived from various combinations of genetic and environmental risk factors. The heterogeneity of ET, as suggested by genetic studies and the mixed response to pharmacological interventions, indicates that several different animal models may be required for the purposes of hypothesis-driven functional experiments and drug or device testing.

Animal Models of Action Tremor

Numerous animal models of action tremor are readily available to laboratory researchers. However, most of these models have poor etiological validity. For example,

action tremor is a prominent phenotypic feature displayed by the Trembler-J (Tr^J) mouse which has a point mutation in the gene coding for peripheral myelin protein 22 (PMP22). Action tremors are also seen in other lines of mice (e.g., vibrator, shiverer and jumpy) and rats (e.g., zitter) with spontaneous mutations; however, unlike humans with ET, these rodents have striking pathological changes such as demyelination in the peripheral nervous system or spongiform degeneration in the CNS. Although occasional patients with Charcot–Marie–Tooth disease will exhibit a prominent action tremor, the presence of a severe neuropathy on neurological examination excludes the diagnosis of ET.

As is the case in humans, a wide variety of pharmacological agents can cause action tremors in primates and rodents. One example is the muscarinic agonist, oxotremorine, which produces a generalized tremor. The tremor elicited by oxotremorine does not require an intact olivocerebellar pathway, and, unlike many cases of ET, does not improve with ethanol. Oxotremorine produces a high-frequency tremor (>12 Hz) that slowly abates as the drug is cleared from the CNS.

Tremor can also be produced by nicotinic agonists. In rats, a tail-tremor can be induced by repeated daily subcutaneous (SC) administration of nicotine; at dosages of 0.5 mg kg^{-1} SC daily, tail tremors emerge on the third day of treatment. A collection of pharmacological studies suggests that the nicotine-induced tail-tremor model is mediated by central nicotine receptor systems. The nicotine-induced tail-tremor model has been proposed as a model for ET, and, in this regard, may have predictive validity. Nicotine-induced tail-tremor is suppressed by nonselective and lipophilic β-adrenergic receptor antagonists like propranolol and pindolol. The beneficial effects of propranolol and pindolol are probably mediated by β2-adrenergic receptors since the β1-selective adrenergic receptor antagonist, metoprolol, exerts minimal effect on nicotine-induced tail-tremor. In the context of ET, these cholinergic and other most other pharmacological models of action tremor have poor etiological validity.

Action tremors may appear as the consequence of strategically located structural lesions or cell-type specific neurotoxins. For instance, lesions of the dentate nucleus and/or superior cerebellar peduncle in monkeys cause an action tremor with significant intentional features. In primates, the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) causes cell death in the catecholaminergic cells of the substantia nigra and locus ceruleus and consistently produces three of the four cardinal features of Parkinson disease: rigidity, bradykinesia, and postural instability. The appearance of tremor after exposure to MPTP is dependent on several technical factors such as route of toxin administration, dosage, species, and dosing schedule. By most accounts, MPTP typically produces an action tremor rather than the classic pill-rolling resting tremor of idiopathic Parkinson disease. The tremorgenic effects of MPTP may evolve over time and depend on relative damage to the locus ceruleus, substantia nigra pars compacta, and other monoaminergic cell groups. Focused studies into the neuropathological and neurophysiological basis for MPTP tremor may provide insight into the clinical association between ET and Parkinson disease.

Neurotoxin (penitrem A), pharmacological (harmaline), and genetic models ($GABA_A$ receptor α-subunit and *Lingo-1* knockout (KO) mice) of ET with etiological and/or predictive validity are well characterized in the current medical literature. Most likely, penitrem A and harmaline have the capability of producing tremor in virtually all mammals. Accordingly, preclinical therapeutic trials can be performed in mice, rats, primates, and other species. In contrast, current genetic models are limited to mice although technology is readily available to generate KO models in rats, pigs, and a few additional mammalian species.

Harmaline

Harmaline is found in numerous species of plants. Harmaline and related alkaloids have been used in traditional/indigenous medicine (Asia, Middle East, and Amazonia) for thousands of years. Harmaline is readily absorbed from the gastrointestinal tract. In experimental studies, harmaline is typically delivered via SC or intravenous routes. All mammals exhibit a readily perceptible tremor after the administration of harmaline. Typical harmaline dosages in rodents are 5–10 mg kg^{-1} SC. After SC injection of harmaline, latency to tremor is less than 10 min. Tremor duration depends on route of administration and dosage, and ranges from 30 to 180 min. A critical aspect of harmaline pharmacology is the rapid development of tolerance to its tremorgenic effects. Tolerance to harmaline tremor is probably due to postsynaptic changes in Purkinje cells. Tolerance constrains the practical utility of the harmaline tremor model.

Harmaline tremor frequency ranges from 4.7 to 7.6 Hz in rhesus macaque monkeys and from 10 to 12 Hz in rats. Tremor amplitude depends on the dosage of harmaline. In contrast, tremor frequency is relative independent of dosage. Harmaline tremor is an action tremor accentuated by movement. In rodents, harmaline tremor is readily detected in the neck, trunk and proximal muscles. In addition, rats and mice typically exhibit ataxia, abducted hindlimbs and reduced locomotion in response to harmaline.

Harmaline tremor originates in the olivocerebellar pathways. Harmaline produces rhythmic firing of inferior olivary neurons. Inferior olivary neurons send climbing fibers to cerebellar cortex. These climbing fibers synapse on the somas and proximal dendrites of cerebellar

Purkinje cells. The climbing fiber input to Purkinje cells results in complex spikes whereas summated parallel fiber input generates simple spikes. Single-unit extracellular recordings from Purkinje cells have shown that harmaline administration is associated with rhythmic complex spike activity and suppression of simple spikes. Harmaline tremor improves with primidone and diazepam. In contrast, the β-blocker propranolol exerts no significant effect on harmaline tremor.

The harmaline tremor model has been employed as a therapeutic screening tool. For example, octanol isomers are structurally similar to ethanol which often exerts beneficial effects on ET. In rats, octanol isomers potently reduced harmaline tremor. In pilot clinical studies, small doses of 1-octanol produced significant reductions in ET tremor amplitude. Thus, the harmaline tremor model has shown predictive validity.

Penitrem A

Penitrem A is one of several known tremorgenic mycotoxins. Other tremorgenic mycotoxins include penitrem B, verruculogen, and fumitremorgen. In mice, dogs, sheep, and humans, tremorgenic dosages of penitrem A produce a neurological syndrome characterized by generalized tremors and ataxia. Higher dosages may produce vomiting and seizures. In rodents, tremors persist for 24–72 h after injection of penitrem A.

Penitrem A has been shown to block high-conductance Ca^{2+} channels and increase neurotransmitter release from synaptosomes. At the pathological and functional levels, the cerebellum appears to be particularly sensitive to penitrem A. Cerebellar cortical blood flow increases several fold shortly after intraperitoneal administration of penitrem A. With penitrem A dosages of 3 mg kg^{-1}, mitochondrial swelling can be detected in rat cerebellar stellate and basket cells although cell death does not occur. Similar mitochondrial changes are seen in cerebellar Purkinje cells. Purkinje cells, particularly those in the vermis and paravermis, also show vacuolation of the smooth endoplasmic reticulum and cytoplasmic condensation with eosinophila. Destruction of the inferior olive does not alter the tremorgenic or pathological effects of penitrem A.

$GABA_A$ Receptor α1-Subunit (GABRA1) KO Mice

$GABA_A$ receptors are pentameric ligand-gated ion channel receptors expressed throughout the CNS. Numerous subunits (α, β, γ, δ, ϵ, etc.) aggregate in various combinations to generate a constellation of channels providing a rich spectrum of pharmacological and electrophysiological attributes. Although widely distributed in brain, the α1 subunit is expressed at particularly high levels in cerebellar Purkinje cells. Deletion of the α1 subunit in KO mice is associated with compensatory changes in the expression of other $GABA_A$ subunits. In humans, mutations in *GABRA1* have been described in juvenile myoclonic and childhood absence epilepsy. To date, no *GABRA1* mutations have been associated with human ET.

Gabra1-KO mice exhibit a pathological action tremor in the frequency range of 16–22 Hz. Tremor amplitude increases with increasing postnatal age. The pathological action tremor of *Gabra1*-KO mice improves with ethanol, primidone and propranolol. Tremor amplitude and frequency increase with diazepam and the GABA agonist allopregnanolone.

LINGO1 KO Mice

LINGO1 stands for leucine-rich repeat and immunoglobulin-domain-containing protein 1. LINGO1 is part of the Nogo-66/p75 receptor signaling complex. Nogo binding activates RhoA, which inhibits axonal outgrowth. LINGO1 is upregulated during activity-dependent plasticity in the CNS. Overexpression of LINGO1 inhibits oligodendrocyte differentiation via downregulation of RhoA. In vivo work also indicates that LINGO1 signaling plays an important role during CNS myelination. In particular, *Lingo-1* KO mice contain more myelinated axon fibers and show earlier onset of myelination than their wild-type littermates. Despite these ultrastructural anomalies, *Lingo-1* KO mice do not exhibit overt developmental or behavioral abnormalities. Intriguingly, *Lingo-1* KO promotes functional recovery in the experimental autoimmune encephalomyelitis (EAE) model.

Currently, there is no evidence to suggest that *Lingo-1* KO mice have any validity as a model of ET. First of all, *Lingo-1* mice do not tremor. Second, it is not known if the intronic *LINGO1* SNPs associated with ET truly implicate downregulation, upregulation or other changes of LINGO1 in the pathophysiology of ET. Other markers, in linkage disequilibrium with these disease-associated SNPs, may reduce, enhance or alter the function of LINGO1.

Future Directions

The development of better animal models will depend on an improved understanding of human ET. Despite the relative prevalence of ET, the genetics, functional anatomy, and neuropathology of this important neurological disorder remain poorly understood. First of all, using genomic and molecular biological tools, the role of LINGO1 in ET must be deciphered. Next, with due

consideration of environmental factors, geneticists must identify other genes which contribute to the hereditability of ET. Clinical–pathological correlations and delineation of ET subphenotypes will require exacting prospective clinical data and equally sophisticated postmortem pathological examination of many ET brains. Ultimately, several animal models may be required to characterize the network and cellular biology of ET.

See also: Harmaline Tremor Model; Tremor; Tremor, Essential (Syndromes); Tremor, Essential: Genetics.

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Event-Related Potentials: Slow Potentials

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Definition and History

From the initial demonstration of the electroencephalography (EEG) with animals, it was some 54 years later that the techniques were demonstrated in humans. In the 1920s, Hans Berger was able to show potential differences between recording sites related to cortical processes. He named this electrical activity the 'Elektrenkephalogramm.' In his first set of papers, Berger sought to determine what factors were involved in the production of the EEG and was able to determine that EEG was related to activity within the brain and to rule out other physiological activities such as cerebral pulsations, cerebral blood flow, blood flow through scalp vessels, heart rate activity, muscle activity, eye movements, and electrical properties of the skin. Berger took his studies beyond the physiological level and was one of the first to suggest that periodic fluctuations of the EEG might be related in humans to cognitive processes such as arousal, memory, and consciousness. In determining the nature of the EEG, Berger was initially surprised to discover that EEG changes were ones of quality rather than quantity. For example, as an individual moved from a relaxed state to one of stimulation and activity, Berger noted that the EEG did not increase in amplitude but rather changed in the quality of the wave forms. He initially identified these two different EEG wave forms as that of alpha activity and that of beta activity with alpha being associated in cortical inactivity and beta with cortical activity.

Event-Related Potentials

When EEG activity is recorded in relation to specific stimuli, it is called an event-related or evoked potential. For example, if a flash of light is viewed by a subject who has one electrode on the rear of his scalp and another on his earlobe, a predictable sequence of voltage variations will be recorded. A very small positive deflection (less than a microvolt) will follow the flash by about 40 ms. This response will be followed by a large negative deflection lasting 10–30 ms and peaking around 60 ms after the flash. Immediately following this wave, there appears a fairly large, positive wave with maximum amplitude occurring about 80 ms after the flash. This pattern is quite predictable; it follows each successive light flash, although it should be stressed, with some variability from flash to flash. By averaging individual stimulus presentations into a grand average, it is possible to note stable response patterns to a variety of stimuli. This succession of waveforms to visual stimulation is termed the

visual evoked response. When the distribution of the responses is examined, it is found to be of maximum amplitude over the occipital area of the brain, and to be less widely distributed than most spontaneous rhythms.

In general, evoked responses regardless of the nature of the stimulus are referred to as event-related potentials (ERPs). Unlike the spontaneous EEG which is recorded in a continuous fashion over a period of time, ERPs are time locked to specific stimuli or responses. In the literature, a distinction is sometimes made between endogenous and exogenous ERPs. Exogenous ERPs are seen to be controlled largely by the physical nature of the stimulus itself. On the other hand, endogenous ERPs are those that are influenced by the individual's perception or interpretation of the event. Overall, the ERP is smaller in voltage than the EEG and requires averaging procedures over many trials for patterns to be clearly seen. The most common ERP procedure is to time lock the EEG signal to a particular tone or visual stimulus. The basic procedure is to repeat the stimulus a number of times and then average the electrocortical signal to each of these stimuli. This results in a wave that is seen to represent the brain's response to a particular type of stimulation. Traditionally, ERPs are referred in terms of whether the deflection is negative or positive when the deflection occurs. Thus, a P300 component is a positive component occurring about 300 ms after the stimulus. It should be noted that the timing of the components is not precise but relative. While it is true that a P300 will follow an N200, the P300 may occur later than 300 ms. In viewing graphs of the ERP, a general procedure is to show the negative components as going upwards and the positive ones as downwards.

In terms of time, the initial components of the ERP are seen as reflecting automatic processing with the later components being more controlled and related to the cognitive processing of the stimulus. For example, if a pain stimulus was delivered to your right finger, then an initial response would be seen on the left side of the cortex. At about 250 ms, an evoked response is seen that some researchers believe to be associated with the subjective response of pain. One of the most well known ERP components is P300 that in actuality can appear anywhere from 300 to 800 ms after the response. P300 is seen as reflecting cognitive processing and has been used in a variety of paradigms. For example, this component is larger if individuals are told to respond to a stimulus than if they are instructed to ignore it. One common P300 paradigm is that of the oddball. In this procedure, a series of tones with a similar frequency is played in which a tone of a different frequency is played randomly. The novel stimulus or 'oddball' results in an increase in the amplitude of the P300. A related component involved with linguistic processing is that of the N400. This component is seen to be especially related to linguistic expectation. Numerous studies indicate alteration of ERP in patients suffering from movement disorders. For example, ERP data (i.e., reduced amplitude of P300 and N200) suggest that there is selective impairment of inhibitory function in Parkinson (PD) patients and that this deficit may be related to impaired inhibitory executive function in the frontal lobe.

Slow Potentials

If you were told that once you heard a tone a picture would follow a few seconds later, you would notice a slow negative potential being generated once the tone sounded. This slow negative potential generally measured at the vertex is the contingent negative variation (CNV). The CNV is generated in the laboratory by presenting the first or a warning stimulus which signals that a second stimulus will follow in a specific time period. In most studies, the second stimulus signals cognitive or task processing. Walter et al. (1964) described the CNV as an expectancy measure since the first stimulus suggests the second will follow.

Another form of event-related potentials is very slow potentials which precede and accompany movement or other activities. If a person is asked to press a button as he/she wishes, it can be seen that as early as a second movement begins, a recognizable EEG waveform starts to develop. A recording made with an electrode placed over the central areas of the cortex displays increasingly negative, in the few milliseconds before a movement occurs, until there is often a slight positive dip in the wave followed by a steep negative slope, which is terminated simultaneously with the beginning of the movement. The beginning of the movement is accompanied by a large positive deflection and a recovery to the original baseline. This complex of waveforms is not uniformly distributed. Technically, this slow increase in surface negativity is referred to as the *Bereitschaftpotential* (BP), see **Figure 1**. Significantly reduced amplitude of BP was consistently observed in patients suffering from traumatic brain injuries (TBI), Parkinson disease (PD), and other neurological populations.

The BP potential is maximal at the vertex and initially equal in amplitude over both hemispheres of the brain. One research paradigm is to signal the person which hand to use to make the movement. Prior to the movement, this potential begins to lateralize and becomes maximal over the motor cortex contralateral to the body part moved. Early speculation suggested that this beginning of lateralization reflects the point in time at which the response side is determined. Since the information contained within the BP includes nonmotor processes as well as motor processes, researchers have suggested that by subtracting the response of one hemisphere from that of the opposite hemisphere, it would be possible to obtain a more pure measure of motoric preparation for a response. This measure has been referred to as the lateralized readiness potential (LRP) and has become an important tool in the study of the neural basis of human cognitive– motor processing.

To summarize, the development of this measure was based on the assumption that the asymmetry of the RP could be used as an index for the preparation of specific

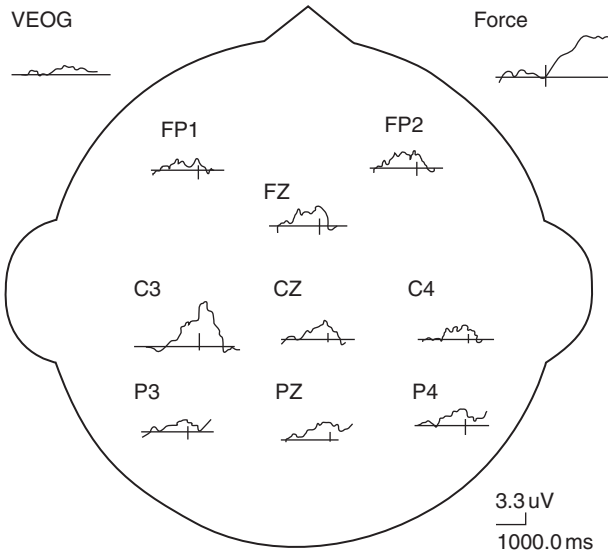

Figure 1 Typical example of BP waveforms and its spatial distribution prior to initiation of isometric force task produced task by the right finger.

motor acts. To eliminate any RP asymmetries that may contain activity lateralized with respect to nonmotoric processes, the LRP was calculated as the difference between recording sites contralateral and ipsilateral to the responding hand, averaged over left- and right-hand responses. The LRP's special significance in cognitive and sensorimotor research stems from the fact that this component offers a continuous analog measure of the differential engagement of the left versus right hand associated with cued or uncued voluntary reactions. The alteration of LRP as an indication of impairment of movement initiation in PD patients has been documented in a number of studies.

See also: Electroencephalography (EEG).

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Executive Dysfunction

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Glossary

Abulia – Lack of will power or drive, accompanied by a lack of spontaneity of speech, thought, and action.
Akinetic mutism – A state characterized by poverty of speech and reduced limb movements, with preserved eye movements.

Chorea – Involuntary, intermittent jerky movement of muscle groups that is associated with disruption of the basal ganglia.
Disinhibition – The temporary removal of an inhibitory process.
Freezing of gait – A temporary inability of movement that is typically associated with Parkinson's disease

or parkinsonism. This event can occur when a patient transverses a threshold (e.g., doorway) or encounters a change in floor pattern.

Subcortical Dementia – Cognitive symptoms may include decreased initiation, slowing of responses, and difficulties with strategy formation and problem solving. A lack of cortical involvement should not be implied; however, specific functions mediated by the cortex are typically spared. Subcortical dementia is common in neurodegenerative disorders such as Parkinson's disease and Huntington's disease.

Definition

Executive function is a term used to describe higher order mental processes, mediated by the frontal lobes of the cerebral cortex, that are involved in the regulation of cognitive and behavioral responses to environmental contingencies. Owing to high connectivity the frontal lobes maintain with various cortical regions, *executive dysfunction* can occur following nonfrontal damage (e.g., to the posterior association cortex and dorsomedial thalamic nucleus). Executive dysfunction has been attributed to several neurological disorders including traumatic brain injury, neoplasms, vascular lesions, as well as cortical and subcortical neurodegenerative processes.

Executive functions are not a unitary construct; in fact, they comprise an assortment of behaviors including: (1) planning and organization, (2) cognitive flexibility/decision making, (3) initiation and self-generation, and (4) response inhibition. First, *planning and organization* involves selecting and executing behaviors necessary for goal attainment that may occur in the near or distant future. Second, given the unpredictable nature of an ever-changing environment, an individual must maintain aspects of *cognitive flexibility* with preserved *decision making ability*. When making a decision, individuals base their responses on various environmental contingencies and past successful or unsuccessful decisions along with their resulting consequences. Other factors that are paramount when weighing in on response options during the decision making process include, the inherent value and emotional salience of a given option. Individuals experiencing executive dysfunction secondary to a brain insult may no longer make decisions that are advantageous. In fact, these patients may decide against their best interests, and fail to learn from past mistakes. Third, in order to successfully achieve a desired goal, one must *initiate and sustain* behaviors. Despite preserved intellect, patients with prefrontal cortical damage may not execute a given behavior or activity due to lack of motivation and/or behavioral self-generation (i.e., abulia or apathy). Lastly, one individual with executive dysfunction may find it difficult to initiate or sustain a given behavior, whereas others may fail to *inhibit behavioral responses*, especially those responses that are socially maladaptive or fail to lead to successful goal attainment. In 'real world' settings, this may be interpreted by others as *behavioral impulsivity* and can have grave consequences on social functioning and social acceptance.

Neuroanatomical Correlates of Executive Functions

Previous work has identified three 'closed loop' frontostriatal cortical circuits that reportedly have a role in mediating executive functions. These circuits originate from the (1) anterior cingulate, (2) orbitofrontal, and (3) the dorsolateral regions of the prefrontal cortex. Each circuit projects to specific striatal regions (via excitatory glutaminergic transmission) in a topographical fashion and remains segregated throughout the basal ganglia and thalamus, allowing other areas of the brain to communicate with each circuit along its respective pathways. The frontostriatal circuits receive inputs from dopaminergic, noradrenergic, serotonergic, and cholinergic cell groups that modulate information processing. All circuits eventually return to the portion of the frontal cortex where they originated.

Individuals with prefrontal cortical damage can present with a myriad of cognitive and behavioral deficits that may fall into one of the three executive dysfunction subtypes. First, an *apathetic–akinetic syndrome* can result from medial prefrontal cortical damage. This syndrome is typically characterized by diminished responsiveness to environmental stimuli along with reduced initiation and maintenance of desired behaviors. Orbitofrontal damage (including the ventromedial cortex) can result in a *disinhibited syndrome*. This syndrome is characterized by personality changes involving poor regulation of inhibitory and emotional mechanisms that can result in socially maladaptive behaviors. Lastly, a *dysexecutive syndrome* can result following damage to the dorsolateral aspect of the prefrontal cortex. This syndrome is typically characterized by 'cognitive' deficits including problems with working memory, associative learning, shifting and maintenance of cognitive set, and memory retrieval.

Anterior Cingulate Cortex

Cognitive impairment following anterior cingulate cortex (ACC) disruption can include deficits in attention such as sustained attention, spontaneous response production, error monitoring, and response intention. By 'intention,' we are referring to attention to action, which

influences the propensity to respond via behavioral readiness, anticipation, and response maintenance. Psychiatric disturbance following ACC disruption is typically characterized by apathy. Apathy is defined as having indifference to one's surroundings, loss of interest or motivation in goal-directed behaviors, and/or flattening of affect that is not attributed to declines in levels of arousal or intellect (i.e., apathetic–akinetic syndrome). Neurological populations with significantly high levels of apathy typically perform worse on neuropsychological measures of executive functions compared to those patients with lower levels of apathy. In the most extreme case, bilateral lesions of the ACC can result in *akinetic mutism* that involves profound apathy with a lack of impulse for speech, action, and psychic initiative. Overlapping projections from the anterior and posterior cingulate with other limbic system nuclei, and the lateral frontal and parietal cortices, along with efferent projections from the ACC to frontal subsystems, may account for the role the ACC maintains in attentional, cognitive, and behavioral processes.

Orbitofrontal Cortex (OFC)

Orbitofrontal cortex (OFC) disruption can lead to emotional instability (e.g., disinhibition, depression, and obsessive–compulsive disorder) due to a dissociation of frontal monitoring systems from limbic input. Brain-damaged patients may exhibit social and/or behavioral deficits such as euphoria, diminished affect, impulsivity, social irresponsibility, and poor reasoning and decision-making abilities with relatively preserved intellect (i.e., disinhibition syndrome). For instance, while engaged in an experimental card gambling task, OFC brain-damaged patients have a tendency to profit from short-term rewards at the expense of long-term consequences. Interestingly, these patients can at times accurately describe the reinforcement contingencies of the task, but are unsuccessful in implementing this knowledge in an attempt to maximize their profits. Moreover, patients with OFC damage have also been reported to present with a diminished ectodermal response (i.e., measure of emotional arousal) when engaged in high-risk responses on a card gambling task, suggesting that the OFC may have a significant role in triggering autonomic reactions while anticipating a reward or punishment. The diminished ectodermal response may reflect a reduction or lack of emotional salience attributed to a given set of response options and their associated consequences, which can negatively impact the decision making process.

Dorsolateral Prefrontal Cortex

The dorsolateral prefrontal cortex (DLPFC) is an area that is considered central to executive functions in humans. Patients with damage to this region may exhibit 'cognitive' difficulties in organizing a behavioral response, memory retrieval, maintaining and shifting behavioral sets, generating motor programs, strategy generation, and use of internal cues to guide behavior (i.e., executive dysfunction syndrome). The DLPFC is critical to new learning when working memory, set-shifting, and attention to action are necessary. Further, this region has been aptly labeled the 'central executive' because its activation tends to overlap with that of the ACC and OFC by maintaining a role in working memory and top-down processing.

Executive Dysfunction and Movement Disorders

The cognitive and behavioral profile of patients with subcortical neurodegenerative processes are similar to those observed in patients with damage to prefrontal and subcortical (i.e., basal ganglia) regions secondary to acquired brain injury. Hence, executive dysfunction in patients with neurodegenerative movement disorders such as Parkinson's disease (PD) or Huntington's disease (HD) (i.e., subcortical dementia) has been attributed to frontostriatal circuit disruption.

Parkinson's Disease

Parkinson's disease (PD) is a neurodegenerative hypokinetic movement disorder characterized by insidious onset with progressive motor and cognitive decline. Previous work has suggested that PD may arise from either one or a combination of several different etiological factors including: environmental toxins, free radical production, mitochondrial abnormalities, abnormal protein degradation and removal, genetic predisposition, and/or aging. The motor impairments characteristic of PD include the clinical triad of resting tremor, bradykinesia (slowness or retardation of movement), and rigidity. Other symptoms such as hypokinesia (impaired movement initiation), freezing phenomena (difficulty with congruent and sequential movements), and postural abnormalities are also common.

Neuropsychological impairment in PD has been documented across all cognitive domains. However, cortical syndromes such as aphasia and alexia are not common. Executive dysfunction is typically regarded as the 'core' deficit in PD, as it appears to influence most cognitive changes observed. The cognitive profiles of patients with PD vary both in frequency and severity across studies due to the multiplicity of factors pertaining to patient samples (e.g., the age of disease onset or presence of a dementing process). Neuropsychological assessment of patients with PD typically yields poor performance on tasks of working memory, trial-and-error learning, planning, memory retrieval, verbal fluency, response monitoring, set-shifting,

and attentional control. Moreover, mood disturbance is common and is often ascribed to symptoms related to depression and/or apathy. Symptoms related to depression and apathy can overlap considerably in any given individual with PD. The relationship between symptom expression and severity across the two is an inconsistent one and may be attributed, in part, to differential frontostriatal circuit involvement (i.e., ACC and OFC).

Executive dysfunction in PD has been characterized by the difficulty that patients may experience in developing their own plan of action or initiating goal-directed behavior as well as maintaining adequate levels of processing resources. In theory, a mechanism such as a central processor within the prefrontal cortex may distribute mental resources according to processing demands so as to govern nonroutine behaviors. This process is believed to influence inhibitory resources by allowing for the suppression of routine behaviors in favor of more goal appropriate ones. For instance, patients with frontal brain-damage, as in PD, may exhibit typical or expected behaviors in familiar settings, but may find it difficult to modify their behaviors when confronted with a novel environment or situation. Furthermore, executive dysfunction in patients with PD may be attributed, in part, to imposing greater resource demands. As a consequence, they may present with difficulties in suppressing competing mental programs. PD patients may find it challenging to inhibit nonrelevant resources while performing a task, which may lead to excessive cognitive load with subsequent decreases in information processing speed with inefficient strategy formation. Thus, it is not surprising that patients with PD can present with deficits across most, if not all, cognitive domains.

Gait Pattern and Postural Abnormalities in PD

Subcortical structures, including the basal ganglia, have a role in maintaining normal gait patterns and postural stability. These structures generate internal cues to initiate sequences of movement at an unconscious level. Further, the success of any given purposeful movement requires the preparation and maintenance of movement plans via connectivity that the basal ganglia maintain with frontal motor regions (e.g., premotor cortex and the supplementary motor area).

Gait pattern and postural abnormalities in patients with PD can be characterized by bradykinesia, reduced stride length and step amplitude, increased stride duration and step cadence, stooped posture, forward head positioning, excessive flexion of the legs, and increased duration of double limb support. Additional influences can include flat foot ground contact, inadequate toe clearance for swing, loss of arm swing and trunk rotation, festinating gait, and freezing phenomena.

Patients with PD demonstrate increased stride variability, a marker of arrythmicity, and reduced automaticity of gait, which compromises both balance and gait. It is believed that impaired internal cueing mechanisms (resulting from executive dysfunction) in PD transform gait rhythmicity into an attention demanding parameter. Thus, patients with PD must recruit additional attentional resources as a compensatory mechanism in order to improve gait pattern discrepancies. The greater demand for the allocation of attentional resources may reduce their ability to appropriately adapt to challenging terrain (uneven paths, narrow areas, etc.) and/or novel environments, leading to a greater fall risk.

Huntington's Disease

Huntington's disease (HD) is a relatively rare neurodegenerative process characterized by a disorder of movement (e.g., chorea), cognitive decline, and psychiatric disturbance. HD has an autosomal dominant pattern of inheritance with full penetrance. Although multiple brain regions, cortical and subcortical, are affected by HD, the area of the greatest and earliest degeneration is the corpus striatum (caudate nucleus and putamen). This is a region with extensive connectivity to the frontal lobe, and as discussed above, it is intimately involved in the frontostriatal circuits important in the processing of cognition and mood. Although they are distinct in their cognitive deficits, the cognitive dysfunction associated with HD is generally similar to the pattern observed in PD (i.e., executive dysfunction). That is, the cognitive decline associated with HD is consistent with the broad concept of subcortical dementia including psychomotor slowing and impairment of recall memory with intact recognition memory.

Patients with HD have been reported to demonstrate early decline in executive functions associated with all three frontostriatal circuits, with deficient memory retrieval, response initiation, and decision making skills. Indeed, changes in cognition and mood are believed to be common in presymptomatic HD gene carriers. Interestingly, early in the course of the disease, patients are often described as exhibiting personality changes, such as increased irritability and short temper, which could be better characterized as the behavioral manifestation of executive dysfunction. Depression is also very common among patients with HD, and there is an increased rate of suicide even prior to the onset of clinical motor symptoms. This could be hypothesized to be related to the presence of depression and impulsivity within the context of poor problem solving, suggesting dysfunction within the OFC and DLPFC systems.

See also: Bradykinesia; Cognitive Assessments and Parkinson's Disease; Dementia with Lewy Bodies; Dementia, Movement Disorders; Frontotemporal Dementia-Parkinsonism; Gait Disturbances in Parkinsonism;

Huntington's Disease; Parkinson's Disease: Definition, Diagnosis, and Management.

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Eye Movement Abnormalities in Movement Disorders

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Glossary

Antisaccade task – Display of an unpredicted visual target with request of the patient to look in the direction opposite to the target.

Convergence insufficiency – Inability to converge or adduct the eyes upon a gaze shift from a distant visual target to a near target.

Convergence spasm – Excessive convergence of the eyes usually due to nonphysiologic causes.

Ocular motor apraxia – Inability to move the eyes voluntarily to objects of interest.

Saccade – Rapid, conjugate eye movement with which gaze is shifted to point the eye at visual targets of interest.

Saccade latency – Time delay between request for saccadic eye movement and initiation of the actual movement.

Supranuclear gaze palsy – Abnormal eye movements because of brainstem premotor, cerebral hemispheric, or cerebellar dysfunction.

Introduction

Eye movements are of considerable importance in movement disorders. From a research perspective, eye movements, especially rapid saccadic movements, offer an opportunity to study the role of the basal ganglia in a motor system in which brainstem neural mechanisms have been extensively studied and are fairly well-understood. From a clinical diagnostic perspective, abnormal eye movements are the key features of certain movement disorders, and recognition is essential to accurate diagnosis. Lastly, from a clinical patient care perspective, patients with movement disorders often experience visual impairment in the presence of normal visual acuity, which may be attributable to disorders of eye movements.

Basal Ganglia Control of Eye Movements

The shared goal of all eye movements is the maintenance of clear, single vision by placement of an object of visual interest on the fovea, the retinal region with the highest

density of photoreceptors, and the best visual acuity. Several functional classes of eye movements coexist to meet this shared goal. These include saccades, smooth pursuit, vergence, optokinetic responses, and vestibular reflexes. Separate premotor command networks exist for initiation and modulation of each functional class of eye movements. These networks converge upon the final common pathway of ocular motoneuron, neuromuscular junction, and extraocular muscle to elicit eye movement.

The premotor networks governing saccades are understood to the greatest extent. Saccades are rapid, conjugate eye movements with which we shift gaze to point the fovea at pertinent details in the visual world. Saccades may be voluntary or reflexive and generated to actual targets (visually-guided) or to memory for target location (memory-guided). The primary source of commands to immediate brainstem premotor saccadic networks is the superior colliculus (SC). The SC has important roles in visual target selection, saccade amplitude and direction preparation, and possibly in the conversion of spatial saccadic target selection signals into temporal signals required for motor output.

The role of the basal ganglia in eye movement control has been extensively studied, and is primarily related to the control of voluntary visually- and memory-guided saccades. This control is predominantly mediated through striato-nigro-collicular connections, as summarized in **Table 1**. In the 1980s, inhibitory connections mediated by γ-aminobutyric acid (GABA) were identified between the primary basal ganglia output structure, the substantia nigra pars reticulata (SNr), and the SC. The importance of the SC in the initiation of eye movements postulated a role of the SNr in eye movement control. This role was subsequently proven by extensive experimentation mostly involving single cell recordings in various basal ganglia structures over the past 20 years. It is now understood that the SNr tonically inhibits the SC, and that just prior to a voluntary visually- or memory-guided saccade, a pause in SNr activity releases the SC from inhibition, resulting in an increase in discharge from the SC and initiation of the saccade. There is no change in the tonic SNr discharge rate for spontaneous saccades in darkness or light and, therefore, no proposed basal ganglia role in initiation of spontaneous reflexive saccades.

Saccadic abnormalities may be induced via biochemical manipulation of striato-nigro-collicular connections, and this may have direct implications with regard to saccadic abnormalities in clinical movement disorders such as Parkinson's disease (PD) and Huntington's disease (HD). Enhancement of the inhibitory effect of SNr on SC with a GABA agonist results in voluntary saccades with longer latency to onset, decreased amplitudes, and lower velocities. Conversely, impaired suppression of saccades and excessive saccades result from administration of a GABA antagonist and excessive release of the SC.

The caudate facilitates saccades via phasic inhibition of the SNr prior to a saccade, allowing the pause in SNr tonic activity with release of the SC to occur. Chemical depletion of dopamine in the caudate results in a decrease in spontaneous saccades and voluntary saccades with decreased velocity and amplitude and increased duration. The caudate, in addition to being directly involved in the motor control of voluntary saccades, also has an important role in cognitive aspects of visual stimulus anticipation and modulation of saccade behavior based on reward expectation. Remarkably, caudate neurons can anticipate the spatial direction of a rewarded stimulus. Such anticipation is modulated by the input of midbrain dopaminergic neurons into the caudate. It is hypothesized that cortical signals for spatial saccadic control and dopaminergic inputs with reward-related signals are integrated in the caudate to guide the eyes to the place where a reward is anticipated. Loss of midbrain dopaminergic neurons, as in PD, has an adverse affect on predictive saccadic behavior.

Table 1 Role of basal ganglia in normal eye movements

Basal ganglia structure	*Role*	*Effect of biochemical alteration on voluntary saccades*
Substantia nigra pars reticulata	Tonic inhibition of SC (neurotransmitter GABA)	GABA agonist (enhances SC inhibition) Increased latency Decreased amplitude and velocity
	Pause just before voluntary saccade releases SC from inhibition, allowing saccade to occur	GABA antagonist (decreased SC inhibition) Impaired suppression of saccades
Caudate	Facilitates voluntary saccades via inhibition of SNr just prior to saccade (allows SNr pause to occur)	Depletion of dopaminergic input Increased duration Decreased amplitude and velocity
	Anticipation of visual saccadic targets and reward-based modulation of voluntary saccades	
Subthalmic nucleus	Suppression of saccades via excitation of SNr Switch from reflexive to voluntary saccades	Not applicable

Abbrevations: SC – superior colliculus; GABA – γ-aminobutyric acid; SNr – substantia nigra pars reticulata.

Table 2 Eye movement abnormalities in movement disorders

Parkinson's disease
Quantitative saccadic eye movements
Increased latency and hypometria of voluntary predictive saccades
Increased latency and hypometria of voluntary memory-guided saccades
Increased latency and high error rates with antisaccades
Abnormal smooth pursuit
Bedside eye movement examination
Hypometric saccades
'Saccadic' smooth pursuit
Mild impairment of upgaze
Convergence insufficiency
Progressive supranuclear palsy
Supranuclear palsy
Saccades affected more than smooth pursuit
Vestibulo-ocular reflexes spared until late in disease
Vertical eye movements affected before horizontal
Slowed saccadic velocities prior to range limitation
Excessive square wave jerks
Decreased latency and high error rates with antisaccades
Corticobasal degeneration
Increased saccadic latency
Square wave jerks
Impaired smooth pursuit
Slowed saccadic velocities (rare and late in disease course)
Oculomotor apraxia with Balint's syndrome (rare)
Multiple system atrophy
Cerebellar subtype
Square wave jerks
'Saccadic' smooth pursuit
Mild saccadic hypometria
Downbeat nystagmus
Gaze-evoked nystagmus
Parkinsonian subtype
Abnormalities of voluntary saccades similar to PD
Huntington's disease
Increased latency, reduced velocity, high error rates of memory-guided saccades
Increased latency, reduced velocity, high error rates with antisaccades
Prominent slowing of saccades with young onset disease
Prominent increased saccadic latency with older onset disease
Impaired fixation
Inability to suppress saccades to novel visual stimuli
Increased saccadic latency in presymptomatic gene carriers
Wilson's disease
Saccadic smooth pursuit – vertical greater than horizontal
Abnormal vertical optokinetic nystagmus
Spinocerebellar ataxias
Cerebellar eye movement abnormalities
Saccadic dysmetria
Saccadic smooth pursuit
Gaze-evoked nystagmus
Downbeat nystagmus (common in SCA6)
Decreased saccadic velocity (SCA2)
Decreased saccadic velocity and supranuclear gaze palsy (SCA7)
Abnormal vestibulo-ocular reflex (SCA3, SCA6, autosomal recessive ataxias)
Oculomotor apraxia (ataxia–telangiectasia)
Psychogenic
Voluntary nystagmus
Convergence spasm

Complete discussion of basal ganglia control of eye movements must include the role of the subthalamic nucleus (STN), especially in light of its current importance in PD treatment with deep brain stimulation (DBS). The STN sends excitatory signals to the SNr, and may have a role in suppression of eye movements via enhancement of SNr inhibition of the SC. Direct afferent projections reach STN from the cortical eye fields. In addition to the suppression of eye movements and enhancement of visual fixation, STN may also mediate behavioral switching between automatic reflexive saccades and deliberate, controlled voluntary saccades via the direct cortical connections.

Idiopathic PD

Quantitative Saccadic Eye Movements

Detailed studies utilizing mechanisms to record and quantify saccadic tasks in patients with PD reveal saccadic abnormalities that correspond well with expected deficits based on predictions from the anatomic and physiologic role of the basal ganglia described in the earlier section (**Table 2**). In general, complex, voluntary, predictive saccades are abnormal, while reflexive saccades are often unaffected. For predictive saccades, increased saccadic latency and hypometric saccades (saccades that fall short of the target) are common. Deficits are particularly marked in tasks requiring memory-guided saccades. Saccadic velocity is, however, typically normal. One specific task, the antisaccade task, has been frequently studied as a measure of the capacity to suppress a reflexive saccade and to generate a volitional one in its place. In this task, the subject is shown an unanticipated visual target and requested to look in the opposite direction of the target. Patients with PD tend to have increased saccadic latencies and high error rates with this task, although these findings are not consistent across all studies. Increased latency on this task may correlate with the degree of bradykinesia in advanced disease. Saccadic latency is of interest as a potential biomarker of PD, as it does correspond to disease severity and the presence of dementia. However, there is wide intersubject variability, as well as overlap of saccadic latency distribution between PD patients and controls, that may hinder its use as a diagnostic biomarker.

Reported treatment effects on saccadic abnormalities are variable. Several studies report beneficial effects on voluntary saccadic latency and amplitude and enhancement of reflexive saccade inhibition with dopaminergic drugs. Others show no effect, and one even demonstrates prolongations of voluntary saccadic latency. The ocular motor effects of DBS in the STN support an STN role in eye movements, with changes in STN neuronal firing rates similar to those in nonhuman primates identified in humans during intraoperative single unit recordings, while the patient performed voluntary saccadic tasks. The accuracy of memory-guided saccades may be improved with bilateral STN stimulation, although an increase in fixation instability with excessive saccades may also occur.

Clinical Abnormalities and Convergence Insufficiency

Although often unremarkable, a number of eye movement abnormalities may occasionally be evident on standard bedside evaluation of ocular motility in PD patients (**Table 2**). These include hypometric saccades, impaired smooth pursuit with 'catch-up' saccades, and mild impairment of upgaze. The antisaccade test can be performed at the bedside by holding up both hands and intermittently, unpredictably moving one finger on one hand and instructing the patient to look in the opposite direction of the moving finger. Abnormalities of vergence eye movements warrant special mention, as they are often symptomatic.

Vergence is a disconjugate eye movement by which a single foveal image is maintained with gaze shifts from near to far (divergence) or from far to near (convergence). The primary stimuli for vergence are retinal blur and retinal disparity. Retinal blur is loss of visual image sharpness, and retinal disparity is image separation when images fall on noncorresponding areas of each retina. Convergence insufficience (CI) is a common cause of binocular diplopia or visual blurring with viewing of near objects in PD. It may occur both in advanced and in early, untreated disease. The most common complaints with CI are binocular horizontal doubling during attempts to read or nonspecific reading difficulty. Examination reveals a full range of eye movements, with possible exception of impaired adduction of each eye during viewing of a near target. The eyes are misaligned significantly at near with outward deviation relative to one another (exotropia). A lesser exotropia is present while the patient views a distant target and is typically only detectable with disruption of binocular fixation during measures of ocular alignment such as cross cover testing.

Two additional examination features helpful in diagnosing CI are the convergence amplitude and the near point of convergence (NPC). Convergence amplitude measurements are performed by using a horizontal prism bar to determine the extent to which a patient can converge the eyes before the development of diplopia or an exotropia. To measure the NPC, the distance at which a patient can maintain convergence without the eyes breaking down into an exotropia (one eye turning out laterally) is measured as the patient views a near object moving closer to the nose. An NPC of >10 cm is highly suggestive of CI. In early PD, the NPC may be normal, but convergence amplitude decreased with resultant symptoms prior to the development of frank CI.

CI can be treated with prisms in the patient's glasses. A prism oriented with its base toward the nose may eliminate diplopia or blurred vision during reading. If prismatic treatment is ineffective, monocular occlusion during reading can be tried. CI may also be responsive to dopaminergic medications.

Oculogyric Crisis

In the early twentieth century, oculogyric crisis (OGC) was a classic feature of postencephalitic parkinsonism. OGC is a forced deviation of the eyes – frequently in an upward or upward and lateral direction. Most cases currently are related to pharmacologic dopamine antagonists utilized as antipsychotic medications.

Progressive Supranuclear Palsy

One of the most salient features of progressive supranuclear palsy (PSP) is a supranuclear ocular motor gaze palsy that initially tends to affect vertical gaze to a greater extent than horizontal gaze (**Table 2**). Within 3–4 years of disease onset, 79% of patients have a vertical supranuclear palsy, with downgaze affected in 67%. This finding is not only helpful in diagnosing PSP, but may also provide prognostic information with early impairment of downgaze predicting shorter survival time.

In keeping with its supranuclear nature, saccades are affected to a much greater extent than smooth pursuit, and the oculocephalic reflex (Doll's eye maneuver) is spared. The earliest feature is slowing of vertical saccades (which may be initially detectable only with quantification on eye movement recordings), followed by limitation in the range of vertical movement. Late in the disease, eye movements may be completely absent. The location of pathology responsible for the saccadic abnormalities in PSP is thought to be the brainstem premotor burst neurons that relay saccadic commands to the ocular motoneurons. Two hypotheses have been proposed to explain the clinical involvement of vertical eye movements prior to horizontal eye movements. The first hypothesis is that GABAergic vertical premotor saccadic neurons may be more susceptible to injury than glycinergic horizontal premotor saccadic

neurons. The second hypothesis is related to the location of vertical versus horizontal premotor saccadic neurons; vertical neurons are located in the mesencephalon nearer to the SC than the more caudal pontine neurons. Degeneration of the SC occurs early in the disease course. This, in combination with the absence of SC pathology in a PSP patient lacking the supranuclear gaze palsy, suggests that the SC may be a 'gateway' via which ocular motor saccadic circuits are affected in PSP.

In addition to the supranuclear gaze palsy, excessive square wave jerks are common in PSP. These are very small saccades that occur during visual fixation and take the eye off the fixation target and return it to the target within ~200 ms. The antisaccade test in PSP characteristically reveals decreased saccadic latencies and a high error rate, demonstrating an inability to suppress reflexive saccades. There is a correlation between decreased saccadic latencies and increased frontal lobe dysfunction, which is not surprising, given the importance of the frontal cortex to the suppression of reflexive saccades.

Corticobasal Degeneration

Abnormal eye movements may occur in corticobasal degeneration (CBD) (**Table 2**). The most characteristic findings are increased saccadic latency, excessive square wave jerks, and impaired smooth pursuit. Saccadic velocities are typically normal. In rare instances, eye movement abnormalities similar to the supranuclear gaze palsy of PSP may be found in patients pathologically identified as CBD. However, they tend to develop much later in the disease course. This is not entirely surprising, given that both conditions are tauopathies, with neuronal and glial inclusions of microtubule-associated tau protein. The presence of a supranuclear gaze palsy at presentation, or even while the patient remains ambulatory, should suggest an alternative diagnosis.

Rare cases of CBD with Balint's syndrome are reported. Balint's consists of a triad of findings: simultanagnosia (inability to see 'the whole picture' – perception of only portions of the whole), optic ataxia (defective visually-guided limb movements), and ocular motor apraxia (inability to move the eyes voluntarily to objects of interest). Eye movements are often elicited by blinks or head thrusting in oculomotor apraxia. The localization of Balint's syndrome is in the bilateral parietal lobes.

Multiple System Atrophy

Studies of eye movements in multiple system atrophy (MSA) are limited, but suggest a wide range of abnormalities, some of which are directly related to cerebellar involvement in the cerebellar subtype of MSA such as downbeat or gaze-evoked nystagmus (**Table 2**). Excessive square wave jerks, 'saccadic' smooth pursuit, and mild saccadic hypometria are common. Supranuclear gaze palsies are infrequently present and tend to be very mild. The presence of a significant supranuclear gaze palsy should suggest an alternative diagnosis. Much of this data is from studies lacking pathologic proof of diagnosis and is not definitive. In the parkinsonian subtype of MSA, abnormalities of voluntary saccades similar to those seen in idiopathic PD may be occur.

Huntington's Disease

A number of eye movement abnormalities are common in HD, most of which are detectable only with quantified eye movement recordings, and most of which involve saccades (**Table 2**). In keeping with the neurophysiologic nonhuman primate knowledge of the effects of the basal ganglia on eye movement control described earlier, the saccadic deficits in HD are primarily related to voluntary saccade tasks such as memory-guided saccades and antisaccades. Abnormalities include delayed initiation with increased latencies, reduced velocity, and high error rates. In patients with younger onset of disease (<30 years), slowing of saccades is more prominent; whereas, in older onset of disease (>30 years), increased saccadic latencies are more common. In addition to voluntary saccadic deficits, impaired fixation with excessive distractibility and the inability to suppress saccades toward novel visual stimuli are very common. Such distractibility is the same regardless of the age of disease onset. Greater involvement of frontal lobe – basal ganglia connections in HD, as compared to parietal lobes, is responsible for these eye movement abnormalities. The relative sparing of the parietal lobes is compatible with the finding that the ability to direct visual attention to a stimulus is normal in HD.

Much attention has been given to the utilization of eye movements as a biomarker to identify presymptomatic HD gene carriers. One study found a decreased number of memory-guided saccades and subtle delay in the initiation of volitional saccades in presymptomatic HD gene carriers compared to nongene carriers. Another study found similar initiation deficits of voluntary-guided saccades. A third study found increased error rates and increased latencies. All studies support abnormalities of eye movements as a sensitive biomarker in the prediagnostic and early stages of HD. The extent of presymptomatic voluntary saccadic deficits has also been shown to correlate with decreasing connections between the frontal cortex and caudate body on diffusion tensor imaging.

Wilson's Disease

Eye movements have not been extensively studied in Wilson's disease, with the exception of one recent study of 34 patients who underwent quantitative eye movement

recording. The most frequent abnormal eye movement is saccadic vertical smooth pursuit, which is relatively nonspecific (**Table 2**). Impairment of vertical optokinetic nystagmus and saccadic horizontal smooth pursuit may be present. Rarely, Wilson's disease may present with OGC or forced deviation of the eyes.

Spinocerebellar Ataxias

Eye movements have been studied in great detail in the hereditary spinocerebellar ataxias (SCA) with the hope that ocular motility phenotypes would allow specific diagnosis of genotype. With a few exceptions, this is generally not the case since many of the SCAs exhibit abnormal eye movements that are nonspecific and generally attributable to cerebellar involvement. Common cerebellar eye movement abnormalities include saccadic dysmetria (saccadic overshooting or undershooting of the visual target), saccadic smooth pursuit, gaze-evoked nystagmus, and downbeat nystagmus. Severe slowing of saccadic velocity, especially in the horizontal direction, is characteristic of SCA2. Slowing of saccades and supranuclear gaze palsy may occur in SCA7. Abnormalities of the vestibulo-ocular reflex (VOR) are common in SCA3, SCA6, Friedrick's ataxia, and ataxia–telangiectasia. Ocular motor apraxia (inability to move the eyes voluntarily to objects of interest) is a characteristic feature of ataxia–telangiectasia. Downbeat nystagmus is very frequently present in SCA6. A recent study of patients with presymptomatic SCA6 identified eye movement abnormalities in this group, including gaze-evoked nystagmus, square-wave jerks, and impaired smooth pursuit.

Psychogenic (Nonphysiologic) Eye Movement Disorders

Nonphysiologic movement disorders are often accompanied by abnormal eye movements that introduce diagnostic uncertainty. The two most common are voluntary nystagmus and convergence spasm (**Table 2**).

The term 'voluntary nystagmus' is actually a misnomer, as the condition would be more accurately called 'psychogenic flutter.' Nystagmus, by definition, is caused by a slow drift of the eyes away from a desired position. Slow phases are often then followed by corrective fast phases. In contrast, the initial abnormality in voluntary nystagmus is a fast saccadic movement that removes the eye from desired position. Low amplitude (small), high frequency (fast), back-to-back conjugate horizontal saccades (saccadic oscillations) are voluntarily generated. Voluntary nystagmus is found in ~5–8% of the population, and may occur as a familial trait. The patient may complain of a sense of visual motion (oscillopsia) or blurred vision. In addition to the characteristic appearance of the eye movement, additional diagnostic clues are the frequent association with eyelid flutter, a strained facial expression, and excessive convergence of the eyes. Individuals who are able to produce voluntary nystagmus may also be able to superimpose voluntary saccades on smooth pursuit eye movements. The clinical challenge is distinguishing voluntary nystagmus, which has no pathologic significance, from ocular flutter and opsoclonus, which are associated with underlying disease. Ocular flutter and opsoclonus are often larger in amplitude and more sustained.

Convergence spasm, the second common nonphysiologic eye movement finding, may mimic unilateral or bilateral cranial nerve VI (abducens nerve) palsies. The eyes are deviated in toward one another (esotropia), and the patient may be unable to abduct one or both eyes just as in sixth nerve palsies. However, the patient with convergence spasm is voluntarily invoking the near triad of convergence, accommodation, and miosis of the pupils. Careful examination should reveal specific features to suggest convergence spasm. The small size of the pupils during convergence is a major clue. Often, the patient is unable to sustain convergence when one eye is covered and the esotropia will resolve and the pupil will enlarge. Abduction deficits are variable – sometimes present, sometimes absent – over the course of a single examination, and they often alternate sides.

See also: Eyelid Opening Apraxia; Supranuclear Eye Movement Control.

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Eyelid Opening Apraxia

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Glossary

Apraxia – The inability to execute a voluntary motor movement despite normal muscle function.
Blepharokolysis – Another term for the clinical findings of eyelid opening apraxia.
Blepharospasm – Involuntary forced eyelid closure because of orbicularis oculi muscle contraction.
Pretarsal – The portion of the orbicularis oculi muscle in the main entropion of the eyelids; outside of the pretarsal segment are the preseptal and orbital portions of the muscle.
Ptosis – Drooping of the eyelid due to mechanical, nerve, neuromuscular junction, or muscle pathology.
Tarsal plate – Another term for tarsus; the fibrous or cartilaginous plate supporting and shaping the eyelid.

Introduction

Eyelid opening apraxia (EOA) is the inability to initiate and sustain eyelid opening despite the absence of clinically evident weakness in the levator palpebrae superioris (LPS). This statement in isolation may suggest that EOA is a true apraxia, defined as the inability to execute a voluntary motor movement despite normal muscle function. However, careful electrophysiologic studies of the orbicularis oculi (OO) and LPS reveal abnormal function. The term 'apraxia' was initially applied to this disorder with the first clinical descriptions in 1965. Regardless of its inappropriateness, it is widely used and deeply ingrained in the published literature on the topic. Additional terms applied to the disorder include blepharokolysis (from the Greek blepharo, meaning eyelid, and kolysis meaning inhibition), akinesia of lid opening, and lid freezing. EOA may render a patient functionally blind. It is a frequent, likely under-recognized, finding in a variety of movement disorders. In order to understand EOA, a baseline understanding of normal eyelid function is necessary.

Normal Eyelid Function

The primary structure responsible for eyelid elevation is the LPS muscle (**Table 1**). The sympathetically innervated Muller's muscle contributes to a very small degree (1–2 mm of lid opening). The LPS is innervated by the superior division of the oculomotor nerve (cranial nerve III), with motoneurons originating for both LPS muscles in the single midline central caudal subnucleus of the oculomotor nucleus in the midbrain. Tonic activation of the LPS muscles in the awake state maintains eye opening at all times other than when inhibition of LPS occurs to permit eye closure. The premotor source of this tonic activation is not known, but may be located in the periacqueductal gray 'supraoculomotor area' in the midbrain just dorsal to the oculomotor nucleus.

The LPS has reciprocal innervation with the main structure responsible for eyelid closure, the OO muscle. Just prior to a blink, the LPS is inhibited and the OO motoneurons generate short, high-frequency discharge bursts resulting in OO contraction. At the end of the blink, OO activity ceases and the eye opens with return of LPS activation to its tonic baseline. Blinks may be spontaneous (in the absence of external stimuli), reflexive (secondary to external stimuli), or voluntary, with

Table 1 Neurologic control of eyelid movements

Anatomic structure	*Role*	*Effect of biochemical alteration on voluntary saccades*
Levator palpebrae superioris	Elevates the eyelid, tonically innervated by the superior division of the oculomotor nerve (cranial nerve III) Innervation inhibited prior to a blink and maintained until after the blink is completed, this inhibition precedes and outlasts orbicularis oculi contraction	N/A
Muller's muscle	Small contribution to elevation of the eyelid, innervated by oculosympathetics	N/A
Frontalis muscle	Assists with eyelid elevation in extreme upgaze, innervated by the facial nerve (cranial nerve VII)	N/A
Orbicularis oculi	Closes the eyelid, innervated by the facial nerve (cranial nerve VII) Innervation reciprocal with LPS: when orbicularis oculi is active, LPS is inhibited	N/A
Cerebral cortex	Provides premotor control for eyelid movements Pathways not entirely delineated Medial frontal lobes, including supplementary motor area, involved in control of blinking	N/A
Substantia nigra pars reticulata	Tonic inhibition of SC (neurotransmitter GABA)	Dopamine depletion lessens inhibitory effect of striatum on SNr and, thereby, increases SNr inhibitory output to SC Decreased blink rate
Superior colliculus	Mediates tonic inhibition of the blink reflex	GABA agonist (enhanced SC inhibition) Decreased blink rate Increased blink reflex excitability GABA antagonist (decreased SC inhibition) Increased blink rate Decreased blink reflex excitability

LPS – levator palpebrae superioris; SC – superior colliculus; GABA – γ-aminobutyric acid; SNr – subtantia nigra pars reticulata.

different portions of the OO contracting for different types of blinks. The pretarsal (innermost part near the lid margins) portion of the OO is responsible for involuntary (spontaneous and reflexive) blinks, and the preseptal (intermediate portion of the muscle between pretarsal and orbital) portion, for voluntary blinks and intentional eyelid closure. Spontaneous blinks are highly dependent on dopaminergic neurotransmission.

The premotor, or supranuclear, control of eyelid function and the mechanisms of LPS disinhibition are not entirely understood, but the cerebral cortex, basal ganglia, and superior colliculus (SC) are thought to play a role (**Table 1**). Functional imaging studies suggest that the medial frontal lobes, including the supplemental motor area, are involved in the control of blinking. The role of the basal ganglia in eyelid control, while not as extensively studied as their role in eye movements, has been studied in normal and dopamine-deficient animal models. This control is mediated primarily through nigro-collicular connections, as summarized in **Table 1**. The substantia nigra pars reticulata (SNr) has an inhibitory effect on the SC via γ-aminobutyric acid (GABA). Experimental biochemical manipulation of the SC confirms its role in inhibition of the blink reflex. Enhancement of SC inhibition with a GABA agonist results in a decreased blink rate and increased reflex blink excitability. It is also known that dopamine depletion similarly decreases blink rate. Even in the absence of EOA, abnormal eyelid and blink function are evident in Parkinson's disease (PD) and fit the model well, with decreased spontaneous blink rates and increased blink reflex excitability with prolonged voluntary blinks due to delayed return of LPS to baseline tonic activity. In contrast, decreased SC inhibition with a GABA antagonist increases the blink rate and decreases blink reflex excitability. This demonstrated role of dopaminergic transmission and the role of the basal ganglia in eyelid function may also be involved in the genesis of EOA in movement disorders.

EOA Versus Blepharospasm

The diagnostic criteria for EOA include inability to initiate and sustain eyelid opening without evidence of ongoing OO contraction (**Table 2**). It must be differentiated from ptosis and blepharospasm (**Table 3**). Marked

frontalis contraction is typically present, but its absence should not exclude the diagnostic possibility of EOA. Electrophysiologic studies with eyelid electromyography (EMG) have revealed two different mechanisms that may result in the clinical appearance of EOA. Initial EMG studies revealed prolonged involuntary LPS inhibition following eyelid closure as the mechanism of EOA. The absence of OO activity was confirmed in these patients and was consistent with the proposed diagnostic criteria. However, additional EMG studies revealed prolonged contraction of the pretarsal portion of the OO that was not visible on clinical examination (probably because the orbital OO was not involved). Some patients with the clinical appearance of EOA have one or the other mechanism and some demonstrate both EMG findings. There is controversy over whether or not both of these mechanisms should be diagnosed as EOA. Patients with isolated persistence of motor activity in the pretarsal OO are sometimes diagnosed with 'pretarsal blepharospasm' – which some believe is a variant of EOA and some believe is a subclinical variant of blepharospasm.

Table 2 Diagnostic criteria for eyelid opening apraxia

1. Inability to initiate and sustain lid opening
2. No evidence of ongoing orbicularis oculi contraction[a]
3. Marked frontalis muscle contraction during a period of inability to raise eyelids
4. No ocular motor or ocular sympathetic nerve dysfunction and no ocular myopathy

[a]Classically defined as no clinically visible evidence of ongoing orbicularis oculi contraction, although some have proposed inclusion of EMG recording to eliminate the presence of abnormal orbicularis oculi activity. Other authors include patients with EMG evidence of ongoing orbicularis oculi activity in the absence of clinically visible evidence of ongoing orbicularis oculi contraction ('pretarsal blepharospasm') as a subtype of eyelid opening apraxia.

Etiology and Treatment of EOA

EOA is occasionally an isolated finding, especially in patients with a family history of dystonia; however, it more often occurs in the setting of coexisting benign essential blepharospasm (BEB). The prevalence of EOA in patients with BEB ranges from 11 to 75% in various studies. Isolated EOA most commonly has onset in the sixth decade and has a female preponderance. EOA is a common finding in progressive supranuclear palsy. These patients also typically have very decreased blink rates. Additional causes of EOA include idiopathic PD, corticobasal degeneration, subthalamic nucleus stimulation (in up to 30% of patients), and cerebral hemispheric infarction. Very rare cases have been reported with putaminal infarction, Wilson's disease, and lithium treatment. Although some cases are responsive to dopaminergic medications, cases of EOA onset or worsening are also reported.

Treatment options for EOA include pretarsal OO botulinum toxin injection, pharmacologic therapy with dopaminergic or anticholinergic medications, eyelid crutches or goggles, and ophthalmologic surgical procedures. Eyelid EMG to identify those patients with the EOA mechanism of persistent pretarsal OO activity may assist

Table 3 Eyelid abnormalities resulting in excessive eye closure

Eyelid sign	*Clinical features*	*Features distinguishing eyelid movement from eyelid opening apraxia*
Ptosis	Partial or complete eyelid closure due to mechanical (LPS dehiscence), neurogenic (oculosympathetic denervation of Muller's muscle, oculomotor nerve denervation of LPS), neuromuscular junction (myasthenia gravis), or myopathic causes Unilateral or bilateral with LPS dehiscence, worse with downgaze Usually unilateral with oculomotor palsy, accompanied by diplopia and abnormal eye movements Unilateral and mild (1–2 mm) with oculosympathetic denervation of Muller's muscle (Horner's syndrome), accompanied by pupillary miosis Unilateral or bilateral and fatigable with neuromuscular junction	Fixed ptosis without intermittent spontaneous opening of eyelid (unless neuromuscular junction, in which ptosis is variable, not fixed) With neuromuscular junction, fatigability with prolonged upgaze
Eyelid opening apraxia	Involuntary inability to open the eyes after lid closure No visible orbicularis oculi contraction Intermittent, spontaneous opening of the eyes	N/A
Blepharospasm	Involuntary, intermittent, forced eye closure with visible contraction of orbicularis oculi During episodes of eyelid closure, eyebrows are located beneath the superior rim of the orbit (Charcot's sign)	Visible contraction of orbicularis oculi

LPS – levator palpebrae superioris.

with identification of the patient group most likely to have a therapeutic response to botulinum toxin injection. Patients with isolated prolonged LPS inhibition are less likely to respond to this treatment. Treatment with eyelid crutches or goggles takes advantage of the phenomenon of 'geste antagonistique,' or alleviation of EOA by sensory stimulation on or around the eyelids via a presumed proprioceptive feedback mechanism. Ophthalmologic surgical procedures of potential use include blepharoplasty, myectomy, frontalis suspension, and aponeurosis repair.

See also: Eye Movement Abnormalities in Movement Disorders; Supranuclear Eye Movement Control.

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Eye-of-the-Tiger Sign

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Definition and History

The eye-of-the-tiger sign refers to the characteristic MRI pattern found in PKAN. Specifically, the sign describes hypointense signal in the globus pallidus in conjunction with a region of central or anteromedial hyperintensity on T_2-weighted imaging (**Figure 1**). These changes are also evident on proton density (PD) and fluid attenuated inversion recovery (FLAIR) imaging. T_1-weighted imaging is normal.

Originally coined in 1988 by Sethi et al. in reference to coronal MRI sections, the term is more commonly used to refer to a similar pattern on sagital sections.

Pathogenesis/Pathophysiology

The eye-of-the-tiger sign is observed as a result of a specific pattern of damage to the globus pallidus in PKAN. The hypointense signal in the globus pallidus on T_2-weighted imaging represents high tissue iron; the central hyperintense signal is associated with edema. These changes are consistent with the current hypothesis of disease. The only other MRI change consistently seen in PKAN is hypointense signal in substantial nigra, which is often not evident until later in disease.

PKAN is an inborn error of coenzyme A metabolism. As such, the very early pathogenic changes in the basal ganglia are hypothesized to arise from perturbed fatty acid metabolism, leading to tissue damage and edema. Early MRI changes in presymptomatic, mutation-positive individuals show a predominance of hyperintense signal indicating less iron. As the disease progresses, iron accumulates and the hypointense signal intensifies. In addition, the hyperintense signal appears to condense.

MRI changes may predate clinical symptoms. Characteristic MRI changes have been documented in clinically normal, mutation-positive siblings of affected individuals. In contrast, at least one case suggests that clinical symptoms may predate MRI changes, although this is probably rare.

Differential Diagnosis

The eye-of-the-tiger sign is considered to be virtually pathognomic for PKAN. Rare reports have offered evidence to refute this notion; however, none of these has provided sufficient data to challenge this robust association. Therefore, especially in the context of supporting clinical data, the eye-of-the-tiger sign indicates PKAN.

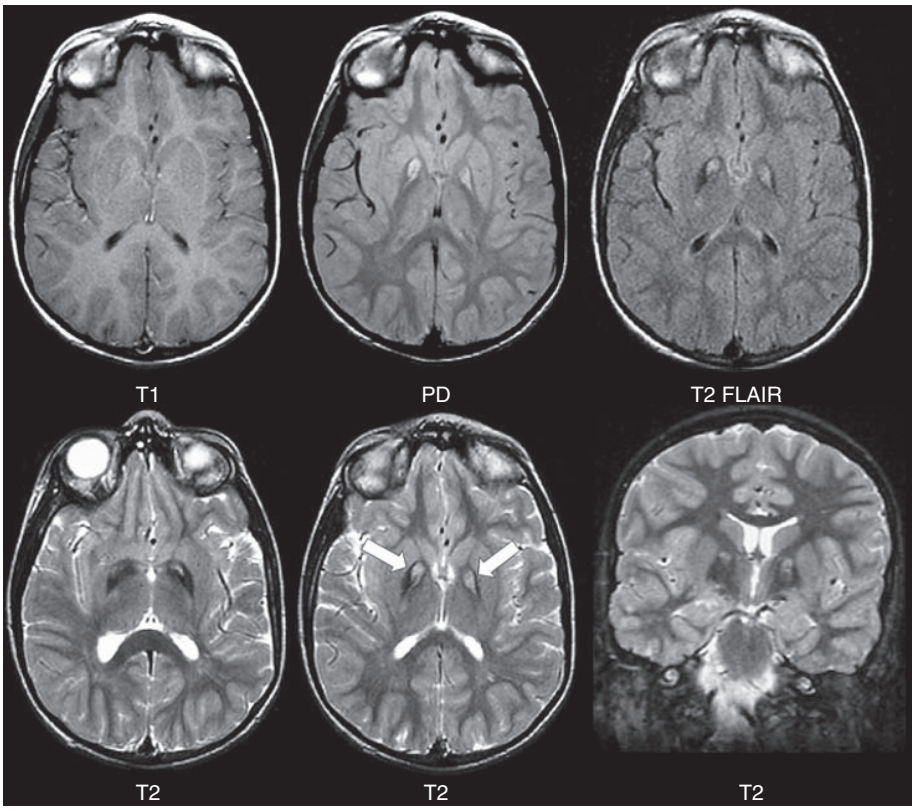

Figure 1 Eye-of-the-tiger sign (arrows). This *PANK2* mutation-positive child shows MR features characteristic of PKAN. The T_1-weighted images appear normal, but high signal can be seen in the globus pallidus on proton density (PD), T_2-weighted fluid attenuated inversion recovery (FLAIR), and T_2-weighted images in both the axial and coronal planes. With increasingly heavier T_2 weighting (PD<FLAIR<T_2), there is increasingly conspicuous T_2 hypointensity at the periphery due the magnetic susceptibility effects of excess iron.

Neurodegeneration with brain iron accumulation (NBIA) describes a heterogeneous group of disorders that includes PKAN. Others are neuroferritinopathy, aceruloplasminemia, infantile and atypical neuroaxonal dystrophy, and idiopathic NBIA. The specific MRI patterns associated with these disorders differ from that of PKAN, although all include high regional iron in the basal ganglia.

Diagnostic Work-up/Tests

When MRI shows the eye-of-the-tiger sign, diagnostic studies for PKAN are indicated. PKAN is a genetic disorder caused by mutations in *PANK2*, the gene encoding pantothenate kinase 2. Blood may be sent for DNA sequencing of *PANK2* in order to confirm the diagnosis. Laboratories currently offering clinical testing can be found at GeneTests. The sensitivity of current screening tests is >98%. Gene Tests: Medical Genetics Information Resource (database online). University of Washington, Seattle. 1993–2009. Available at http://www.genetests.org.

See also: Hallervorden–Spatz Syndrome (PKAN).

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F

Factitious Disorders

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Glossary

Antisocial personality disorder – Antisocial personality disorder is a psychiatric diagnosis in the *Diagnostic and Statistical Manual of Mental Disorders.* The essential feature for the diagnosis is a pervasive pattern of disregard for, and violation of, the rights of others that begins in childhood or early adolescence and continues into adulthood. Deceit and manipulation are considered essential features of the disorder.

Borderline personality disorder – Borderline personality disorder is a psychiatric diagnosis in the *Diagnostic and Statistical Manual of Mental Disorders* that describes a prolonged disturbance of personality function characterized by depth and variability of moods. The disorder typically involves unusual levels of instability in mood; 'black and white' thinking, or 'splitting'; chaotic and unstable interpersonal relationships, self-image, identity, and behavior; as well as a disturbance in the individual's sense of self.

Confabulations – The formation of false memories, perceptions, or beliefs about the self or the environment as a result of neurological or psychological dysfunction.

Histrionic personality disorder – Histrionic personality disorder is a personality disorder characterized by a pattern of excessive emotionality and attention-seeking, including an excessive need for approval and inappropriate seductiveness, usually beginning in early adulthood. The essential feature of histrionic personality disorder is an excessive pattern of emotionality and attention-seeking behavior.

Malinger – To feign illness, injury, or incapacitation in order to avoid work or obligation, or to secure tangible benefits.

Projective identification – A psychological process in which a person engages in the ego defense mechanism projection in such a way that his behavior towards the object of projection invokes in that person precisely the thoughts, feelings, or behaviors projected.

Pseudologica fantastica – Terms applied by psychiatrists to the behavior of habitual or compulsive lying; pathological lying.

'Sick role' – Term widely used in medical sociology concerning the social aspects of falling ill; individual who has fallen ill is not only physically sick, but now adheres to the specifically patterned social role of being sick.

Somatoform – Manifesting physical symptoms whose primary cause is psychological.

Splitting – Can be explained as thinking purely in extremes, for example, good versus bad, powerful versus defenseless, and so on. Splitting can be seen as a developmental stage and as a defense mechanism.

Definition and History

Factitious disorder is diagnosed when a person *intentionally* feigns or produces physical or psychological symptoms in order to assume the sick role. By definition, these symptoms are produced *consciously*; however, the underlying motivation to produce them may be *unconscious.* Distinguishing conscious from unconscious intention and motivation are important for differentiating a factitious disorder from somatoform disorders and malingering. These distinctions can be challenging for the clinician because even though patients with factitious disorder often present to the healthcare provider requesting medical care intentionally concealing the known source of their symptoms, they may not be consciously aware of why they are seeking the sick role.

DSM-IV-TR outlines three diagnostic criteria for factitious disorder:

1. The intentional production of physical or psychological signs or symptoms.
2. The motivation is to assume the sick role.
3. External incentives for behavior such as financial gain or avoidance of legal responsibility, or improving physical well-being (as in malingering) are *absent*.

The DSM-IV-TR further subclassifies factitious disorders into those with predominantly *psychological* signs and symptoms, those with predominantly *physical* signs and symptoms, those with combined *psychological and physical* signs and symptoms, or factitious disorder, not otherwise specified.

Evaluating physicians who suspect factitious disorder need to rule out undiagnosed illness that may not have been previously detected, or an undiagnosed illness that may coexist with a superimposed factitious disorder. At the same time, clinicians need to balance a thorough evaluation of the patient's symptoms with the need to avoid extensive and unnecessary medical procedures, which bear their own risks, expenses, and liabilities.

Munchausen syndrome refers to a subtype of factitious disorder. It is a severe, chronic form of factitious disorder characterized by three traits: fabrication of signs or symptoms that are often bizarre and marked ('pseudologica fantastica'); 'doctor seeking,' including migrating from hospital to hospital for multiple and often invasive procedures; and disguising one's identity.

Munchausen syndrome by Proxy, also known as factitious disorder by Proxy, involves a caretaker inducing symptoms in a child which results in unnecessary medical testing and procedures, presumably motivated by the caretaker's wish to assume the 'sick role' via the child. It is considered a form of child abuse.

Clinical Features and Diagnostic Criteria

Clinical presentations are quite variable, and patients may present with a wide array of symptoms, diseases, and conditions. Factitious disorder in its milder forms may present with minimal symptoms, which may not inspire the clinician to consider factitious disorder as a diagnosis. Early identification of patterns common to factitious disorder can help the clinician initiate early intervention when appropriate, which may help avoid progression to a more chronic course.

A number of features in the presentation of factitious disorder that are nonspecific may be useful diagnostic clues. History obtained from patients often contains unexplained gaps, confabulations, or fabrication of symptoms. Familiarity with medical terminology and procedures are often evident in patients with factitious disorder, and this may in part be explained by the frequency with which these patients have intimate familiarity with healthcare settings. A review of cases conducted by Krahn et al., found that 72% of these patients were women and 65.7% either had healthcare-related jobs or training. Ingestion of psychoactive substances to produce symptoms, such as emetics, hormones, anticoagulants, laxatives, or even utilizing contaminants like feces, bacteria, and sputum to induce illness, have been reported. Tampering with instruments such as thermometers, IV lines, or laboratory specimens may mislead healthcare providers to order unnecessary procedures. Patients often become highly indignant when questioned about discrepancies in their reports. Reactions can range from denial to extreme rage, or making threats of legal action if the clinician continues to question their reports. Factitious disorder patients are often uncooperative with attempts to obtain collateral information. Typically, nurses on inpatient units note that these patients do not receive phone calls from friends or family, and are deemed 'loners' and introverts.

Pathogenesis/Pathophysiology

Current understanding of the pathogenesis of factitious disorder is speculative, based mainly on clinical observation and interpretation thereof. Factitious disorder patients often implicitly express an intense need to be taken care of as part of their assuming the sick role. Ongoing psychiatric evaluation is required to understand why this need has developed, and why this strategy has been undertaken in order to meet this need. Stress-related issues, either past or present, are often exposed during thorough interviews with patients, which may influence the desire to adopt the sick role. These issues can include loss, abandonment, illness, disappointment, or abuse. Personality disorders are a common finding, specifically, those that utilize 'splitting' and 'projective identification' such as borderline, antisocial, and histrionic personality disorders.

Epidemiology

Prevalence data are sparse and difficult to collect. A survey of 26 physicians in independent practice, and 83 senior hospital consultants in the specialties of internal medicine, surgery, neurology, and dermatology estimated that a 1 year prevalence of factitious disorder averaged 1.3% (0.0001–15%). Poor recognition of symptoms and associated diagnosis results in underreporting of this disorder. Suspected cases, when confronted, may sign out of the hospital, evading diagnosis and follow-up. Typically, only the most severe cases are reported, giving a diminished picture of the disorder's prevalence.

Differential Diagnosis

Undiagnosed medical illness is the most important exclusion for the evaluating physician. The investigation of possible underlying medical illness should proceed even if strong evidence points to the presence of a psychogenic component of the presenting symptoms, since these two conditions may coexist.

Malingering, which is not a psychiatric disorder, involves the intentional production of physical or psychological signs or symptoms with the clear objective of pragmatic gain. This includes financial gain, evasion of legal responsibility, obtaining narcotics or other controlled substances, or avoidance of work or other responsibilities. The history given in both malingering and factitious disorder can be sophisticated and convincing. Poor cooperation during the evaluation and treatment process are common in both. Furthermore, both these conditions can coexist.

Somatoform disorders connote the presence of signs or symptoms suggestive of a medical condition, but no underlying organic etiology is established after appropriate diagnostic evaluation. The symptoms are deduced to be of psychological origin, but on a basis that is *not* consciously evident to the patient. These disorders cause significant impairment in functioning, and are not due primarily to substance abuse or another psychiatric disorder. Some psychological or minor 'secondary gain' benefits may pertain, but they are not intentionally pursued by the patient.

Diagnostic Work-up

Taking a thorough history, along with a meticulous chart review and collaboration with other medical care providers is essential. Obtaining prior medical records and speaking with past caretakers may legitimately be made a precondition for treatment, once this diagnosis is suspected. Laboratory studies and imaging can be useful to help rule out organic disease, and also to assist in confirming suspicions of feigned illness. As with any evaluation, these studies need to be based on clinical indication. For example, checking serum insulin/c-peptide ratio in hypoglycemic patients with suspected exogenous insulin administration can confirm a diagnosis of self-induced hypoglycemia. Diagnosis relies on a high index of suspicion, and making full use of all obtainable clinical information.

Utilizing a nonjudgmental approach, however, predicated on the possibility of a somatoform disorder (without conscious intent) is important to avoid alienating the patient by premature confrontation. Early introduction of the psychiatrist as an integral part of the evaluating team can help clarify psychopathological features and enhance receptivity to a treatment plan that includes a psychiatric component.

Management

Once a factitious disorder is suspected or identified, psychiatric consultation is needed for further diagnostic assessment and treatment formulation. To facilitate collaboration with medical and psychiatric services, a supportive, nonconfrontational approach is desirable. Delineating the role of 'stress' in many medical illnesses, and delineating neurotransmitter roles in the neuropsychiatric genesis of many medical conditions may allow a more nuanced and less judgemental approach to the issue of intentionality and unconscious motivating factors, while allowing the team and patient to focus on symptom attenuation. If possible, engaging a stable family member in the diagnostic debriefing and treatment planning, with the patient's consent, can be a valuable resource. Psychotherapeutic modalities, along with psychopharmacology, may help ameliorate symptoms. However, due to the absence of controlled clinical trials, evidence-based treatment strategies cannot be currently delineated. Supportive individual psychotherapy and family therapy may be helpful in identifying patient needs and uncovering predisposing, precipitating, and perpetuating factors that can inform treatment strategies. Psychopharmacologic agents may be useful in treating comorbid conditions such as affective and anxiety disorders. Addressing coexisting personality disorders is warranted if the patient is amenable.

Prognosis

In the absence of controlled treatment trials and follow-up studies, but based on uncontrolled clinical experience, it is generally assumed that the prognosis for factitious disorders is less favorable than that of somatoform disorders. Some uncontrolled studies suggest that chronic and severe factitious disorders follow an unremitting course. This, however, is true for many psychiatric disorders; it should not dissuade the clinician from concerted efforts at early diagnosis and treatment.

See also: Malingering; Psychogenic Movement Disorders; Somatoform Disorders.

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Fahn–Marsden Rating Scale

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Glossary

Dystonia – Sustained muscle contractions of agonists and antagonists causing involuntary twisting movements and postures.
Reliability – Consistency of the assessment or measurement of a given tool (e.g., a scale), at different times or by different evaluators.
Validity – Degree to which a test (e.g., a scale) measures what it is intended.

Definition and History

Dystonia is a hyperkinetic movement disorder characterized by sustained twisting and posturing movements, which may affect single or multiple body areas. While there are characteristic electrophysiologic features of dystonia, such as muscle agonist–antagonist cocontraction, these do not yet allow quantification of severity of dystonia in different body sites. Further, the features of dystonia are not static and vary according to activity. In order to better characterize the clinical course, and to assess the efficacy of treatments, scales to capture both the severity of the dystonia (including the dynamic features) and the functional disability of the dystonia are needed. Scales may encompass dystonia affecting all body sites, such as the Fahn–Marsden (F–M) rating scale, which may be used for generalized, segmental, or focal dystonia, or may be focused on one body area, such as cervical dystonia.

Both the structure and validity and reliability of the F–M rating scale were first reported in 1985. The scale was subsequently first used in the context of a therapeutic trial with trihexyphenidyl for the treatment of torsion dystonia.

The F–M rating scale is composed of two sections: a movement scale based on the neurological examination and a disability scale based on the patient's opinion of his disability in activities of daily living. The movement scale is further divided in nine body regions: eyes, mouth, speech and swallowing, neck, right arm, left arm, trunk, right leg, and left leg. Individual scores are obtained for each body region; from 0 to 8 for the eyes, mouth, and neck, and from 0 to 16 for the other body parts. The individual scores are calculated for each body region using a formula that takes a provoking factor, a severity factor and a weighting factor into account. The eyes, mouth, and neck are 'down-weighted' because when involved, these regions were not suggested to cause as much disability. The provoking factor is scored from 0 to 4 as following: 0 – No dystonia, 1 – Dystonia on particular action, 2 – Dystonia on many actions, 3 – Dystonia on action of a distant body part (overflow) or intermittently at rest, and 4 – Dystonia at rest. For speech and swallowing, the provoking factor is slightly different, and is based on frequency. The severity factors are scored similarly for all regions except speech and swallowing. Some site-specific criteria apply according to the specific abnormal movement or posture caused by the dystonia (e.g., bending of the trunk with truncal dystonia, blinking or spasms of eye closure with blepharospasm). In general, the severity factors range from 0 to 4, with 0 – No dystonia, 1 – Slight dystonia, 2 – Mild dystonia, 3 – Moderate dystonia, and 4 – Severe dystonia, with different ratings for speech and swallowing. Once individual scores for each body part are calculated, they are summed to obtain the movement scale score. The scale ranges from minimum of 0 to maximum of 120.

For the disability score, seven activities of daily living are rated according to the patient's perception of his/her disability: speech, writing, feeding, eating, hygiene, dressing, and walking. The scores are from 0 to 4 (except for walking, from 0 to 6), and scores are task specific. In general, scores are determined according to the following scale: 0 – Normal, 1 – Slight difficulty, 2 – Some difficulty, 3 – Marked difficulty, and 4 – Severe difficulty, unable to perform the activity. The scale for walking is slightly different, ranging from 0 to 6; with a score of 6 assigned if the subject is wheelchair bound. Once the scores for all the individual activities of daily living are obtained, they are summed to obtain the total disability score, which ranges from 0 to 30.

Metrics of the Scale: Reliability and Validity

The validity of the scale assesses how well the scale reflects a gold standard rating. As clinical assessment of dystonia remains the de facto 'gold standard,' the validity of the motor portion of the scale reflects how well the scores correlate with the clinical impression of dystonia severity. For example, when the dystonia is perceived as severe by an experienced neurologist, a valid scale would lead to a high score. The converse is true for a dystonia perceived as mild by the clinician. On the other hand, the reliability of the scale corresponds to how reproducible the score is, among different examiners (interrater reliability), but also from the same examiner at different times (intrarater reliability).

The validity and reliability of the F–M rating scale were first evaluated by Burke and colleagues in 1985. The validity was evaluated by comparing the F–M score with the global clinical impression of severity and with the disability score. The reliability was assessed by first, comparing evaluations of the 10 patients on two occasions by two examiners (intrarater validity) and second, by examining the correlation of the ten evaluations of the three examiners. The scale was shown to be both reasonably valid and reliable for patients with primary torsion dystonia. However, only a small number of patients were assessed, and because dystonia is so heterogeneous, the broader spectrum of dystonia was not tested. Further, the degree of agreement for individual body sites was not reported.

Two large multicenter studies have since evaluated the F–M scale. Comella and colleagues evaluated the reliability of the scale using 20 videotaped patients, and 25 dystonia experts, and compared the scale to the UDRS (Unified Dystonia Rating Scale) and GDS (Global Dystonia Rating Scale). They concluded that all three scales were internally consistent, showed good to excellent interrater reliability (intraclass correlation coefficient, 0.71–0.78), but that the provoking factor in the F–M demonstrated less interrater agreement than the motor severity ratings. Further, they found that the GDS (which includes rating for proximal and distal limbs separately, and does not include subjective speech and swallowing ratings, and does not include weighting factors) was easier to administer than the F–M. Krystkowiak and colleagues further demonstrated reliability in a prospective assessment of the F–M scale used to track severity and disability of primary generalized dystonia treated with deep brain stimulation.

Applications of the Scale

The F–M scale was first used to assess the efficacy of trihexyphenidyl as a treatment for primary and secondary dystonia. It is now primarily used to assess the efficacy of deep brain stimulation surgery in both primary and secondary dystonia, usually in cases with generalized dystonia.

Problems with the Scale

As noted, the F–M rating scale has several limitations. The major drawback in using the F–M scale is lack of ease in administration, which relates to separately determining provoking and severity factors. The GDS was developed as an alternative to the F–M, and has been shown to be at least as reliable and valid but simpler and easier to apply. The UDRS was developed to address the F–M scale's limitations regarding the flexibility to report specific sites as the rated areas are smaller and more defined, and shows great promise. The F–M scale is also limited in its applicability for some dystonia plus syndromes and secondary dystonias as it is focused on dystonia, and additional movement disorders, such as myoclonus and features of secondary dystonia, such as that due to Wilson disease, or spasticity associated with other forms of secondary dystonia are not captured. In these situations, disease specific scales, such as the Wilson Disease Scale, may be more applicable.

See also: Basal Ganglia; Dystonia; Dystonia in Amish-Mennonite and Mennonite Families; Dystonia: Animal Models; DYT1; DYT2, Autosomal Recessive Generalized Dystonia; DYT4, Autosomal Dominant Type Dystonia or Whispering Dysphonia; DYT5; DYT11, DYT15, Myoclonus-dystonia; DYT12, Rapid Onset Dystonia-parkinsonism; Generalized Primary Torsion Dystonia; Rating Scales in Movement Disorders; Wilson's Disease.

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Foot Print Analysis

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Glossary

ALS – Amyotrophic Lateral Sclerosis, a syndrome in which peripheral and central motor neurons degenerate leading to progressive paralysis and eventually death due to respiratory failure (generally several years after diagnosis).
CNS – Central nervous system, the brain and spinal cord.
Contact electrode – Electrode fitted under the paw on an animal which is used to sense presence of paw–floor contact.
Gait diagram – Graphical representation of timing and duration of paw–floor contact in relation to the other foot or paws. Support and Gait formulas are simplifications hereof (see e.g., Hamers et al., Figure 1).
Gait formula – See Gait diagram.
SFI – Sciatic functional index, a measure that is used to assess completeness of functional motor recovery after sciatic nerve lesion.
Support formula – See Gait diagram.

Introduction

The ability to walk is taken for granted by healthy people, and regaining this ability after it has been lost because of an accident or disease is often one of the most important goals of patients in rehabilitation medicine: In my current practice, 'to leave the hospital walking' is among the most formulated wishes of patients when asked for their goals. Many eventually attain this goal although gait may never completely normalize.

Causes of gait disturbances are many: In principle, every disorder affecting the nervous system (peripheral as well as central), the skeleton, the muscles, the tendons, the skin, and the senses potentially affect gait.

Animal models are important both in the elucidation of the pathogenesis of such disorders, and in the search for effective therapies. Because gait is easily observed, gait disturbances have the potential both for assessing the degree of malfunctioning as well as for testing experimental therapies. However, theory is simple, practice is not: The rats and mice most often employed in such research are moving considerably faster than humans and describing and especially quantifying gait is far from easy.

In this paper, I will introduce methods to describe and quantify gait in rats and mice (foot print analysis being one of them), and their application to specific disease models. Given the limited space, I can only discuss the basics and some of the most interesting techniques. The interested reader is referred to the *Further Reading list* at the end.

Describing and quantifying gait

Open field testing

The oldest and most simple way of performing gait print analysis is by visual observation: Although hampered by the speed with which animals move around, one can by focusing on specific elements of gait such as plantar/dorsal stepping (does an animal trip over its toes at initial contact?), gross rotation of the feet (inner/outer rotation as opposed to parallel placement) and toe drags (which are listened for) obtain sufficient data to create sensitive scoring systems with excellent reproducibility. Two of the most important scoring systems in this respect are the Basso, Beattie, and Bresnahan (BBB) rating scale,

and the Basso Mouse Score (BMS), developed for respectively spinal cord injured rats and mice.

Foot Print Analysis

One of the most widely used methods to quantify gait disturbances caused by experimental sciatic nerve lesions was developed by de Medinaceli: Measurements of stride length, print length, and toe spread are measured from walking tracks and the Sciatic Functional Index (SFI) – essentially a measure for the degree of asymmetry between lesioned and control paw – is computed hereof: recovery of symmetry (SFI of 0) indicates functional recovery. By using only specific terms in the equation, one can also discriminate between recovery of innervation of the triceps surae muscle and intrinsic foot muscles. Because of its simplicity, it is still widely used in some way or another. Prints may, however, be difficult to recognize, especially in the first weeks after sciatic nerve injury when most of the recovery of the SFI occurs, and interobserver variability can be quite large.

Weight Bearing

An animal may place its paw without bearing weight. If you have a painful wound in your foot, you try to do the same by shifting weight to some other part of the foot (which is clearly visible to the trained observer). Tetrapods can keep one of their paws (almost) completely unloaded, which is neither visible in the open field nor on de Medinaceli walking tracks. However, the possibility to quantify weight bearing has the potential to uncover subtle gait disturbances due to central nervous system (CNS) disease and can also be used to measure pain (in an indirect manner). Two techniques have the potential to do so, one quantitative technique relying on pressure sensor grids which was recently described by Boyd and coworkers, the other one being semiquantitative and to be discussed later (**Figure 1**).

Timing Relationships

Among the most difficult parameters to assess are timing relationships between paw placements. Nonetheless, they have been used for a long time in the description of gait, for example, in the characterization of horse gait (e.g., trot, gallop, walk).

Timing of paw placement relative to other paws can be expressed in the gait diagram and its derivatives, the support and gait formulas. These have been used to describe changes between gaits in a single animal (e.g., from trotting to galloping) and changes induced by disease. Hildebrand extensively used them in his description of a gait in a wide variety of tetrapods. Until recently such research was prohibitively expensive and time consuming, at least on a regular basis. Nonetheless, changes in timing relationships, or phase shifts, can provide deeper insight in the control of gait. Majczynski, Zmyslowski, and coworkers developed a rather elegant method which circumvents the need of high speed photography to study such relationships by using contact electrodes in spinal cord injured animals. Few others have followed their lead, however.

With the ready availability of fast and cheap computers and video capture hardware, high throughput systems for gait analysis have been developed for animals and humans. Essentially two different techniques that have been used in disease models have been introduced in the past decade. The first is the CatWalk, based on a walkway with some special properties that enable easy visualization of paw prints and (semi)quantitative pressure estimations for these prints, the other, DigiGait, is treadmill based and does not offer pressure estimation. A third technique which requires significantly more user interaction and which will

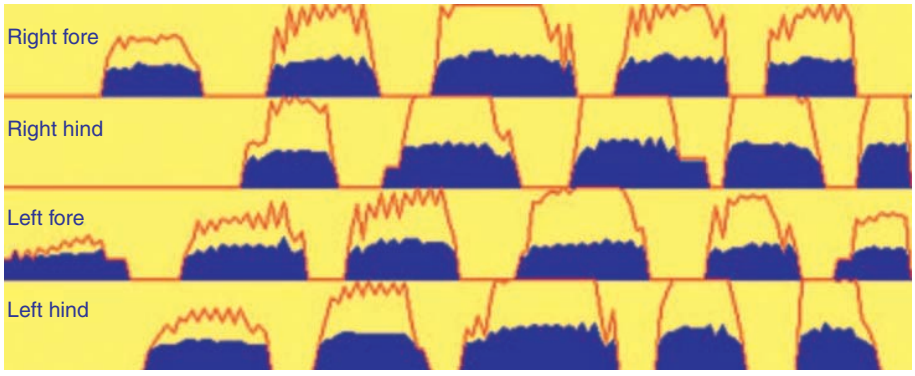

Figure 1 The average intensities (filled area: averaged over the whole contact area of the paw at any moment) and the max intensity (upper line) anywhere at that moment as function of time. These intensities are related to weight bearing. In this experiment we were not interested in weight bearing, otherwise we would have made sure that max intensity did not exceed the dynamic range of the camera.

not be discussed further in this manuscript was developed by Gruntman, Benjamini, and Golani.

CatWalk

Development of CatWalk started in 1996 after I visited the Beattie–Breshanan lab for learning to use the newly developed BBB score. The goal was to better assess forelimb–hindlimb (FL–HL) coordination than is possible in the open field. I build a walkway such as originally described by Dr Kenneth Clarke of the University of Sheffield, a walkway which was based on a device originally developed by Drs Betts and Duckworth for measuring plantar pressures under human feet. The most important property of this walkway is that only places of paw–floor contact light up, with paws that are only minimally raised being invisible. In short: walkway crossing are filmed from underneath with a CCD-camera connected to a PC and controlled by the CatWalk software which stores the films in a format that retains the important details (most video compression algorithms discard the details!). The program can be used to measure almost every parameter discussed thus far. Input from my own research (experimental spinal cord injury) and many collaborators from all over the world (on neuropathic and arthritic pain, developmental (Hox genes) mutants, cerebellar disease, hereditary motor-sensory neuropathy) was incorporated in the analysis section.

Although originally developed to quantify locomotor disturbances in models of spinal cord injury, the method has from its inception also been used in other models. The use in pain models was suggested already in 1999 by Dr Tinna Angeby-Möller. Dr Guido Koopmans, working on his PhD thesis in Dr Bert Joosten's lab, eventually combined CatWalk provided evidence for normal FL–HL coordination with open field BBB scoring, ending up with a more sensitive BBB score. For our paper on insulin-like growth factor-1 (IGF-1) and enriched environment housing we also performed some major quantitative analyses of timing relationships (couplings) between FLs and HLs, an area with great potential when it comes to understanding the generation of gait and its feedback loops. CatWalk has also proved its value in models for Refsum's disease, Stroke, Parkinsonism, and Sciatic Nerve Injury.

DigiGait

DigiGait was developed by Dr Thomas Hampton in the early years of this decade. Animals are filmed from underneath while walking on a transparent treadmill belt and almost the same set of data as that acquired with CatWalk can be analyzed, although paw–floor contact is probably somewhat less reliably assessed than with CatWalk. However, animals can be forced to walk at chosen speeds and for longer periods, which may be helpful to find deficits that only show up under greater stress. Publications exist on the use of this system in models of ethanol intoxication, in trisomic mice (a model for Down syndrome) and models for Parkinson's disease and Huntington's disease. Interestingly, early changes in neurological functioning in a model for amyotrophic lateral sclerosis (ALS) have also been described employing this system, which can be helpful to identify animals with subtle but well described locomotion deficits very early in the disease process, enabling one to gain more insight in the early stages of the disease process.

Conclusion

Gait analysis has evolved significantly over the years. The availability of fast and inexpensive computers and video acquisition hardware in the last decade has led to powerful new analyses that can be performed routinely. This review has only tipped some of the basics and the interested reader is kindly referred to the papers listed in the *further reading list* below for further background.

See also: Drug-induced Movement Disorders; Gait Disturbances in Parkinsonism; Multiple System Atrophy: Animal Models; Parkinson's Disease: Animal Models; Parkinson's Disease: Definition, Diagnosis, and Management; Rating Scales in Movement Disorders; Refsum Disease- a Disorder of Peroxisomal Alpha-oxidation; Spinocerebellar Ataxia Type 19, 20, 21, 22, 23, 26; Tourette Syndrome: Animal Models.

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Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS)

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Glossary

FMR1 – Fragile X mental retardation 1 gene, the gene mutated in fragile X syndrome and fragile X tremor/ataxia syndrome.
FXTAS – Fragile X-related tremor/ataxia syndrome, neurodegenerative disorder resulting from small (premutation size) expansion mutations in a CGG repeat sequence in *FMR1*.
MCP sign – High signal in the middle cerebellar peduncle seen on T2 and flair MRI.
POI – Primary ovarian failure, early ovarian insufficiency; FX-POI, ovarian insufficiency related to the *FMR1* premutation.
Premutation – Small mutation which does not cause disease, but just propensity to pass disease to descendants.

Definition and History

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a recently discovered late-onset (>50 years) neurodegenerative disorder, occurring in carriers of a premutation CGG repeat expansion in the fragile X mental retardation 1 (*FMR1*) gene. The disorder is associated with a variable presentation which may include intention tremor, ataxia, parkinsonism, executive dysfunction and cognitive decline, neuropathy, and psychiatric features. FXTAS was first described in 2001, when it was noted that grandfathers of individuals being seen for management of fragile X syndrome (FXS) often had unexplained neurological symptoms categorized as tremor or atypical parkinsonism.

Genetics/Molecular Pathogenesis/ Pathophysiology

The *FMR1* gene, located on the X chromosome, has a trinucleotide (CGG) repeat sequence located in the first exon of the gene, which functions as part of the promoter, and codes for a sequence in the 5′ untranslated region of the *FMR1* mRNA. The normal repeat length is 5–44 CGG triplets; 'gray zone' alleles are defined as 45–54, premutation alleles as 55–200, and full mutations as above 200 CGG repeats. Repeat lengths in the gray zone may occasionally be unstable, or expand, when passing from one generation to the next, but are not known to cause disease.

Full mutation alleles cause hypermethylation and silencing of the *FMR1* promoter and a consequent deficiency or absence of *FMR1* protein (FMRP). FMRP is an RNA-binding protein that regulates translation at dendrites

in response to neural activation, thereby modulating synaptic plasticity and dendritic morphology. Absence or deficiency of FMRP results in FXS, a developmental disorder associated with intellectual disability, autistic-features, and characteristic physical signs.

Two phenotypes are specifically associated with permutation alleles. The first is fragile X-associated primary ovarian insufficiency (FX-POI) which leads to ovarian dysfunction, and, in 20% of female carriers, to premature ovarian failure (POF). The second phenotype is FXTAS, which occurs in a proportion of carriers, predominantly in men.

Although FXS results from lack of FMRP, there are normal or near-normal levels of FMRP in premutation carriers with FXTAS. Thus, an alternative molecular mechanism has been proposed for FXTAS based on the finding of a mild translational deficit of FMRP compensated by elevated *FMR1* mRNA levels in cells from premutation carriers, particularly at larger CGG repeat sizes. Accumulated *FMR1* mRNA containing the CGG repeat is thought to exert a neurotoxic effect by sequestering and perturbing function of nuclear proteins. This mechanism is consistent with the findings of nuclear inclusions in mice expressing an *fmr1* gene with a premutation expansion allele (~100 CGG repeats) and neurodegeneration in *Drosophila* expressing expanded CGG repeats. As predicted by the *FMR1* mRNA toxicity mechanism for FXTAS, individuals with the *FMR1* full mutation and FXS do not develop FXTAS because the *FMR1* gene silencing in FXS results in absent or reduced *FMR1* mRNA and FMRP. **Figure 1** illustrates the relationships between FMR1 CGG repeat length, type of mutation, FMR1 mRNA levels, FMRP levels, and clinical phenotype.

Pathological findings in humans with FXTAS, including ubiquitin-positive intranuclear inclusions in neurons and astrocytes throughout the brain, are also consistent with the RNA toxicity mechanism. Immunohistochemical and mass spectrometric analyses of purified brain inclusions show they are composed of more than 20 proteins and include the FMR1 mRNA. Proteins identified in the inclusions also include lamin A/C, a nuclear structural protein associated with neuropathy, suggesting some features of FXTAS may reflect a functional laminopathy. Indeed, disruption of nuclear architecture and abnormal nuclear lamin localization has been observed in neurons in brain autopsy samples from individuals with FXTAS.

The nuclear inclusions in FXTAS are seen throughout the brain, most numerous in the hippocampal formation, and only rarely seen in Purkinje cells. The number of CGG repeats is highly correlated with the fraction of inclusion-bearing neural cells. Inclusions are found in spinal autonomic neurons and astrocytic nuclei of the spinal cord, but not in motor neurons of the spinal cord. Patches of subcortical and deep cerebellar white matter show pallor and spongiosis with axonal spheroids, accompanied by loss of axons and myelin, and correspond to areas of increased T2-weighted signal intensity on MRI images.

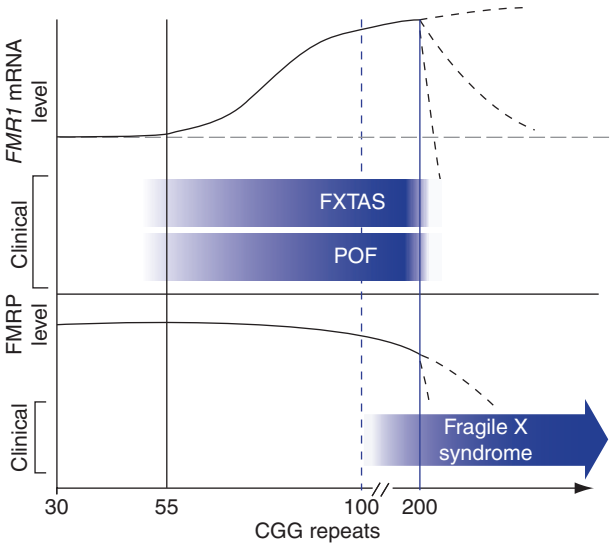


Figure 1 Graphs of the relative levels of *FMR1* mRNA and protein (FMRP) as a function of the number of CGG repeats, and the associated clinical phenotypes. FXTAS and premature ovarian failure (POF) are largely confined to the premutation range, and are thought to occur through an RNA toxic gain-of-function due to excess *FMR1* mRNA; however, occasional patients with full mutation alleles continue to express mRNA and are at risk of developing FXTAS. By contrast, FXS is caused by reduced/absent FMRP, due to silencing of the *FMR1* gene in the full mutation range, and is generally confined to the full mutation range. Features of the FXS spectrum may occur in the upper premutation range due to reduced protein production. Dashed lines for mRNA levels in the full mutation range reflect variations in degree of silencing; dashed lines for FMRP levels represent reductions due to both lowered mRNA levels and intrinsic reductions in translational efficiency.

Clinical Features and Diagnostic Criteria

The major motor features of FXTAS are demonstrated on accompanying video clips. Tremor on the Clinical Rating Scale for Tremor (CRST) and limb and gait/stance ataxia on the International Cerebellar Ataxia Rating Scale (ICARS) were distinct clinical features identified in adult male premutation carriers as compared to age-matched control groups. As evidenced by the statistically significant differences in all subdomains of the CRST, tremor in FXTAS is multidimensional, involving rest, postural, and kinetic elements. Postural and kinetic tremors are typically more obvious initially and rest tremor may appear as the condition progresses. The gait is typically slow and lurching, and patients have difficulty with tandem stance and gait, consistent with cerebellar ataxia. Parkinsonian signs, primarily rigidity, are usually less obvious. This suggests that the phenotype in FXTAS premutation carriers is not a

typical presentation of Parkinson disease (PD), but an overlapping tremor-predominant syndrome with cerebellar ataxia and mild parkinsonism. Despite high interindividual variation, even within families, the mixture of gait ataxia, postural/intention tremor, and parkinsonism in older men is characteristic of FXTAS but overlaps the spectrum of clinical features seen in inherited cerebellar ataxias and multiple system atrophy – cerebellar subtype (MSA-C). The mean age (±SD) of FXTAS onset is 60.2 (±7.2), and larger CGG repeat numbers in the *FMR1* premutation correlates with earlier age of onset of both tremor and ataxia.

In addition to tremor and ataxia, neuropathy and autonomic dysfunction also occur in FXTAS. Signs of peripheral neuropathy, including decreased reflexes and impaired vibration sense in the distal lower extremities, are present in many affected persons and are more frequent in male premutation carriers than in matched controls. Severity of neuropathic signs correlates with CGG repeat length and with severity of ataxia in both male and female premutation carriers.

Cognitive deficits are frequent in FXTAS, most often a dysexecutive syndrome. The initial signs of cognitive impairment in FXTAS are relatively subtle deficits of the executive cognitive functions (ECF) and working memory, which may be overlooked until they begin to affect behavior. There are deficits on the WAIS III performance IQ, and the speed of information processing is slowed and its capacity is decreased relative to normal persons of the same age and education. Deficits in semantic memory – especially retrieval – are common, probably secondary to the dysexecutive syndrome. There appears to be little impairment of primary declarative memory, especially episodic recall, until much later in the disorder, and constructional praxis, visuospatial functioning, language, and verbal reasoning are typically intact. One of the most striking executive cognitive deficits as FXTAS advances is impairment in the initiation of purposeful, goal-directed activity, and in the inhibition of inappropriate or irrelevant behavior. The neuropsychiatric inventory (NPI), which quantitates behavioral consequences of dementia, may be more abnormal in FXTAS than overall cognitive screening instruments such as the Folstein Mini Mental State Examination (MMSE). This MMSE may be paradoxically relatively well-preserved early FXTAS dementia, as it does not assess executive cognitive deficits directly. FXTAS can be associated with a combination of psychiatric features, predominantly generalized anxiety disorders and mood disorders of the depressed type that evolve with disease progression. Some of the psychiatric symptoms in FXTAS may be due to the stress of living with a disabling illness.

It is not known when cognitive impairment begins in relation to the neurological signs of FXTAS or whether progression of motor and cognitive signs correspond. Further, given findings of anxiety, subtle executive and social disorders, and mood disorders among carriers of premutation alleles without FXTAS, cognitive and psychiatric issues may in some cases be a developmental manifestation of the premutation, unrelated to FXTAS.

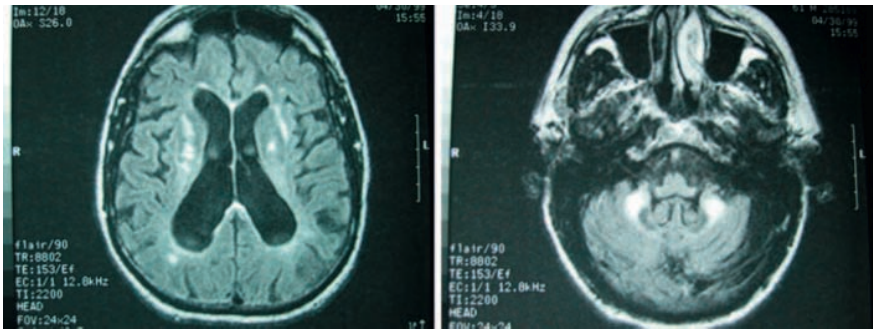
FXTAS affects predominantly male premutation carriers, although individual female carriers can have clinical and neuropathological features of FXTAS. The prevalence of FXTAS in females has been estimated at 8% over age 40. Female carriers with and without FXTAS experience higher rates of neuropathy, muscle pain, and thyroid dysfunction in addition to FX-POI. Neurological disability is typically much milder in females than in males, presumably due to protection provided by the expression of *FMR1* from the normal allele on the active X chromosome in a percentage of cells. Indeed, females with FXTAS symptoms tend to have skewed X-inactivation, with a greater fraction of cells expressing an active premutation.

Radiological features associated with FXTAS (**Figure 2**) include increased signal intensity on FLAIR or T2-weighted brain MRI in white matter of the middle cerebellar peduncles (MCP sign), and in underlying cerebellar white matter lateral to the dentate nuclei. The MCP sign is not specific to FXTAS; and not all persons with FXTAS demonstrate this finding. FXTAS-associated MRI findings also include patchy or confluent areas of increased signal intensity on T2-weighted or FLAIR images in periventricular and deep white matter of the cerebral hemispheres and corpus callosum, and significant volume loss involving the cerebellum, cerebral cortex, amygdalo-hippocampal complex, thalamus, and brainstem. Cerebellar volume loss, increased ventricular volume, and whole brain white matter hyperintensity correlate with CGG repeat length in premutation carriers.

Diagnostic criteria for FXTAS have been proposed (**Table 1**) for use in clinical studies. In routine medical practice the diagnosis can be made by finding the *FMR1* premutation in a person with a late-onset neurological disorder consistent with previously published cases. Presence of the MCP sign on MRI is useful in confirming the diagnosis, but not necessary, since it is observed in only about 60% of affected carriers.

Epidemiology/Risk Factors

The penetrance of FXTAS in male *FMR1* premutation carriers over 50 years is ~40%, with an age-related penetrance of 17%, 38%, 47%, and 75% for male carriers aged 50–59, 60–69, 70–79, and ≥80 years, respectively. It has been estimated that 1/100–1/250 females and 1/250–1/800 males in the general population are carriers of an *FMR1* premutation, suggesting that for males, FXTAS may be one of the most common late-onset, progressive neurological diseases associated with a single gene mutation, similar in prevalence to MSA and amyotrophic lateral sclerosis.



(a) Abnormal white matter signal gray and white matter atrophy (b) MCP sign

Figure 2 MRI findings on FLAIR images in FXTAS showing MCP sign, abnormal cerebellar white matter signal, and cerebellar atrophy (a), and increased signal in deep white matter and volume loss in the cerebral hemispheres (b).

Table 1 Proposed diagnostic criteria for FXTAS

Molecular	*55–200 CGG repeats*	
Clinical		
Major	Intention tremor Cerebellar gait ataxia	
Minor	Parkinsonism Moderate to severe working memory deficit Executive function deficit	
Radiological		
Major	MRI white matter lesions involving middle cerebellar peduncles	
Minor	MRI lesions involving cerebral white matter Moderate to severe generalized brain atrophy	
Diagnostic categories		
Definite	Probable	Possible
One major clinical, and one major radiological, or presence of FXTAS inclusions	Two major clinical; or one minor clinical, and one major radiological	One major clinical, and one minor radiological

Source: Brunberg JA, Jacquemont S, Hagerman RJ, et al. (2002) Fragile X premutation carriers: Characteristic MR imaging findings in adult males with progressive cerebellar and cognitive dysfunction. *American Journal of Neuroradiology* 23: 1757–1766.

FXTAS represents the etiology of disease in ~1.5–2.1% of cases presenting with ataxia and 2.4% of cases with the cerebellar subtype of MSA. Results of published screening studies likely underestimate the true contribution of the *FMR1* premutation to movement disorders because the overall clinical picture for many patients with FXTAS is complex and the multiplicity of neurological problems in FXTAS would often result in atypical presentations, difficulty with classification, and thus exclusion from studies involving groups of subjects with typical ET, PD, or ataxia.

Differential Diagnosis

The differential diagnosis of FXTAS is broad and depends on what symptoms are most evident in the individual being evaluated. For patients presenting with the most common features of FXTAS the differential might include MSA (especially MSA-C), olivopontocerebellar atrophy, other inherited ataxias, syndromes with mixed tremor such as thyroid disease, Wilsons disease, lithium toxicity, multiple sclerosis or even severe essential tremor, atypical PD, and parkinsonism-dementia syndromes. A fraction of cases diagnosed with multiple sclerosis or PD with dementia, likely actually have FXTAS, particularly when multiple family members are affected. For a patient presenting with symptoms of FXTAS, a family history of mental retardation, autism, behavioral/learning disorders in children or grandchildren, infertility or premature menopause suggestive of POI in daughters or female relatives, or syndromes of difficult-to-classify neurological and psychiatric problems in other family members, suggest a diagnosis of FXTAS.

Diagnostic Work-up/Tests

Diagnosis of FXTAS is accomplished through DNA analysis designed to evaluate the size of the CGG repeat sequence in *FMR1.* The DNA test performed is the same for identification of either FXS or FXTAS, and may be

Table 2 Testing guidelines for FXTAS[a]

Clinician should test for FMR1 mutation if the patient has any of the following:
Onset of cerebellar ataxia of unknown cause in an individual over 50 years
1. Onset of action tremor of unknown cause in individual over 50 years with parkinsonism or cognitive decline
2. Prior diagnosis of multiple system atrophy, cerebellar subtype
3. MCP sign on T2/FLAIR images of MRI in a patient with signs consistent with FXTAS[b]
4. Positive family history of *FMR1* mutation in an individual who could be a carrier based on position in pedigree if signs consistent with FXTAS are present[b]
5. Family or patient history of infertility/premature menopause in a patient with signs consistent with FXTAS[b]

[a]Presence of an MCP sign (increased T2 signal intensity in the middle cerebellar peduncles), family history of *FMR1* mutation and possible carrier status, and patient history of POF (premature ovarian failure), even without clinical signs of FXTAS would be appropriate criteria for *presymptomatic* screening for an *FMR1* mutation.
[b]Signs consistent with classic FXTAS include action tremor, cerebellar gait ataxia, parkinsonism, and cognitive decline, especially executive function deficits. Additional features that are often associated with, or may be the presenting features of FXTAS, include peripheral neuropathy, parkinsonism, autonomic dysfunction, dementia, a family history of ataxia, autism spectrum disorder or mental retardation, and a family or personal history of POF. Males are more commonly affected than females.

termed *fragile X DNA test*, *FMR1 DNA test*, or *FXTAS DNA test*, depending on the laboratory. The fragile X DNA test is readily available at numerous University and commercial laboratories in the USA and through health services laboratories in many countries. Based on current literature, reasonable guidelines for testing for FXTAS are presented in **Table 2**.

Management

Currently, there is no specific treatment for FXTAS targeted to the underlying pathogenic mechanism. Strategies for supportive intervention and clinical monitoring include: (1) treatment for specific neurological and psychiatric symptoms; (2) monitoring for progression and degeneration; (3) treatment of hypertension; (4) referral to psychiatry, gerontology, movement disorder specialist, speech therapy for evaluation and management of swallowing, occupational therapy and/or physical therapy as necessary; and (5) genetic counseling for the patient and family. Symptomatic treatment of tremor with primidone or β-blockers. parkinsonism with carbidopa/levodopa or amantadine, neuropathic pain with gabapentin, anxiety and depressive symptoms with antidepressants or benzodiazepines, and dementia with donepezil, rivastigmine, galantamine, or memantine may be helpful.

Genetic counseling is imperative for all individuals diagnosed with FXTAS, but is challenging because of the complex multigenerational inheritance, variable phenotype, and implications for families. All women with a premutation are at risk of having offspring with a full mutation and FXS. All daughters of males with a premutation will be obligate carriers of the premutation. Thus, when a male patient with FXTAS is identified, the patient's mother is then an obligate carrier and offspring and relatives of the patient and his mother are at risk for FXS or for carrying a prermutation and possible FX-POI and FXTAS.

Prognosis

Definition of the natural history of FXTAS is difficult because the initial symptoms may be subtle (ECF dysfunction or mild tremor) and difficult to recognize and because the disorder has only recently been discovered. A single family-based, retrospective, longitudinal study analyzed the progression of FXTAS in 55 male premutation carriers. Defining onset as the first report of tremor or ataxia, tremor usually occurred first, with median-onset at ~60 years. From occurrence of the initial motor sign, median delay of onset of ataxia was 2 years; onset of falls, 6 years; dependence on a walking aid, 15 years; and death, 21 years. Preliminary data on life expectancy were variable, ranging from 5 to 25 years. In the few months before death patients were bedridden, dysarthric, dysphagic, without bladder or bowel control, and had severe parkinsonism (rigidity, rest tremor, and bradykinesia). Given the relentless course of the disease in some patients, extensive support, including psychological support, for the patient and family may be needed. It is hoped that in the future, mechanism-specific treatments that can reverse the course of the disease will become available through molecular and translational research. Specifically small molecules including siRNAs that disrupt the *FMR1* RNA CGG repeat interactions are being investigated.

See also: Ataxia; Dementia, Movement Disorders; Multiple System Atrophy; Postural Tremor; RNA Interference; Tremor; Tremor, Essential (Syndromes); Trinucleotide Repeat Disorders.

Further Reading

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Relevant Websites

www.NSGC.org – National Society of Genetic Counselors.
www.fragilex.org – National Fragile X Foundation (NFXF) website.
www.genetests.org – Genetests site for Genetics reviews and testing labs.
www.FRAXA.org – FRAXA Foundation website.

Freezing of Gait

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Glossary

Cueing – Using sensory signals (visual, auditory, tactile, haptic, etc.) to facilitate initiation or ongoing motor activity (gait).
Festination – Taking increasingly rapid and small sequential steps during walking in an attempt to maintain the center of gravity above the feet, while the trunk leans progressively forward.
Freezing of gait – Sudden feeling of 'being glued to the floor' with an impossibility to generate effective forward stepping movements, in the absence of another cause than parkinsonism or higher cortical deficits.
OFF state freezing of gait – Freezing of gait that is mainly present when the response to dopaminergic treatment has vanished.
ON state freezing of gait – Freezing of gait that is mainly present when the response to dopaminergic treatment is optimal.
Sequence effect – Progressive decrease in step length combined with disturbed timing of steps, commonly seen prior to a freezing of gait episode.

Definition and History

Freezing of gait (FOG) is a common and disabling feature of Parkinson's disease (PD). It is a remarkable gait disorder, because of its episodic character. Patients with FOG experience sudden and often unexpected episodes during which their feet subjectively are 'being glued to the floor,' while their trunk continues to move forward. A FOG episode is thus defined as a brief episode during which patients find it impossible to generate effective forward stepping movements, in the absence of another cause than parkinsonism or higher cortical deficits. It is most commonly experienced during turning and step initiation, but also when faced with spatial constraint, stress, and distraction. Focused attention and external stimuli (cues) can overcome the episode. Because of the sudden and unpredictable nature, FOG often leads to falls and injuries.

Already in 1817, James Parkinson described in his classical essay '*The Shaking Palsy*' the typical 'propensity to bend the trunk forwards, and to pass from a walking to a running pace.' This phenomenon is currently known as 'festination': taking increasingly rapid and small sequential steps during walking, in an attempt to maintain the center

of gravity above the feet while the trunk leans progressively forward. Although festination and FOG appear to be closely related, James Parkinson did not specifically describe FOG. The first description of a FOG episode presumably stems from Charcot in 1877 who described gait initiation failure, followed by forward propulsion with festination. During the last 10 years, interest in the clinical impact, underlying pathophysiology and treatment methods of FOG have increased rapidly.

Epidemiology/Risk Factors

Epidemiology as Related to Different Etiologies

FOG is common in idiopathic PD; it occurs in 20–80% of PD patients, depending on disease severity, disease duration, and treatment status. Interestingly, some patients experience FOG in early stages of their disease, while other patients never develop FOG. It is also seen in some 25–60% of patients with atypical parkinsonism caused by vascular parkinsonism, normal-pressure hydrocephalus, or neurodegenerative diseases such as progressive supranuclear palsy or multiple system atrophy. FOG is less often seen in patients with corticobasal degeneration (8–25%) and rarely occurs in neuroleptic-induced parkinsonism. Primary progressive FOG is an uncommon condition starting with FOG, often with frequent falls. Patients initially do not experience bradykinesia, rigidity, or tremor and usually do not respond to treatment with levodopa. With extended follow-up, this condition may clinically progress to progressive supranuclear palsy or corticobasal degeneration. Post-mortem examination in these patients may reveal pallidonigroluysian degeneration or diffuse Lewy body disease, underscoring how heterogenic the underlying etiology can be.

Risk Factors

In idiopathic PD, the most important risk factors for developing FOG include a more advanced disease and a longer disease duration. A longer duration of levodopa treatment is also seen as a risk factor for FOG, although it is difficult to uncouple this from the disease duration and disease severity. Also, medicated patients may show more FOG simply because they can walk for a longer period, increasing the likelihood of witnessing FOG episodes. Other risk factors include disturbances in gait, posture, and speech, but bradykinesia and rigidity are not related to the occurrence of FOG. Remarkably, the presence of tremor is associated with a lower risk of developing FOG. FOG is further associated with frontal cognitive (executive) deficits, including even overt dementia and urinary incontinence (which may also reflect frontal dysfunction). FOG is itself a strong risk factor for falls and ensuing injuries.

Clinical Features/Diagnostic Criteria

Circumstances of Freezing

FOG episodes most commonly occur in complex environments that necessitate integration of multiple sensory stimuli. Therefore, they are typically seen during a shift of attention or a circumstantial or directional change. Thus, in daily life, FOG particularly occurs under specific conditions such as starting, turning, walking in tight quarters (e.g., passing a narrow doorway), or upon reaching a destination, but it may also occasionally occur during straight walking in open space. Turning around appears to be the strongest provoking factor. Dual tasks or stressful demands may also increase the occurrence of FOG. Furthermore, the majority of FOG episodes occur when the response to dopaminergic treatment has vanished (i.e., during an OFF phase), when FOG is both lengthier and more severe (see also the section on Management).

Characterization

The main characteristic of FOG is a loss of efficient forward movement generation, which can manifest itself as three different subtypes. The least severe subtype consists of taking very small shuffling steps, with only minimal forward movement. A more severe subtype includes trembling of the leg, without any effective forward motion, known as 'trembling in place.' The most severe subtype is a complete akinesia, without any observable motion of the legs. The duration of a FOG episode is usually very brief, typically ranging from less than a second to up to 10 s. Episodes longer than 10 s are very rare and only occur during the OFF phase, when FOG episodes last longer compared to the ON phase.

Diagnosis

The current 'gold standard' of diagnosis of FOG is the observation of FOG by an experienced examiner. However, FOG is notoriously difficult to elicit in the examination room, so the patients' subjective feeling of periodically being 'glued to the floor' often serves as surrogate marker to establish the diagnosis. FOG is currently only classified as being either 'present' or 'absent,' and reliable gradations of severity are not yet available. More elaborate assessment techniques will be discussed under section Diagnostic workup.

Pathophysiology

The precise pathophysiology underlying FOG remains unknown, but the following hypotheses are commonly heard.

Neuroanatomical Substrate

FOG appears to be an independent motor symptom, caused by a pathology different from tremor, bradykinesia, or rigidity. Dopaminergic cell implants into the putamen of PD patients improve bradykinesia and rigidity of the legs, but do not improve FOG, whereas levodopa can decrease FOG in PD patients that do not improve rigidity or bradykinesia. Hence, FOG might be related to dopamine deficiency outside the putamen. Case reports of freezing after stroke and after misplaced deep brain stimulation (DBS) electrodes suggest a role for the pedunculopontine nucleus (PPN). Furthermore, studies using neuroimaging techniques have implicated the caudate nucleus, the orbitofrontal cortex, and central noradrenergic systems as being possibly involved in generating the freezing phenomenon. It is most likely that FOG does not result from localized pathology within a specific locus in the brain, but rather reflects dysfunction in an organized network that involves the frontal cortex, the basal ganglia (perhaps mainly the caudate nucleus), and the connections between these areas. For at least some of the patients, non-dopaminergic circuitries (possibly involving noradrenergic pathways) may be additionally involved.

Neurophysiology

Basal ganglia dysfunction in patients with PD leads to a faulty production of adequate amplitude and timing of movements. The basal ganglia play two important roles in the performance of learned automatic movement sequences. The first role is to match and maintain the movement amplitude of a cortically selected movement plan (motor set), and the second role is to run each component of the plan in a timely manner (motor cue production). In patients with FOG, basal ganglia dysfunction leads to failure in generating adequate movement amplitudes (reflected by a progressive decrease in step length), combined with a disturbed timing of steps, a phenomenon known as the 'sequence effect.' Movement timing difficulties in freezers are reflected by a disturbed timing of stepping movements during gait. This becomes apparent as an increased variability of gait (even outside overt FOG episodes) and a premature timing of muscle activations immediately prior to FOG episodes. More recent work specifically pointed to disturbances in the fine regulation of interlimb coordination, as reflected by a marked temporal gait asymmetry in patients with FOG. This indicates an impairment in controlling the simultaneous timing and pacing of stepping movements of both legs, rather than an inability to regulate steps per se. Finally, a newly emerging concept is that failure to initiate compensatory stepping could be due to impairment of anticipatory postural adjustments (a lateral weight shift is normally required to allow for a contralateral limb swing). Apparently, a walking problem (gait akinesia) may be caused by a deficit in the integration of balance and gait programs, or by a primary balance deficit, that is, the inability to shift weight. This notion is supported by the finding that PD patients, when provided with an assistive (externally imposed) anticipatory postural adjustment, can step faster.

Neuropharmacology

Levodopa generally alleviates FOG, both with respect to severity and frequency, which implies that dopamine depletion in the striatum is the main neurochemical substrate of FOG. Methylphenidate may improve gait and reduce FOG in PD, conceivably by increasing the availability of striatal dopamine or by improving attention. Furthermore, increasing striatal dopamine using monoamine oxidase type B (MAO-B) inhibitors (selegiline, rasagiline) is also associated with reduced FOG, although the effects in clinical practice are rarely convincing.

However, FOG is sometimes resistant to dopaminergic therapy. This does not necessarily exclude a role for dopamine deficiency in the underlying pathophysiology, because the threshold for therapeutic relief may simply be higher for FOG than for other symptoms, falsely creating the impression of 'levodopa-resistance.' More puzzling is the observation that dopaminergic therapy can also paradoxically cause or aggravate FOG, and this may be particularly true for dopamine receptor agonists. This might point to a role for excessive dopaminergic stimulation in extra-nigrostriatal circuitries (much like the dopamine dysregulation syndrome), or alternatively, to a role for lesions within non-dopaminergic circuitries. The latter assumption is supported by the fact that FOG rarely occurs in patients with neuroleptic-induced parkinsonism. Further support could be derived from therapeutic trials with non-dopaminergic compounds, such as the noradrenaline precursor L-threo-dihydroxyphenylserine (L-threo-DOPS), but this has only been tested in small series and with crude outcome measures.

Differential Diagnosis

FOG should be differentiated from a voluntary stop or hesitation (e.g., because the patient feels unsafe), overall rigidity, or festination. Overall rigidity differs from FOG because the episodic character is absent: patients with overall rigidity have the feeling of being glued all the time, while patients with FOG experience the glued feeling only episodically. Festination should also be differentiated from real FOG episodes. During festination, the feeling of being glued to the floor is lacking. Festination typically occurs during gait, while FOG mainly occurs during gait initiation and turning. Moreover, festination leads to a fastening instead of slowing of walking velocity. Finally, FOG should also be differentiated from central nervous system overloading that occurs during complex

multitasking, as may occur when patients undertake a secondary task during walking (e.g., carrying a tray). A classical example is the 'stops walking when talking' phenomenon, where patients stop walking because the task of maintaining a simultaneous conversation is too demanding. Such multitasking can provoke real FOG, but some stops simply reflect a conscious adaptive strategy: it is better to temporarily stop walking when the overall task has become too complex. Voluntary stops lack the typical trembling of the legs, the preceding sequence effect, and the flexed posture seen in FOG.

Diagnostic Workup

History Taking: Subjective Assessment

Patients often do not realize what FOG is, which may complicate history analysis. It is essential to specifically ask about the characteristic feeling of 'being glued to the floor.' In addition, details can be obtained about the frequency, circumstances, and characteristics of the FOG episodes. These questions are incorporated into a specialized Freezing of Gait Questionnaire (FOG-Q). A recently modified version of this FOG-Q also uses a video to ascertain that the patient and caregiver accurately realize what FOG episodes look like. It often helps when the examiner gives a demonstration of the different subtypes.

The influence of medication on FOG episodes should also be ascertained, as this has important implications for therapy, and because it may provide clues about the underlying etiology. In contrast to ON period FOG, OFF period freezing is present upon awakening prior to the intake of medication, and improves with treatment. Sometimes, the presence of falls is the only clue about the presence of FOG. Typical falls that are associated with FOG are forward falls, lateral falls during turning, and unexplained, seemingly spontaneous falls.

Physical Examination

Clinical assessment of FOG should be done in both a subjectively 'good ON' state and a 'practically defined OFF' state (at least 12 h after intake of the last dose of antiparkinson medication). It is crucial to use a standardized gait trajectory where patients are instructed to execute a series of walking tasks that typically elicit FOG episodes such as turning, negotiating a narrow passage, initiating gait, and performing dual tasks while walking. The best way to provoke a FOG episode is through rapid axial turns (360°, with a narrow turning circle because wide turns are less likely to provoke FOG). Ask the patient to turn in both ways (leftward and rightward), because FOG can show a marked directional dependence. The type of FOG, the duration of an episode, and the frequency of FOG should be noted. Note that FOG can be asymmetric and may affect only one leg, usually on the clinically most affected side. No validated instrument to objectively assess FOG exists, so the clinical eye of an experienced clinician remains the gold standard (see **Figure 1**). Cognitive examination, especially concerning the frontal executive and attentional functions, should always be a part of the physical examination. The effect of external cues (to improve FOG) and dual tasking (to provoke or worsen FOG) should also be monitored.

Quantitative Assessment

There is a need for validated methods to quantitatively assess FOG, for example using kinematic gait analyses, pressure-sensitive insoles, or surface electromyography of leg muscles. This may be done during overground walking with specific provoking circumstances (narrow passages, turning, dual tasks). Recent work has shown that it may be possible to provoke FOG in a gait laboratory, asking patients to walk on a treadmill using obstacle avoidance tasks. Specific spatiotemporal characteristics, that is, an increase in cadence and decrease in stride length, precede a FOG episode. Furthermore, accelerometers placed on the shanks during walking show characteristic high-frequency components of leg movement when FOG episodes occur. However, these assessments have not yet been validated, and a general problem is that the sheer awareness of being tested typically suppresses FOG during the measurements. Therefore, quantitative assessment is currently used only for research purposes.

Neuroimaging

Structural neuroimaging helps unravel the differential diagnosis, for example, by showing leukoaraiosis in a patient suspected of having vascular parkinsonism, or atrophy of the mesencephalon in a patient suspected of having progressive supranuclear palsy. Nuclear imaging and functional neuroimaging are currently used to study the pathophysiology of FOG, but this is currently only utilized in a research setting.

Management

Medication

Most patients suffer from OFF state FOG, with more frequent and severe episodes when the effect of medication has worn off. However, a minority of the patients experience FOG in the ON state. Paradoxically, dopaminergic medication (especially dopamine receptor agonists) can sometimes cause FOG. In patients with mainly OFF state FOG, increasing the dose of antiparkinson medication often leads to improvement, while ON state FOG may be alleviated by tapering the antiparkinson medication.

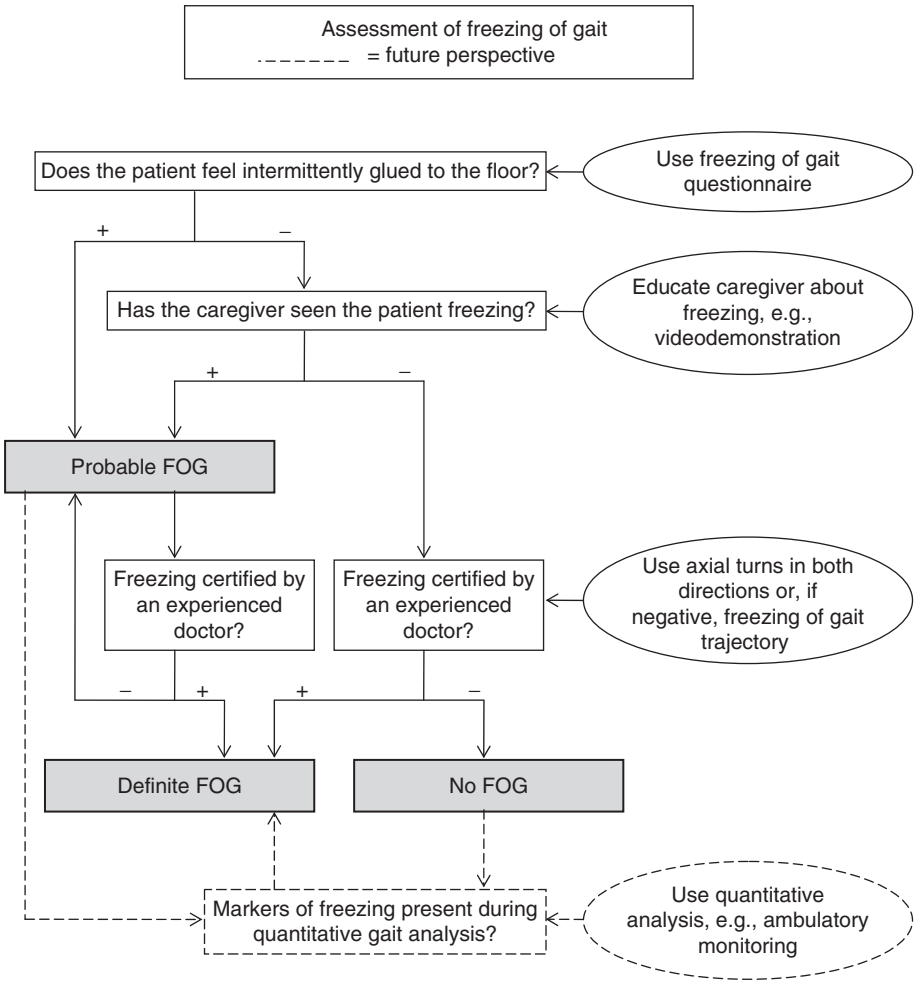

Figure 1 Flow-chart for diagnosing freezing of gait.

Selegiline may prevent the development of FOG – possibly by the improvement of the visuomotor system – but is less effective once the symptoms are fully developed. Another MAO-B inhibitor, rasagiline, improved FOG in a double-blind, placebo-controlled study. However, the small improvement seen in this study is unlikely to be clinically relevant.

Other pharmacological approaches focus on improving attention and executive function, but only small case series have been published. Methylphenidate may improve OFF state FOG in PD, but a negative study has also been published. Methylphenidate is mainly seen as a dopaminergic agent, but may also improve FOG by influencing noradrenergic systems. L-threo-DOPS, an immediate precursor of noradrenaline, was effective in Japanese patients with primary progressive FOG, but subsequent studies failed to confirm this. Small studies using donezepil, an acetylcholinesterase inhibitor specifically used to enhance attention, had beneficial effects in patients with pure FOG. Further placebo-controlled blinded studies with adequate numbers of patients and proper outcome measures remain much needed.

Physiotherapy

Specific cueing techniques using rhythmic auditory cues can reduce the severity of FOG by improving step length and walking speed. Furthermore, physiotherapists can teach patients to avoid or better deal with dual tasks, as FOG typically occurs during a shift of attention. Avoiding stress might also be beneficial to prevent FOG episodes. Using a wide arc while turning, instead of making an axial turn 'in place,' is also effective in preventing FOG episodes.

Deep Brain Stimulation

A relatively new method for the treatment of FOG is DBS. Currently, the preferred target for DBS in advanced PD is the subthalamic nucleus (STN), but the globus pallidus remains a good alternative according to some. There is

evidence that STN stimulation improves FOG, but only when it occurs in the OFF state. The general rule of thumb is that FOG that fails to improve with dopaminergic treatment will neither respond to DBS. Moreover, there are concerns about the development of secondary gait worsening or postural deficits postoperatively, not immediately after surgery but only after several years, even in the face of a persistent beneficial effect on 'appendicular' motor control. Possibly, reducing the frequency of DBS (to frequencies more typically used to stimulate the PPN) can be used to optimize DBS treatment.

A new area of interest is DBS of the dorsal mesencephalon where the PPN is situated, because the PPN has extensive connections with the basal ganglia, as well as with descending spinal pathways. Furthermore, the PPN has been suggested to play an important role in the initiation and maintenance of locomotion. Patients with FOG may respond to PPN stimulation, even when STN stimulation and drug treatment are optimized, but only small groups were tested. Moreover, the precise localization of the PPN for DBS remains difficult.

Prognosis

FOG will worsen with advancing disease. Most treatment methods fail to provide a lasting effect and may even paradoxically aggravate FOG. Patients with gait disorders such as FOG have an increased mortality risk, mainly due to a direct result of falling. In addition, the ensuing immobility results in secondary cardiovascular disease and cognitive decline. The mobility problems related to FOG are among the most distressing symptoms of PD. Hence, there is an urgent need for further understanding and management of this intriguing phenomenon.

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See also: Basal Ganglia; Bradykinesia; Deep Brain stimulation; Dopamine Depletors and Movement Disorders; Electromyography (EMG); Freezing of Gait; Gait Disturbances in Parkinsonism; Gait Ignition Failure; Monoamine Oxidase Type B Inhibitors; Neuroimaging, Parkinson's Disease; Parkinson's Disease: Definition, Diagnosis, and Management; Parkinsonism: Vascular; Primary Progressive Freezing Gait; Progressive Supranuclear Palsy; Subthalamic Nucleus.

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Relevant Websites

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www.rescueproject.org – Rescue Project.

Friedreich's Ataxia and Variants

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Glossary

Ataxia – Impaired coordination, dexterity, or gait in the absence of significant muscular weakness.
Frataxin – A highly conserved nuclear-encoded protein localized in mitochondria.
***FRDA* gene** – The *FRDA* gene is localized on the long arm of chromosome 9, just below the pericentromeric heterochromatic region.
Friedreich's ataxia – The most common autosomal recessive and hereditary ataxia due to the hyperexpansion of a GAA triplet repeat in the first intron of the *FRDA* gene.

Definition and History

In 1863, Nicholaus Friedreich described a specific form of spinal degeneration with distinctive clinical and pathological findings in nine members of three siblings attending the university clinic. Originally termed 'degenerative atrophy of the posterior columns of the spinal cord,' Friedreich was able to pinpoint all essential clinical and pathological features of the disease, including progressive ataxia, sensory loss, muscle wasting and weakness, often with scoliosis, foot deformity, and heart disease, but just to miss deep tendon reflexes. He also noted the tendency of the disease to afflict several individuals in a sibship, but not affect parents. Initially suspected to be a form of neurosyphilis, it was not until 1882 when the new disease was given the name Friedreich's ataxia [MIM229300] (FRDA) or Friedreich's disease by some authors since ataxia is not always a principal feature. During the past 40 years, a number of landmark studies were carried out to establish the autosomal recessive (AR) pattern of inheritance as well as define vigorous diagnostic criteria, which are the key for the collection of clinically homogeneous families to be used for biochemical and molecular genetic studies.

Pathogenesis

Neuropathology

Despite Friedreich's emphasis on the degeneration of the posterior columns of the spinal cord as the hallmark of the disease, the main pathological features of FRDA are not limited to the central nervous system, but start with an early loss of large sensory neurons in dorsal root ganglia, followed by degeneration of posterior columns, spinocerebellar and pyramidal tracts. Indeed, the pattern of atrophy of the long tract fibers suggests a 'dying back' process (severely atrophic at the lumbar level, much less so in the cervical cord and in the brainstem, and of normal appearance in the cerebral peduncle), suggesting that the degenerative process more likely affects first the axon before cell bodies.

Difference from the severity of ataxia is observed in patients, and cerebellar atrophy is not a characteristic feature of FRDA. Only a mild loss of Purkinje cells and axonal torpedoes are observed in the cerebellar cortex. This is in contrast to the early loss of large primary sensory neurons in the dorsal root ganglion, while the motor component is well preserved, resulting in the presence of sensory axonal polyneuropathy on clinical examination.

In summary, the main neuropathological findings in FRDA are characterized by atrophy of the central sensory and cerebellar efferent pathways as well as the distal portion of the corticospinal tracts, which carry crucial information to the brain and cerebellum for correct execution of movement and for equilibrium. As a result, the degeneration of each of these systems contributes to the characteristic clinical picture of FRDA.

Systemic Consequences

Since many patients with FRDA die as a consequence of heart disease, we may assume that degeneration probably affects independent sites outside the nervous system. Indeed, the heart is clinically or subclinically affected in the vast majority of patients. While hypertrophic cardiomyopathy is the typical finding in most patients, dilated cardiomyopathy is frequently observed after a long disease course. Microscopically, hypertrophic cardiomyocytes are intermingled with fibers undergoing atrophy or granular degeneration. In addition, 10% of FRDA patients have diabetes mellitus at later stages due to a loss of β-pancreatic islet cells.

Genetics and Frataxin

By the application of molecular genetic methods, we now understand that degeneration in FRDA develops as a result of a loss of frataxin, a highly conserved

210-amino acid nuclear encoded protein localized to the mitochondria. Current evidence suggests that loss of frataxin, which is caused by a GAA triplet repeat expansion within the first intron of the *FRDA* gene (previously known as *X25*) on chromosome 9q13 in 98% of mutant alleles impairs mitochondrial iron handling and respiratory chain function and contributes to increased oxidative stress and cellular damage. Frataxin expression is generally higher in mitochondrial-rich cells, as cardiomyocytes and neurons, explaining a disease predilection to the nervous system and the heart. While there are 33 or fewer GAA triplets normally, pathological expansion accounts from 67 to more than 1000 triplets. The expansion is homozygous in 96% of patients while the remaining patients carry a GAA expansion on one allele and an inactivating mutation in the coding region of the other allele. Point mutations are rare, accounting for only 2–4% of patients but can cause the disorder. There is an inverse correlation between the size of the expansion measured by the number of GAA repeats, in particular the shorter of the two expanded alleles, and a number of clinical features, including age at onset, cardiomyopathy, and scoliosis.

Table 1 Diagnostic criteria for FRDA according to Harding

Autosomal recessive inheritance
Onset before age 25
Within 5 years from onset
Limb and truncal ataxia
Absent tendon reflexes in the legs
Extensor plantar responses
Motor NCV>40 m/sec in upper limb with small or absent SNAPs
After 5 years since onset
As above plus dysarthria
Additional criteria, not essential for diagnosis, present in >2/3 of cases
Scoliosis
Pyramidal weakness of the legs
Absent reflexes in upper limbs
Distal loss of joint position and vibration sense in lower limbs
Abnormal EKG
Other features, present in <50% of cases
Nystagmus
Optic atrophy
Deafness
Distal weakness and wasting
Pes cavus
Diabetes

NCV: Nerve conduction study; SNAP: Sensory nerve action potential; EKG: Electrocardiogram

Epidemiology

FRDA is the most common autosomal recessive ataxia and the most common hereditary ataxia, comprising about 50% of cases in large series, with an estimated prevalence of 1 in 29 000 – 1:50000 populations in central Europe and a carrier frequency of approximately one in 110 in European populations. Birth incidence has been estimated to be from 2.1 to 5.4×10^{-5} in the United Kingdom and from 3.6 to 4.0×10^{-5} in southern Italy. However, the incidence is probably much lower in Asians and those of African descent.

Clinical Features, Diagnostic Criteria, and Prognosis

Although progressive, unremitting ataxia is the cardinal feature of the disease, detailed genetic and family studies have recently emphasized the potential heterogeneity in presenting phenotype and age of onset of patients with FRDA. As a result, strict diagnostic criteria have been proposed by Quebec Cooperative Study on FRDA and by Harding to define a homogeneous group of patients. Primary criteria initially proposed for the diagnosis of FRDA included progressive gait ataxia without remission, dysarthria, loss of joint position sense in the lower limbs, muscle weakness, deep tendon areflexia in the lower limbs, and onset before the age of 20 years. These criteria were later modified, with the upper limit for the age of onset increased to 25 years and the realization that dysarthria, signs of pyramidal tract dysfunction and sensory changes were not necessarily present in the first 5 years after onset of the illness (**Table 1**). Less common but supportive manifestations include scoliosis, pes cavus, optic atrophy, oculomotor abnormalities (fixational instability), and deafness. Patients who exhibit all these clinical features listed by Harding (**Table 1**) are considered to have the 'typical' or 'classic' form of the disease.

Symptoms in FRDA usually begin with clumsiness in gait and frequent falls. Hand coordination, dysmetria, and intention tremor later follow. As with age at onset, there is a great variability in clinical features, including the rate of progression, severity, and the extent of the disease involvement. However, progression is usually steady in each individual until patients lose the ability to perform fine motor activities to walk, stand, and eventually sit without support. Slow jerky speech is usually evident within 5 years after onset, and most patients become wheelchair bound within the first 15 years. While muscular weakness is common, affecting the proximal muscles of the lower limbs first, most patients indicate that ataxia, and not weakness, is the primary cause for their loss of ambulation.

In contrast to intact pain and temperature perception, loss of vibration and position sense is another cardinal manifestation of FRDA. As a consequence, tendon reflexes are usually diminished or absent at least in the lower limbs, due to axonal degeneration of afferent fibers. Extensor plantar responses may be later elicited, reflecting the pyramidal tract involvement. About 30% of the patients

develop optic atrophy, particularly in the later stages of the disease. More than half of the patients manifest progressive scoliosis, pes cavus, pes equinovarus, and clawing of the toes. Interestingly, optic atrophy and sensorineural hearing loss tend to be associated in the same patients, and with diabetes, more often than expected by chance alone, but rather as a sign of more severe, widespread disease. Similarly, skeletal deformities and cardiomyopathy are found in a majority of patients who also have an increased frequency of impaired glucose tolerance and diabetes.

Progression in typical FRDA is relentless and death usually occurs in the third or fourth decade of life as a consequence of arrthythmias and heart failure. While a significant portion of FRDA patients may deny cardiac symptoms, electrocardiographic evidence of cardiomyopathy was observed in two-thirds of patients, and all patients were found to have abnormalities on more detailed studies, including ambulatory monitoring, echocardiography, and isotope ventriculogram. Atrial fibrillation has been considered as a negative prognostic sign as it precedes fatal cardiac complications by 6 months or less in almost 25% of patients in which these occur. Despite its clinical heterogeneity, a recent multivariate analysis demonstrated that age at diagnosis, which may incorporate other genetic and environmental factors, is more important than GAA length in predicting cardiomyopathy, scoliosis, and ultimately disease progression.

For an autosomal recessive disease, patients with FRDA display an unusual degree of clinical variability. It is now recognized that up to 25% of patients may be considered atypical with respect to the established diagnostic criteria. At least 10% of patients with recessive or sporadic ataxia who do not fulfill the FRDA diagnostic criteria were also homozygous for GAA expansion. As a result, the phenotype of FRDA has been broadened to include the following variants, which are considered atypical FRDA.

Late-Onset FRDA (LOFA)

While the onset of typical FRDA is usually before 20 years of age, it may also vary from 2 to 3 years of age to over 25 years of age. Arbitrarily, LOFA patients are defined as having onset between 25 and 39 years and very late-onset FRDA (VLOFA) refers to onset at 40 years and after ($\geq$40 years). These patients tend to have an overall milder, slowly evolving disease associated with smaller GAA expansion. The time from disease onset to wheelchair confinement was also slower in patients with LOFA. Compared with patients with typical FRDA, those with LOFA have fewer skeletal abnormalities. The frequency of cardiomyopathy in LOFA was found to be similar to that in typical FRDA in some studies, but significantly lower in others.

FRDA with Retained Reflexes (FARR)

Although lower limb areflexia is considered as essential criterion for typical FRDA, there are, however, families with retained reflexes who are homozygous for GAA expansion. The occurrence of FARR is not rare, ranging from 5 to 10% in reported series. The sequences of GAA repeats on the smaller allele are shorter in FARR than typical FRDA without tendon reflexes, suggesting a correlation between allele sizes and preservation of tendon reflexes. In addition to retained reflexes in the lower limbs, patients with FARR may exhibit increased tone in the lower limbs associated with milder form of the disease, including later onset, lower incidence of impaired vibration sense, pes cavus, and echocardiograohic signs of left ventricular hypertrophy. Furthermore, these patients may not demonstrate electrophysiological evidence of the usual severe afferent axonal neuropathy as in patients with typical FRDA.

Acadian Ataxia (Louisiana Form)

A FRDA variant has been described among the descendants of French colonizers who settled in eastern Canada during the seventeenth century. These people, known as Acadians, later moved to Louisiana, where they became known as 'Cajuns' while some returned to the Canadian Atlantic provinces. Acadian ataxia has probably been introduced into this population by very few individuals, a so-called 'founder effect.' However, both Acadian ataxia and FRDA share the same dynamic mutations at the same locus on chromosome 9, but the specificity of the Acadian phenotype is still unexplained at the molecular level. In general, Acadian ataxia is milder than classical FRDA as it starts at later age of onset, evolves more slowly with less severe cardiomyopathy. Recently, a subtype of Acadian ataxia (Spastic ataxia of Acadian, SPA-Acadian) has been described in four patients from New Brunswick families. They had a slowly progressive ataxia with retained reflexes and spasticity, but without cardiomyopathy.

Differential Diagnosis

As in FRDA, the key feature in all progressive cerebellar ataxias is spinocerebellar ataxia, involving cerebellum, brainstem and spinocerebellar tracts, typically characterized by poor balance with falls, imprecise coordination, kinetic tremor, dysarthria, vertigo, and diplopia. With these clinical features, the physicians may be unable

Table 2 Differential diagnosis of autosomal recessive ataxias

Differential diagnosis	*Gene/Protein*	*Gene name*	*Protein function*
1. Friedreich's ataxia-like syndromes			
-Friedreich's ataxia	Frataxin	FRDA	Mitochondrial iron
-Ataxia with vit.E deficiency	α-tocopherol transfer protein	TTPA	Vit. E homeostasis
-Abetalipoproteinemia	Microsomal triglyceride transfer protein	MTP	Lipoprotein metabolism
-Refsum's disease	Phytanol-CoA-hydroxylase	PHYH	Fatty acid oxidation
2. FRDA-like with cerebellar atrophy			
-Late-onset Tay-Sach's disease	β-hexosaminidase A	HEXA	Glycosphingolipid metabolism
-Cerebrotendinous xanthomatosis	Sterol 27-hydroxylase	CYP27	Bile-acid synthesis
-DNA polymerase γ disorders	DNA polymerase γ	POLG	Mitochondrial repair & replication
-SCA with axonal neuropathy	Tyrosyl-DNA phosphodiesterase 1	TDP1	DNA repair
3. Early-onset ataxia with cerebellar atrophy			
-Ataxic-telangiectasia (AT)	AT-mutated	ATM	DNA damage response
-AT-like disorder	Meiotic recombination 11	MRE11	DNA damage response
-Ataxia with oculomotor apraxia type 1	Aprataxin	APTX	DNA repair
-Ataxia with oculomotor apraxia, type 2	Senataxin	SETX	DNA repair
-Ataxia of Charlevoix-Saguenay	Sacsin	SACS	Protein folding
-Infantile-onset SCA	Twinkle, twinky	C10orf2	DNA replication
-Cayman ataxia	Caytaxin	ATCAY	Neurotransmitter metabolism
-Marinesco-Sjögren's syndrome	BiP-associated protein	SIL1	Protein folding

FRDA: Friedreich's ataxia; SCA: Spinocerebellar ataxia
Modified from Fogel BL and Perlman S (2007) Clinical features and molecular genetics of autosomal recessive cerebellar ataxias. *Lancet Neurology* 6(3): 245–257.

to differentiate AR ataxia from other forms unless the patient can disclose a characteristic family history of affected relatives. However, most AR ataxias are early onset, but not universally applicable. In contrast to autosomal dominant spinocerebellar ataxias (ADCAs), which may have diverse neurological features (such as retinopathy, extrapyramidal signs), most AR ataxias are generally associated with peripheral sensorimotor neuropathy, notably with loss of proprioception and vibration sense. In further contrast to ADCAs, AR ataxias tend to have involvement outside the nervous system.

From a diagnostic viewpoint, once AR ataxias are suspected, they can be categorized to either resembling FRDA phenotype or as having early-onset phenotype with cerebellar atrophy (**Table 2**). Due to the heterogeneity among these disorders, further differentiation will generally require detailed assessment of the phenotype as well as additional diagnostic studies, particularly neuroimaging. Patients with ataxia due to vitamin E deficiency can present with a clinically similar phenotype to FRDA, but serum concentrations of vitamin E are low. Like FRDA, age at onset is before 20 years, and cardiomyopathy is the most common systemic finding. However, decreased visual acuity or retinitis pigmentosa may be an early finding to distinguish this disorder from FRDA. Another FRDA-like syndrome; abetalipoproteinemia, neurological manifestations may occur before the age of 20 but is associated with lipid malabsorption, hypocholesterolemia, acanthocytosis, and retinitis pigmentosa. With an early onset by age 2 years and severely disabled, ataxic-telangiectasia has a complex multiorgan phenotype, including immune deficiency, high incidence of hematologic malignancies, gonadal failure, truncal instability, oculomotor apraxia, ataxia, and hypotonia.

Diagnostic Tests

Once FRDA is suspected, magnetic resonance imaging (MRI) of the brain and cervical cord is usually indicated, and its appearance closely reflects the findings of postmortem neuropathological studies. The cervical spinal cord is the most severely affected structure, appearing much more compromised than any other part of the central nervous system (CNS), including the cerebellum. Indeed, this pattern contrasts with other inherited degenerative ataxias in which the cerebellum is much more atrophic than the cervical spinal cord. Thinning of the cervical spinal cord can be observed on sagittal and axial images in almost all FRDA patients. Other CNS structures, including brainstem, cerebellum, and cerebrum are less evidently affected, but not completely spared.

Electromyographic and nerve conduction studies in FRDA generally disclose the presence of 'dying-back'

axonal sensory neuropathy, with severe reduction of sensory nerve action potentials (SNAPs) and relatively preserved motor and sensory nerve conduction velocities. These findings help distinguish an early case of FRDA from demyelinating hereditary sensorimotor neuropathy. Furthermore, the amplitudes of the visual evoked potentials (VEPs) are markedly reduced with a normal P100 latency.

Because of its prevalence and its variability in presentation, almost all patients with AR ataxias should be screened initially for FRDA. In addition, direct genetic testing can be done to definitely establish the diagnosis. Currently commercially available, the most common mutation causing FRDA (98%) is the hyperexpansion of a GAA triplet repeat in the first intron of the *FRDA* gene. While repeats in normal chromosomes contain up to 40 triplets, disease-associated repeats contain from approximately 70 to more than 1000 triplets, most commonly in the range between 600 and 900.

Additional biochemical investigations, including lipoproteins, vitamin E level, lactate, pyruvate, urinary organic acids, serum very long chain fatty acids, serum phytanic acid, and leukocyte or fibroblast lysosomal enzymes, are usually performed to exclude the diagnoses of abetalipoproteinemia, ataxia with vitamin E deficiency, mitochondrial disorders, adrenoleukodystrophy, Refsum's disease, and a number of lysosomal storage disorders. The cost of each individual test can be expensive and the decision to perform above tests should be considered on a case-by-case basis.

Management

FRDA is a progressive neurodegenerative disorder due to a loss of frataxin. The downstream consequences of frataxin deficiency result in excess of mitochondrial iron and oxidative stress, incorporating by other unknown genetic and environmental factors. On the basis of these principles, therapeutic approaches aimed at free radical control and respiratory chain activation may be attempted. However, no currently available drug can specifically remove iron from the mitochondrial compartment, as well as protect the cells against the damage caused by the free radicals involved in the disease. Nevertheless, antioxidant molecules, and respiratory chain stimulants, such as coenzymeQ-10 (CoQ-10) and idebenone have shown some promising results, not only in experimental models, but also in clinical trials. A recent uncontrolled, open-label, 4-year pilot study of patients taking CoQ-10 and vitamin E reported improvement in cardiac function and suggested possible stabilization or reduce decline in certain neurological symptoms. Similarly, studies of low-dose idebenone, a synthetic analog of CoQ-10, seem to show reduction of cardiac wall thickness, but no improvement of neurological symptoms was observed. Unfortunately, no drugs have led to any improvement in ataxia or other associated neurological features and primary treatment for this disease still remains symptomatic. Therefore, rehabilitation programs and orthopedic interventions should be aimed at maximizing the residual capacity of motor control.

Remarkable progress has been made in understanding the pathogenesis of FRDA since the discovery of responsible gene in 1996. If it were possible to increase the patients' frataxin production even to levels that are similar to healthy carriers, one could possibly halt the progression of the disease and may even lead to improvement. The possible role of frataxin in controlling mitochondrial iron homeostasis suggests ways of pharmacological intervention that may be worth considering. Although still in their infancy, all these approaches are under study and encouraging results have been obtained at least for gene replacement therapy.

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See also: Abetalipoproteinemia (ABL); Aprataxin; Ataxia; Ataxia (Familial Cerebellar) with Muscle CoQ_{10} Deficiency; Ataxia with Isolated Vitamin E Deficiency; Ataxia-Telangiectasia; Ataxin; Cayman Ataxia; Friedreich's Ataxia Rating Scale (FARS); Marinesco–Sjogren's Syndrome; Refsum Disease- a Disorder of Peroxisomal Alpha-oxidation; SCA1; SCA2; SCA4; SCA6; SCA10; SCA11; SCA12; SCA13, 14, 15, and 16; SCA17; SCA27; Senataxin; Spinocerebellar Ataxia Type 19, 20, 21, 22, 23, 26; Spinocerebellar Ataxias Genetics; Tauopathies; Tocopherol Transfer Protein and Ataxia with Vitamin E Deficiency; Trinucleotide Repeat Disorders.

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Friedreich's Ataxia Rating Scale (FARS)

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Glossary

Ataxia – Literally (Greek) absence of order. Clinically referred to as a specific motor syndrome with difficulty to stabilize the trunk against gravity, difficulty to stabilize gaze, difficulty in goal-directed limb movements, and dysarthria.
Cerebellar sign – Neurological sign attributed to lesions of the cerebellum.
Clinical rating scale – Assessment tool used to document and compare disease status, for example, in clinical trials, that is based on a standardized clinical examination of selected disease features. Standardization refers to instructions of test performance and rating.
Outcome parameter – Type of assessment that is chosen to document and compare the effects of an intervention in clinical trials. This can be a clinical scale or any instrumental or laboratory test known to change with disease severity.
Reliability – Accuracy of an assessment tool, that is, how consistent or repeatable are the measurements. For clinical rating scales, reliability is usually documented by good internal consistency and minimal variance between different raters (interrater), or between test and retest.
Sensitivity – Ability of an assessment tool to pick up differences between different disease states. Sufficient sensitivity (or responsiveness) to change over time is a prerequisite for use of a clinical rating scale as an outcome parameter in clinical trials.
Validity – Appropriateness of content of an assessment tool, that is, does it measure what it is intended to measure. It is usually documented by good correlations with other assessments of the same construct: for example, a clinical scale supposed to measure disease severity could be compared to other measures known to change with disease severity.

Definition and History

The conduct of multicenter therapeutic trials requires reliable and sensitive assessment tools. Consequently, clinical rating scales have been established for different diseases once therapeutic agents became available for testing. Friedreich ataxia is an autosomal-recessive disorder, with typically juvenile onset that is genetically characterized by GAA repeat expansions in the frataxin gene, in the majority of cases. Clinically, the disease manifests with progressive gait and limb (sensory) ataxia, loss of vibratory and position sense, dysarthria, diabetes, scoliosis, and cardiomyopathy. A larger size of the shorter expanded allele has been associated with younger age of onset and more severe disease. The Friedreich Ataxia Rating Scale (FARS) published in 2005 was developed as a disease-specific rating scale for use in Friedreich ataxia (see **Figure 1**).

Development

As no validated clinical assessment tool was available, previous trials in Friedreich ataxia often preferred surrogate markers of disease severity like echocardiography as outcome parameters. Therefore, the North-American Cooperative Ataxia Group (CAG) developed the FARS

to evaluate both function and neurological deficits in Friedreich ataxia patients. The authors of the scale acknowledged the need for more sensitive outcome measures in this rare disorder with variable and slow progression. Further, Friedreich ataxia patients often present with concomitant nonataxia (such as muscle weakness) and non-neurological manifestations (such as cardiac, endocrine, or skeletal abnormalities). In contrast to other ataxia rating scales, the FARS does not aim to measure only ataxia, extracted from a more complex neurological syndrome, but instead includes all clinically meaningful neurological signs that reflect the neural substrates of Friedreich ataxia. These disease-specific signs are assessed by clinical examination, assessment of functional level, and quantitative performance measures.

Scale Structure

In the original publication, the FARS was presented as a four-component assessment to test functional disability and neurological deficits in Friedreich ataxia. Part I is a global staging of patient's mobility, which ranges from 0 (normal) to 6 (confined to wheelchair) and allows 0.5 ratings. Part II is a nine-item functional assessment that ranges from 0 (normal) to 36 (total dependence) and also allows 0.5 increment. Part III consists of 23 items based on a standardized neurological examination, which are grouped into five subscales A–E for bulbar, upper limb coordination, lower limb coordination, peripheral nervous system, and upright stability/gait function (the specific subscales have 4, 5, 2, 5, and 7 items with maximal scores

Rating Scale for Friedreich's Ataxia

I. Functional Staging for Ataxia
(Increment by 0.5 may be used if the status is about the middle between two stages)

STAGE 0: Normal.

STAGE 1.0: Minimal signs detected by physician during screening. Can run or jump without loss of balance. No disability.

STAGE 2.0: Symptoms present, recognized by patient, but still mild. Cannot run or jump without losing balance. The patient is physically capable of leading an independent life, but daily activities may be somewhat restricted. Minimal disability.

STAGE 3.0: Symptoms are overt and significant. Requires regular or periodic holding onto wall/furniture or use of a cane for stability and walking. Mild disability. (Note: many patients postpone obtaining a cane by avoiding open spaces and walking with the aid of walls/ people etc. These patients are grades as stage 3.0)

STAGE 4.0: Walking requires a walker, Canadian crutches or two canes. Or other aids such as walking dogs. Can perform several activities of daily living. Moderate disability.

STAGE 5.0: Confined but can navigate a wheelchair. Can perform some activities of daily living that do not require standing or walking. Severe disability.

STAGE 6.0: Confined to wheelchair or bed with total dependency for all activities of daily living. Total disability.

II. Activites of Daily Living
(increments of 0.5 may be used if strongly felt that a task falls between 2 scores)

1. Speech
0 -Normal
1 -Mildly affected. No difficulty being understood.
2 -Moderately affected. Sometimes asked to repeat statements.
3 -Severely affected. Frequently asked to repeat statements.
4 -Unintelligible most of the time.

2. Swallowing
0 -Normal.
1 -Rare choking (< once a month).
2 -Frequent choking (< once a week, > once a month).
3 -Requires modified food or chokes multiple times a week. Or patient avoids certain foods.
4 -Requires NG tube or gastrostomy feedings.

Figure 1 (Continued)

of 11, 36, 16, 26, and 28, respectively). Upper limb and lower limb coordination items are rated separately for each limb. The subscores can be summed to an unweighted FARS part III total score, ranging from 0 (no neurological deficit) to 117 (maximal deficit). Part IV contains two items of instrumental testing, a timed test of speech (syllable repetition rate) and performance time for the nine-hole pegboard test (9HPT) in each hand. In addition, time for a 25 ft walk is taken in the gait function subscale of part III. Further studies suggested the use of Sloan charts for visual acuity as an additional performance measure in Friedreich ataxia. Of note, some later studies using FARS refer to it as only neurological examination. In this text, we use FARS part III for the neurological examination and FARS for the whole multicomponent scale.

3. Cutting Food and Handling Utensils
0 -Normal.
1 -Somewhat slow and clumsy, but no help needed.
2 -Clumsy and slow, but can cut most foods with some help needed. Or needs assistance when in a hurry.
3 -Food must be cut by someone, but can still feed self slowly.
4 -Needs to be fed.

4. Dressing
0 -Normal.
1 -Somewhat slow, but no help needed.
2 -Occasional assistance with buttoning, getting arms in sleeves, etc. or has to modify activity in some way (e.g. Having to sit to get dressed; use velcro for shoes, stop wearing ties, etc.).
3 -Considerable help required, but can do some things alone.
4 -Helpless.

5. Personal Hygiene
0 -Normal.
1 -Somewhat slow, but no help needed.

2 -Very slow hygienic care or has need for devices such as special grab bars, tub bench, shower chair, etc.
3 -Requires personal help with washing, brushing teeth, combing hair or using toilet.
4 -Fully dependent

6. Falling
(assistive device = score 3)
0 -Normal.
1 -Rare falling (< once a month).
2 -Occasional falls (once a week to once a month).
3 -Falls multiple times a week or requires device to prevent falls.
4 -Unable to stand or walk.

7. Walking
(assistive device = score 3)
0 -Normal.
1 -Mild difficulty, perception of imbalance.
2 -Moderate difficulty, but requires little or no assistance.
3 -Severe disturbance of walking, requires assistance or walking aids.
4 -Cannot walk at all even with assistance (wheelchair bound).

8. Quality of Sitting Position
0 -Normal.
1 -Slight imbalance of the trunk, but needs no back support.
2 -Unable to sit without back support.
3 -Can sit only with extensive support (Geriatric chair, posy, etc.).
4 -Unable to sit.

9. Bladder Function
(if using drugs for bladder, automatic score of 3)
0 -Normal.
1 -Mild urinary hesitance, urgency or retention (< once a month).
2 -Moderate hesitance, urgency, rare retention/incontinence (> once a month, but < once a week).
3 -Frequent urinary incontinence (> once a week).
4 -Loss of bladder function requiring intermittent catheterization/indwelling catheter.

TOTAL ACTIVITIES OF DAILY LIVING SCORE:

Figure 1 (Continued)

Metric Properties and Validation Studies

The FARS was originally published with data on interrater reliability in a sample of 14 patients examined separately by seven examiners over 1 day. The sample included patients with a wide range of impairment. Time to complete was <30 min, and no effects of practice or fatigue were noticed with repeated testing over 1 day. Factorial analysis (excluding 25 ft walking time) yielded two factors that roughly represented upper and lower body function.

III. Neurological Examination

**(rate each item on the basis of the patient status during examination.
To the extent possible, sequential patient examinations should be carried out at the same time of the day. If the patient is taking any medication, the examination should be carried out prior to dosing, or at a fixed time following the dosing based on the maximum expected therapeutic response. Increments of 0.5 may be used if examiner feels an item falls between 2 defined severities)**

A. BULBAR

1. Facial Atrophy, Fasciculation, Action Myoclonus, and Weakness:
0 -None
1 -Fasciculations or action myoclonus, but no atrophy.
2 -Atrophy present but not profound or complete.
3 -Profound atrophy and weakness.

2. Tongue Atrophy, Fasciculation, Action Myoclonus and Weakness:
0 -None.
1 -Fasciculations or action myoclonus, but no atrophy.
2 -Atrophy present but not profound or complete.
3 -Profound atrophy and weakness.

3. Cough: (Patient asked to cough forcefully 3 times)
0 -Normal.
1 -Depressed.
2 -Totally or nearly absent.

4. Spontaneous Speech (ask the patient to read or repeat the sentences "The President lives in the White House" or "The traffic is heavy today"):
0 -Normal.
1 -Mild (all or most words understandable).
2 -Moderate (most words not understandable).
3 -Severe (no or almost no useful speech).

TOTAL BULBAR SCORE:

B. UPPER LIMB COORDINATION

1. Finger to Finger Test
(The index fingers are placed in front of each other with flexion at the elbow about 25 cm. from the sternum. Observe for 10 seconds. Score amplitude of oscillations):
Rate both sides separately
0 -Normal.
1 -Mild oscillations of finger (< 2 cm.).
2 -Moderate oscillations of finger (2-6 cm.).
3 -Severe oscillations of finger (> 6 cm.).

2. Nose-Finger Test
(Assess kinetic or intention tremor during and towards the end of movement: examiner holds index finger at 90% reach of patient; test at least 3 nose-finger-nose trials; movement slow > 3 sec.)
Rate both sides separately
0 -None
1 -Mild (< 2 cm. amplitude).
2 -Moderate (2-4 cm. amplitude or persisting through movement).
3 -Severe (> 6 cm. & persisting through movement).
4 -Too poorly coordinated to perform task.

Figure 1 (Continued)

3. Dysmetria (Fast Nose-Finger) Test
(Assess dysmetria: The patient touches tip of examiner's finger 8 times as rapidly as possible while the examiner moves his finger and stops at different locations at about 90% reach of the patient. Assess dysmetria – i.e. inaccuracy of reaching the target-at examiner's finger):
Rate both sides separately
0 -None.
1 -Mild (misses 2 or fewer times).
2 -Moderate (misses 3-5 times).
3 -Severe (misses 6-8 times.).
4 -Too poorly coordinated to perform task.

4. Rapid Alternating Movements of Hands
(Forearm pronation/supination 15 cm. above thigh; 10 full cycles as fast as possible; assess rate, rhythm, accuracy; practice 10 cycles before rating, if time > 7 sec. add 1 to score. Use stopwatch):
Rate both sides separately
0 -Normal.
1 -Mild (slightly irregular or slowed).
2 Moderate (irregular and slowed).
3 -Too poorly coordinated to perform task.

5. Finger Taps
(index fingertip-to-thumb crease; 15 reps as fast as possible; practice 15 reps once before rating; if time > 6 sec., add 1 to rating. Use stopwatch):
Rate both sides separately
0 -Normal.
1 -Mild (misses 1-3 times).
2 -Moderate (misses 4-9 times).
3 -Severe (misses 10-15 times).
4 -Cannot perform the task.

TOTAL UPPER LIMB COORDINATION SCORE

C. LOWER LIMB COORDINATION

1. Heel Along Shin Slide
(under visual control, slide heel on the contralateral tibia from the patella to the ankle up and down, 3 cycles at moderate speed, 2 sec./cycle, one at a time. May be seated with contralateral leg extended or supine but perform same way each time. Circle which: supine - seated):
Rate both sides separately
0 -Normal (stay on shin).
1 -Mild (abnormally slow, tremulous but contact maintained).
2 -Moderate (goes off shin a total of 3 or fewer times during 3 cycles).
3 -Severe (goes off shin 4 or more times during 3 cycles).
4 -Too poorly coordinated to attempt the task.

2. Heel-to-Shin Tap
(patient taps heel on midpoint of contralateral shin 8 times on each side from about 6-10", one at a time. May be seated with contralateral leg extended or supine but perform the same way each time. Circle which: supine seated):
Rate both sides separately
0 -Normal (stays on target).
1 -Mild (misses shin 2 or < times).
2 -Moderate (misses shin 3-5 times).
3 -Severe (misses shin > 4 times).
4 -Too poorly coordinated to perform task.

TOTAL LOWER LIMB COORDINATION SCORE

Figure 1 (Continued)

However , a recent study in 96 FRDA patients determined five different factors, only one of which - bulbar function - coincided with the proposed FARS III subscale. Interrater reliability was excellent for all FARS parts, and the part III subscales upper limb, lower limb, and upright stability/gait. Of note, some rater bias was reported for FARS part I, part II, and part III, and its upper limb coordination and peripheral nervous system subscores, but not for part IV. In a later study, reliability of performance measures was high in immediate retest, but method errors were within the range of predicted yearly changes. Floor effects were noted with 25 ft walk and 9HPT in later disease stages, that is, severely affected patients were mostly unable to perform the tests. Therefore, a composite score of two or three performance measures was proposed to improve sensitivity over the whole course of the disease. Validity

D. PERIPHERAL NERVOUS SYSTEM

1. Muscle Atrophy
(score most severe atrophy in either upper or lower limb):
Rate both sides separately
0 -None.
1 -Present -mild/moderate
2 -Severe/total wasting

2. Muscle Weakness
(Test deltoids, interossei, iliopsoas and tibialis anterior. Score most severe weakness in either upper or lower limb):
Rate both sides separately
0 -Normal (5/5).
1 -Mild (movement against resistance but not full power 4/5).
2 -Moderate (movement against gravity but not with added resistance 3/5)
3 -Severe (movement of joint but not against gravity 2/5).
4 -Near paralysis (muscular activity without movement 1/5).
5 -Total paralysis (0/5).

3. Vibratory Sense
(Educate patient regarding the sensation. Tested with 128 cps tuning fork set to near full vibration; eyes closed; test over index finger and great toe. Abnormal < 15 seconds for toes and <25 seconds for hands):
Rate both sides separately

Time felt for toes: _____ _____
Time felt for fingers: _____ _____
0 -Normal.
1 -Impaired at toes.
2 -Impaired at toes or fingers.

4. Position Sense
(test using minimal random movement of distal interphalangeal joints of index finger and big toe)
Rate both sides separately
0 -Normal.
1 -Impaired at toes/or fingers.
2 -Impaired at toes and fingers.

5. DTR
(0-absent; 1 -hyporeflexia; 2 -normal; 3 -hyperreflexia; 4 -pathologic hyperreflexia)
Right:
BJ_____ BrJ_____ KJ_____ AJ_____
Left:
BJ_____ BrJ_____ KJ_____ AJ____
Rate both sides separately
0 -No areflexia.
1 -Areflexia in either upper or lower limbs.
2 -Generalized areflexia.

TOTAL PERIPHERAL NERVOUS SYSTEM SCORE

Figure 1 (Continued)

of FARS part III was demonstrated by the association with FARS parts I and II (lower for bulbar subscore) and by correlation with 9HPT, 25 ft walking time, and disease duration. In a two other studies in 74 and 76 FRDA patients, part III correlated well with ICARS ratings, SARA rating, and different functional measures. Independent effects of age and the length of the shorter GAA repeat were seen on FARS part III total and subscores as well as 9HPT and 25 ft walk. Estimates of progression rates were derived from regression with disease duration: progression in FARS part III scores was higher at patient's age below 30 or with length of the shorter repeat above 250 GAA repeats. The authors

E. UPRIGHT STABILITY

(For sitting posture patient can sit in a chair or examination table. For standing and walking assessment instruct patient to wear best walking shoes and record below if barefoot, footwear or AFOs used. Stance assessment begins with feet 20 cm apart. Place marker tapes in the exam room 20 cm apart and the insides of the feet are lined up against these. Subsequent stance tests get more difficult. For feet together the entire inside of the feet should be close together as much as possible. For tandem stance, the dominant foot is in the back and the heel of the other foot is lined with the toes of the dominant foot but not in front of the toes (because this makes it even more difficult). For one foot stance, the patient is asked to stand on dominant foot and the other leg is elevated by bringing it forward with knee extended; this gives some advantage to the patient. If a patient can stand in a particular position for 1 minute or longer in trial 1, the trials 2 and 3 are abandoned. Otherwise each of 3 trials is timed and then averaged. Grading scores are then given as noted. Tandem walk and gait are performed in a hallway. Preferably no carpet but at least serial examinations should be on the same surface. For gait place markers 25 feet apart. Patient walks the distance turns around and comes back and the activitiy is timed. Note if the gait was achieved with or without device and serial examinations should be done with the same device as in the first examination. Stance and gait tests may be done barefoot if patient does have appropriate footwear, however, it should be done the same way for serial measurement.)

Circle which: Barefoot - Footwear
Also, indicate if AFOs are used: Yes - No

1. Sitting Posture
(Patient seated in chair with thighs together, arms folded, back unsupported; observe for 30 sec.):
0 -Normal.
1 -Mild oscillations of head/trunk without touching chair back or side.
2 -Moderate oscillations of head/trunk; needs contact with chair back or side for stability.
3 -Severe oscillations of head/trunk; needs contact with chair back or side for stability.
4 -Support on all 4 sides for stability.

2. Stance feet apart
– Inside of feet 20 cm apart marked on floor. (use stopwatch; 3 attempts; time in seconds):

Trial 1
Trial 2
Trial 3
Average:_____

0 -1 minute or longer.
1 -<1 minute, >45 sec.
2 -<45 sec., >30 sec.
3 -<30 sec., >15 sec.
4 -<15 sec. or needs hands held by assistant/device.

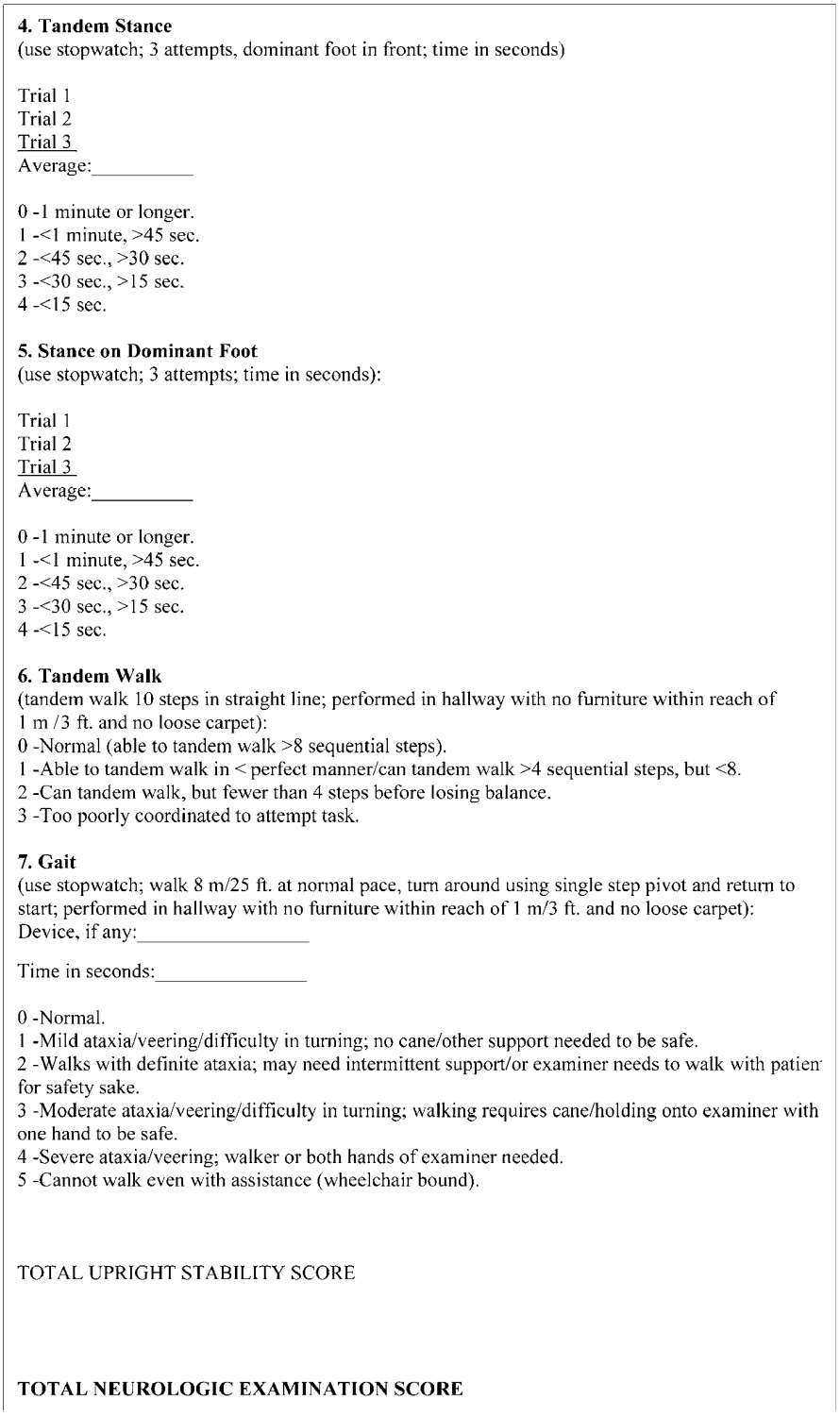
3. Stance -Feet Together
(use stopwatch; 3 attempts; time in seconds):

Trial 1
Trial 2
Trial 3
Average:_____

0 -1 minute or longer.
1 -<1 minute, >45 sec.
2 -<45 sec., >30 sec.
3 -<30 sec., >15 sec.
4 -<15 sec.

Figure 1 (Continued)

of that study suggested stratifying future patient samples in this respect. In an evaluation of scale responsiveness, FARS seemed to perform better than ICARS with respect to effect size. The clinical relevance of FARS part III and IV score differences was supported by correlations with health-related quality of life measures (physical component of the SF-36). Further, velocity in 25 ft walk predicted everyday ambulation measures in Friedreich ataxia in one study.



4. Tandem Stance
(use stopwatch; 3 attempts, dominant foot in front; time in seconds)

Trial 1
Trial 2
Trial 3
Average:_____

0 -1 minute or longer.
1 -<1 minute, >45 sec.
2 -<45 sec., >30 sec.
3 -<30 sec., >15 sec.
4 -<15 sec.

5. Stance on Dominant Foot
(use stopwatch; 3 attempts; time in seconds):

Trial 1
Trial 2
Trial 3
Average:_____

0 -1 minute or longer.
1 -<1 minute, >45 sec.
2 -<45 sec., >30 sec.
3 -<30 sec., >15 sec.
4 -<15 sec.

6. Tandem Walk
(tandem walk 10 steps in straight line; performed in hallway with no furniture within reach of 1 m /3 ft. and no loose carpet):
0 -Normal (able to tandem walk >8 sequential steps).
1 -Able to tandem walk in < perfect manner/can tandem walk >4 sequential steps, but <8.
2 -Can tandem walk, but fewer than 4 steps before losing balance.
3 -Too poorly coordinated to attempt task.

7. Gait
(use stopwatch; walk 8 m/25 ft. at normal pace, turn around using single step pivot and return to start; performed in hallway with no furniture within reach of 1 m/3 ft. and no loose carpet):
Device, if any:_____

Time in seconds:_____

0 -Normal.
1 -Mild ataxia/veering/difficulty in turning; no cane/other support needed to be safe.
2 -Walks with definite ataxia; may need intermittent support/or examiner needs to walk with patien for safety sake.
3 -Moderate ataxia/veering/difficulty in turning; walking requires cane/holding onto examiner with one hand to be safe.
4 -Severe ataxia/veering; walker or both hands of examiner needed.
5 -Cannot walk even with assistance (wheelchair bound).

TOTAL UPRIGHT STABILITY SCORE

TOTAL NEUROLOGIC EXAMINATION SCORE

Figure 1 (Continued)

Clinical Trials

The FARS part II and part III have been used as secondary outcome measures in a recent NIH trial of high-dose idebenone in Friedreich ataxia. In a sample of 47 patients with mean baseline scores in part II/III of 13.7/51.4, mean changes in the treatment and placebo arm over a 6 month interval were reported between 1 and −1.5 for part II and between −2 and −6 for part III (estimates from figures in the original publication). As no treatment effect was detected, these data can be seen as an estimate of the 'natural' progression in Friedreich ataxia. FARS parts II and III are also used as secondary outcome measures in an ongoing multinational trial of high-dose idebenone in Friedreich ataxia. One single-center study related eye movement abnormalities to FARS part III, and found correlations with saccadic latency.

Criticism

The development of the scale as disease-specific has advantages and disadvantages, including limiting its use to Friedreich ataxia. While the time to administer and

IV. Instrumental Testing

1. PATA Rate
(Use a tape recorder that can play at slow and fast speeds (1.2 & 2.4 cm/sec).
Record at normal (2.4) speed. Use a digital stopwatch. Patient seated comfortably and instructed to repeat the syllable "pata" as quickly and distinctly as possible for 10 seconds until told to stop. Start recorder and record patient's name and date. Preset stopwatch for 10 seconds. Say "go" and as soon as patient starts speaking, start timer. Say "stop" when timer beeps at end of 10 seconds. Perform test twice and count # of "patas" for each 10 seconds, using playback at slower speed. Record number for each trial and also the average score):

Trial 1
Trial 2
Average:_____

2. Nine-Hole Pegboard
(Make sure the stopwatch is set to zero. Introduce this section by saying, "Now, we're going to be measuring your arm and hand function." If this is the first visit, as, "Are you right-or left-handed?" Make a note of the dominant hand for subsequent instructions. Place the 9-HPT apparatus on the table directly in front of the patient. Arrange the apparatus so that the side with the pegs is in front of the hand being tested and the side with the empty pegboard is in front of the hand not being tested. Secure with Dycem. Read the following instructions to the patient: "On this test, I want you to pick up the pegs one at a time, using one hand only, and put them into the holes as quickly as you can in any order until all the holes are filled. Then, without pausing, remove the pegs one at a time and return them to the container as quickly as you can. We'll have you do this two (2) times with each hand. We'll start with your [DOMINANT] hand. You can hold the peg board steady with you [NON-DOMINANT] hand. If a peg falls onto the table, you retrieve it and continue with the task. If a peg falls on the floor, keep working on the task and I will retrieve it for you. See how fast you can put all the pegs in and take them out again. Are your ready? Begin." Start timing as soon as the patient touches the first peg, and stop timing when the last peg hits the container. If a peg drops on the floor, the examiner will retrieve it and put it back in the peg box. However, if a peg drops onto the table, the patient is to retrieve it unless it is beyond their arm reach then you can retrieve it for them. It is possible that a peg may fall beyond the reach of the examiner therefore; we recommend that you keep a few extra pegs in hand so that testing is not interrupted. Do not put extra pegs in the testing apparatus as this may confuse the subject. Record the patient's time under "Dominant hand --Trial 1." If the subject stops after having put all the pegs into the holes, prompt the subject to move them as well by saying, "And now remove them all." If the subject begins to remove more than one peg at a time, correct him/her by saying, "Pick up one peg at a time."

The total time to complete the task is recorded in seconds including one decimal place rounded as needed. Round up to the next tenth if hundredth's place is > = .05, round down in hundredth's place is < 0.5.)

Rate both sides separately

Trial 1
Trial 2
Average:_____

Figure 1 Illustration of full FARS text. From Subramony et al. (2005) Measuring Friedreich ataxia: Interrates reliability of a neurologic rating scale. *Neurology* 64(7): 1261–1262.

interrater reliability are acceptable for clinical trials, the rater bias for part II, II, and III reported in the original paper underlines the need for rater training. The metric properties, validity, and specificity (as well as the standards of application) of part II have not yet been sufficiently specified. Although reliability and validity data are sufficient for part III, data on factorial analysis are controversial and question the proposed subscale structure. According to the variance in the validation studies, part III seems sensitive over a wide range of disease severity while part IV items have some shortcomings with floor effects in later stages. Depending on the study purpose, additional information would be desirable, for example, no data are available from assessments in controls, and sensitivity to change as well as linearity of FARS parts have not been established.

Conclusion

FARS has recently been published as a compound assessment of Friedreich ataxia severity. Part I functional staging seems useful to classify study samples, while the usefulness of part II is not well established; it might give a more subjective perspective of functional deficits, but without further validation seems currently not recommendable as an outcome parameter for interventional trials. The neurological examination (part III) total score can be used separately and has already been used in clinical studies, which suggested sensitivity to change and yielded estimates of progression rates. However, these are currently derived only from a small sample. Part IV performance measures have shown less rater bias than part III, but their sensitivity seems restricted in later disease stages. A total sum score of all four FARS parts is currently not supported (although used in one validation trial). In sum, FARS part III provides an appropriate measure for any intervention that aims to change severity or progression of neurological deficits in Friedreich ataxia patients.

See also: Ataxia; Friedreich's Ataxia and Variants; Idebenone and Friedreich Ataxia; Rating Scales in Movement Disorders.

Further Reading

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Frontotemporal Dementia-Parkinsonism

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Glossary

FTD (frontotemporal dementia) – One of the FTLD phenotypes characterized by behavioral troubles and personality changes.

FTDP-17 (frontotemporal dementia-parkinsonism linked to chromosome 17) – Familial FTLD with evidence of genetic linkage to chromosome 17q21.

FTLD (frontotemporal lobar degeneration) – Generic term encompassing, among others, FTD, SD, PNFA, FTDP-17, PSP, and CBD.

MAPT (microtubule-associated protein tau) – Mutations in this gene on chromosome 17q21 cause FTDP-17 (tau-positive).

PGRN (progranulin) – Mutations in this gene on chromosome 17q21 cause FTLD-U (tau-negative, ubiquitin-positive).

PNFA (progressive nonfluent aphasia) – One of the FTLD phenotypes characterized by progressive nonfluent language impairment.
SD (semantic dementia) – One of the FTLD phenotypes characterized by progressive fluent language impairment.
TDP-43 (TAR DNA-binding protein 43) – Major ubiquitinated protein content of neuronal and glial inclusions in FTLD-U, FTD-MND, and ALS.

Definition and History

Arnold Pick was the first to demonstrate patients with dementia and severe atrophy of the frontal and temporal lobes in 1892. Almost two decades later, Alois Alzheimer reported the neuronal inclusions characteristic of this condition, which was soon to be known as Pick's disease.

Frontotemporal lobar degeneration (FTLD) is a group of neurodegenerative diseases in which patients display behavioral and language impairment, with atrophy of the frontal and temporal lobes. The behavioral variant of FTLD is clinically referred to as frontotemporal dementia (FTD) or as its behavioral variant (bvFTD), whereas language impairment is the core feature in progressive nonfluent aphasia (PNFA) and semantic dementia (SD). Some authors refer to FTD as a group of diseases encompassing bvFTD, PNFA, and SD. In this article, however, we will refer to FTLD as an umbrella term designating the clinical and pathological entities, FTD, PNFA, and SD. Some FTLD patients can also develop associated features of motor neuron disease (FTD-MND). In addition, FTLD has clinical and pathological similarities with other motor syndromes such as corticobasal degeneration (CBD) and progressive supranuclear gaze palsy (PSP), which are considered a part of the same spectrum. CBD and PSP are presented elsewhere in this encyclopedia.

FTLD is the second most common cause of early-onset dementia (<65 years) after Alzheimer's disease (AD), and the third cause of overall cortical dementia. Behavioral, cognitive, and motor impairment begins in the fifth of sixth decade, and has a relentless progression. A positive family history is reported in up to 50% of patients, mostly those with FTD and PNFA. Conversely, only ~10% of SD patients display familial aggregation.

Parkinsonism is a frequent finding in patients with FTLD, particularly in those with a familial form of the disease. In this article, we discuss the clinical, genetic, and neuropathologic features of FTLD, with emphasis on familial forms associated with parkinsonism.

Pathogenesis/Pathophysiology

The cause of FTLD remains largely unknown, and the main risk factors are age and a positive family history. However, recent advances in genetics and neuropathology have shed light into mechanisms that may be involved in the FTLD pathogenesis.

Genetics

Over the past decade, two major genes have been identified as causally involved in familial FTLD, progranulin (*PGRN*), and microtubule-associated protein tau (*MAPT*) (**Figure 1**). Screening for both genes is now commercially available (see Relevant Websites). Two other genes and one locus have been associated with rarer forms of FTLD, valosin-containing protein (*VCP*), charged multivesicular body protein 2B (*CHMP2B*), and a locus on chromosome 9, which will not be discussed in this article.

Microtubule-associated protein tau (MAPT)

The first family in which linkage to chromosome 17q21 was reported displayed the disinhibition–dementia–parkinsonism–amyotrophy complex phenotype. In 1996, at a consensus conference, the term 'frontotemporal dementia' with parkinsonism linked to chromosome 17 (FTDP-17) was coined. Two years later, this was followed by the discovery of pathogenic mutations in *MAPT*. Since then, over 40 *MAPT* pathogenic mutations have been described (**Figure 1**), accounting for about one-third of familial FTLD patients and 5–10% of all FTLD cases.

MAPT encodes the tau protein, which is implicated in microtubule assembly and stabilization. The protein has six human isoforms, generated by alternative splicing of exons 2, 3, and 10. These isoforms can be divided into those with three (3R) and four (4R) microtubule binding domains, which differ in their binding and assembling properties. Hyperphosphorylated tau protein assembles into filaments in human disease, defining taupathies which include Pick's disease, AD, PSP, CBD, argyrophilic grain disease, and FTDP-17 with mutations in *MAPT*. Mutations in *MAPT* alter the expression of the 4R or both the 3R and 4R isoforms, thereby modifying the interaction with microtubules or the formation of fibrils.

Subtypes of *MAPT* mutations are clinically relevant, since they may be associated with distinct phenotypic features. For example, mutations in exons 9 and 13 are usually not associated with motor symptoms, whereas mutations altering the *MAPT* splicing are more commonly found in patients with FTD and parkinsonism. Furthermore, mutations altering the first two microtubule binding domains seem to be associated with earlier age of onset and shorter disease duration.

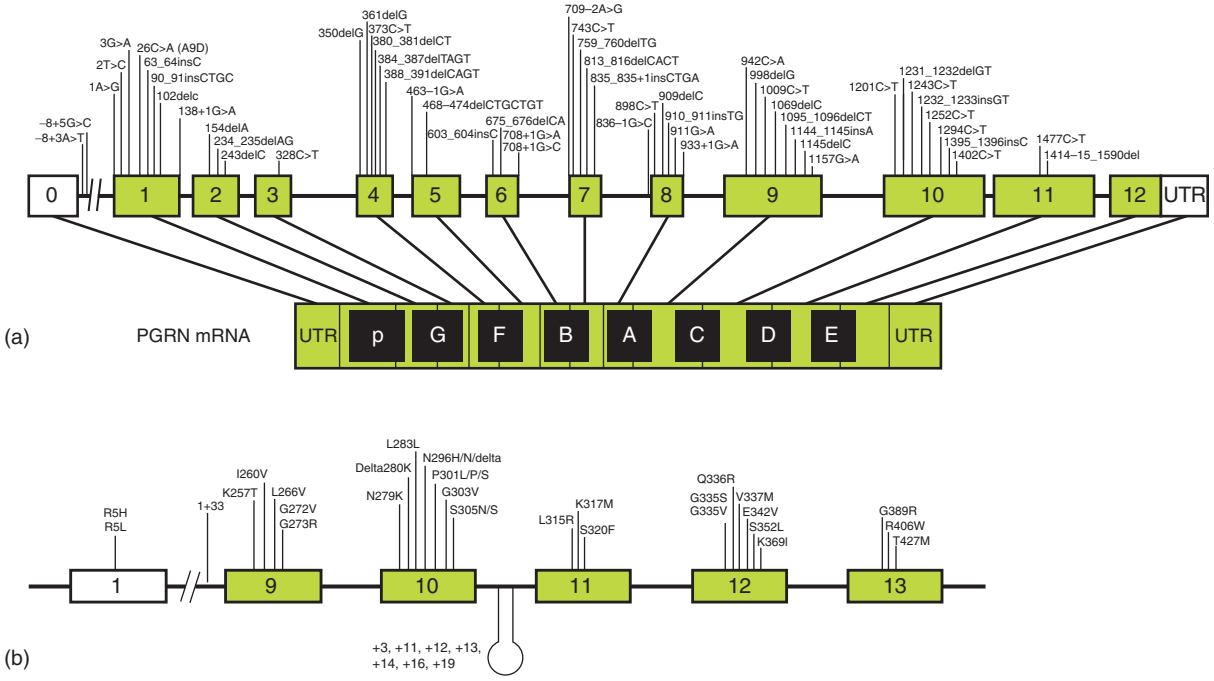

Figure 1 Schematic representation of the *PGRN* (a) and *MAPT* genes (b) with known mutations. Exons are numbered in Roman numerals. *PGRN* mRNA is depicted and lettered boxes represent individual granulin repeats.

Progranulin (PGRN)

Only 2 years after its discovery, over 50 pathogenic mutations have been identified in *PGRN* (**Figure 1**), which account for 5–10% of FTLD cases and 20–30% of familial cases. All the mutations discovered so far create functional null alleles resulting in reduced protein levels (haploinsufficiency). *PGRN* encodes a precursor protein which can be proteolytically cleaved in a family of granulins. The exact function of the protein in the brain remains to be established, but studies have suggested a role in cell cycle regulation and cell migration, tumorigenesis, inflammation and wound repair, and as a mitogenic factor. Recently, a functional link has been established between the PGRN protein and TAR DNA-binding protein 43 (TDP-43), the major protein content of intraneuronal inclusions in FTLD-U (see below).

Neuropathology

In recent years, neuropathologic classification of FTLD has seen marked changes, which have stemmed from new immunohistochemistry techniques and genetic discoveries. Macroscopically, FTLD is characterized by cortical degeneration of the frontal and temporal lobes. Histologically, there is neuronal loss and gliosis in affected areas. Immunohistochemistry, however, has allowed defining two main categories of FTLD, FTLD with tau-positive pathology (tau-positive FTLD), and FTLD with tau-negative, ubiquitin-positive inclusions (FTLD-U). Most cases previously referred to as dementia lacking distinctive histopathology have been reclassified as FTLD-U, which has emerged as the major pathology found in FTLD. About 45% of FTLD cases display tau-positive pathology (tau-positive FTLD), whereas ~50% of patients have ubiquitin-positive inclusions (FTLD-U). Recently, TDP-43 has been identified as the major ubiquitinated protein component of ubiquitin-positive neuronal and glial inclusions in FTLD-U, FTLD-MND, and amyotrophic lateral sclerosis (ALS). Based on these findings, consensus criteria for the pathological diagnosis of FTLD were revised, and now include TDP-43 proteinopathy as a distinct category that encompasses FTLD-U with or without MND, FTLD-U caused by *PGRN* or *VCP* mutations, FTD-MND linked to chromosome 9p, and ALS.

FTLD with tau-positive pathology includes classical Pick's disease with Pick cells (tau-positive swollen achromatic neurons) and Pick bodies (round argyrophilic inclusions), CBD, PSP, argyrophilic grain disease, and familial cases of FTLD with a mutation in *MAPT*. Histology and immunohistochemistry show neuronal loss, gliosis, and accumulation of hyperphosphorylated tau protein in the cytoplasm of neurons and glial cells. Specific tau isoforms are found preferentially in some taupathies, defining 3R taupathies (e.g., Pick's disease) and 4R taupathies (e.g., PSP and CBD).

FTLD-U pathology includes neuronal cytoplasmic (NCI) and intranuclear (NII) inclusions, glial inclusions, and dystrophic neurites. Heterogeneity exists in the relative intracortical and hippocampal distribution of NIIs, NCIs, and dystrophic neurites. Four main subtypes have

been identified, which are clinically relevant and associated with different phenotypes. Most of the Mackenzie type-I patients have FTD or PNFA, type-II is associated with SD, and cases with FTD-MND have type-III pathology. Patients with *PGRN* mutations display atrophy in the frontotemporal lobes, caudate nucleus, medial thalamus, substantia nigra, and in the CA1 sector of the hippocampus. Immunohistochemistry shows NCIs, NIIs, dystrophic neurites, and glial inclusions.

Although the link between *PGRN* mutations, TDP-43 positive inclusions, and the disease phenotype remains elusive, a recent cell biology study has shown that the PGRN protein alters caspase-dependant cleavage of TDP-43. Suppression of *PGRN* expression by small interfering RNA led to an altered cleavage and redistribution of TDP-43 from the nucleus to the cytoplasm, a pattern seen in FTLD-U patients.

Epidemiology

In the United Kingdom, FTLD prevalence was reported to be 15 per 100 000 among subjects between 45 and 64 years. Figures were comparable in The Netherlands, with a prevalence rate of 3.6 per 100 000 between ages 50 and 59, 9.4 per 100 000 between ages 60 and 69, and 3.8 per 100 000 between ages 70 and 79. Incidence (new patients per 100 000 person-years) in Rochester, MN, was found to be 2.2 for ages 40–49, 3.3 for ages 50–59, and 8.9 for ages 60–69. In comparison, the incidence of AD in the same series was expectedly lower for ages 40–49, similar for ages 50–59, and higher for ages 60–69. Most of the studies have not reported significant gender differences.

Clinical Features and Diagnostic Criteria

Clinical Features

Frontotemporal dementia (FTD)

The core presenting symptoms of FTD are personality changes and impaired social behavior (**Table 1**). These include mental inflexibility, loss of volition, emotional blunting, lack of insight, inertia, and impulsive and inappropriate behavior. Changes in religious or political beliefs may occur. In addition, patients present a wide range of frontal-type behaviors, mostly of the disinhibited form, along with speech alterations, albeit without true aphasia. Frontal release signs and parkinsonism are commonly observed in FTD patients. Parkinsonism tends to occur late in the disease, and usually consists of akinesia and rigidity, sometimes with postural tremor. Rest tremor is virtually always absent. Severe amnesia, aphasia, and spatial perceptual alterations are the clinical diagnostic exclusion criteria.

Progressive nonfluent aphasia (PNFA)

Expressive language is mostly affected in PNFA patients, who present with (nonfluent aphasia), including agrammatism, anomia, alexia, agraphia, and phonemic paraphasia. The meaning of words is retained in early stages, in contrast with SD patients. With disease progression, patients often present with frontal behavioral impairment, along with parkinsonism, mostly of the akinetic-rigid type. Mutism is common in end-stage disease.

Semantic dementia (SD)

SD patients present with fluent aphasia and early loss of the meaning of words, characterized by altered comprehension and naming, empty speech, impaired face (prosopagnosia) and object (agnosia) recognition, and semantic paraphasias. Patients often retain the ability to read aloud and write to dictation, which can be misleading; however, their understanding of the content is severely impaired. As in FTD and PNFA, parkinsonian signs may occur in later stages of the disease.

FTD-MND

About 10% of FTLD patients present with MND symptoms, particularly those with the FTD phenotype. Any degree of association may occur, ranging from subclinical motor neuron involvement, only seen at autopsy, to severe MND compatible with a diagnosis of ALS. The common clinical association of FTLD and MND is reflected at the neuropathologic level, where similar neuronal and glial inclusions are found in both conditions. The anatomic distribution of pathology (frontotemporal cortex vs. motor neurons) determines the proportion of FTLD or MND phenotypes, respectively.

FTD with parkinsonism linked to chromosome 17

FTDP-17 designates patients with a familial form of the disease, who display evidence of genetic linkage to chromosome 17. Two genes, *MAPT* and *PGRN*, have been identified within this locus and causally associated with disease.

FTDP-17 families with tau-positive pathology

Tau-positive FTDP-17 is caused by mutations in *MAPT*. The clinical phenotype is dominated by personality and behavioral changes, cognitive impairment, and motor symptoms, with an earlier age of onset (49 years, range: 25–76) than that of the overall FTLD population (**Figure 2**). Motor impairment consists of parkinsonism with rigidity, bradykinesia, postural tremor, and postural instability. In contrast with sporadic FTLD, parkinsonism often occurs early in the disease, sometimes resembling Parkinson's disease (PD), thereby leading to misdiagnosis. However, similar to sporadic FTLD, response to levodopa is usually poor and, if present, is not long-lasting. There is a high variability in clinical presentation not only across but also within families. In addition to FTD and parkinsonism, vertical

Table 1 Diagnostic criteria for FTLD

(a) Frontotemporal dementia (FTD)		
Core criteria	Insidious onset, gradual progression	
	Early occurrence of	• impaired social behavior
		• impaired personal conduct
		• emotional blunting
		• loss of insight
Supportive criteria	Behavioral disorder	• personal hygiene decline
		• mental rigidity, inflexibility
		• distractibility, impersistence
		• hyperorality, dietary changes
		• perseveration, stereotyped behavior
		• utilization behavior
	Speech, language	• altered speech output, stereotypy, echolalia, perseveration, mutism
	Physical signs	• primitive reflexes, incontinence, parkinsonism
(b) Progressive nonfluent aphasia (PNFA)		
Core criteria	Insidious onset, gradual progression	
	Nonfluent spontaneous speech, with at least one of the following: agrammatism, phonemic paraphasia, anomia	
Supportive criteria	Speech and language	• stuttering, oral apraxia, impaired repetition, alexia, or agraphia
		• early preservation of word meaning
	Behavior	• early preservation of social skills, late behavioral changes similar to FTD
	Physical signs	• late controlateral primitive reflexes, parkinsonism
(c) Semantic dementia SD		
Core criteria	Insidious onset, gradual progression	
	Fluent empty spontaneous speech or loss of word meaning	
	and/or	• prosopagnosia or agnosia
		• preserved drawing reproduction
		• preserved word repetition
		• preserved ability to read aloud and write to dictation
Supportive criteria	Speech, language	• press of speech, idiosyncratic word usage, no phonemic paraphasia, preserved calculation
	Behavior	• loss of sympathy and empathy, narrowed preoccupation
	Physical signs	• absent of late primitive reflexes, parkinsonism

Source: Neary D, Snowden JS, Gustafson L, et al. (1998) Frontotemporal lobar degeneration: A consensus on clinical diagnostic criteria. *Neurology* 51(6): 1546–1554.

Figure 2 Clinical (*left, middle*) and MR findings (*right*) in a patient from the pallido-ponto-nigral degeneration family carrying the N279K *MAPT* mutation. A 49-year-old woman presented, at age 42, with right-predominant tremor, postural instability, and rigidity. Associated findings over the next few years included dystonia, depression, personality changes, insomnia, and cognitive impairment. Symptoms responded partly to levodopa with dyskinesia. The patient currently requires help for ambulation. The figure shows staring gaze and frontal dystonia (*top left*), eye opening apraxia with upper eyebrows above the superior orbital rim (*bottom left*), upper limb dystonia (*top middle*), foot dystonia (*bottom middle*), frontal atrophy (*top right and bottom right*), and temporal atrophy (*bottom right*).

gaze palsy, anosmia, pyramidal signs, severe memory loss, myoclonus, dystonia, autonomic dysfunction, and rarely, epileptic seizures have been described.

FTDP-17 families with tau-negative, ubiquitin-positive pathology

Mutations in the *PGRN* gene cause FTLD with ubiquitin-positive inclusions (FLTD-U). The mean age of onset is 59 years (range: 48–83 years), with an age-dependant penetrance (>90% mutation carriers affected by age 70). The most common phenotype is FTD with some degree of language impairment, followed by PNFA. Parkinsonism occurs in ~50% of patients, and tends to appear late in the disease. It is mainly characterized by akinetic-rigid and axial symptoms, although postural tremor may occur. As in *MAPT* mutation carriers, response to levodopa is poor. The association with MND is distinctly rare. Hallucinations have been described in as many as 30% of patients. Families have been reported with phenotypes suggestive of CBD, PD, dementia with Lewy bodies, and AD.

Diagnostic Criteria

Clinical diagnostic criteria were published in 1998 by Neary et al., and have proven very useful for both clinical practice and research purposes (**Table 1**). However, several drawbacks have emerged, related to the dynamic nature of FTLD and to the poor sensitivity in early stages of the disease. For example, patients may present with a FTD phenotype and later evolve into SD or PNFA. Studies have found that two-thirds of FTLD patients present additional phenotypes with disease progression. Also, while some studies have reported good sensitivity and specificity (80% and 99%, respectively), other authors have found that only about one-third of the patients fulfill all the core diagnostic criteria at presentation, hence, a poor sensitivity in early stages (60%). Finally, while anterograde amnesia is an exclusion criterion, patients have been described even with AD type memory impairment. Other diagnostic criteria have been proposed by McKhann et al., which are easier to use in a general neurology setting (**Table 2**). These criteria are, however, prone to miss patients with SD. No specific criteria have been developed for FTDP-17; useful diagnostic tools are given in **Table 3**.

Table 2 Clinical diagnostic criteria for FTLD

Behavioral or cognitive deficits	Early progressive personality changes with difficulty in modulating behavior, inappropriate responses, or activities; or Early progressive language difficulties, with expression impairment or severe naming difficulties and problems with words meaning
Behavioral/cognitive deficits cause significant functioning impairment, and clearly represent a decline	
Gradual onset, progression	
No other cause is identified	
The deficits do not occur exclusively during a delirium	

Source: McKhann GM, Albert MS, Grossman M, et al. (2001) Clinical and pathological diagnosis of frontotemporal dementia: Report of the work group on frontotemporal dementia and Pick's disease. *Archives of Neurology* 58(11): 1803–1809.

Table 3 Clinical features of the most common forms of autosomal dominant FTLD

	MAPT	*PGRN*
Mean age of onset (years)	49 (range 25–76)	59 (range 37–84)
Mean duration (years)	7 (range 2–30)	7 (range 2–30)
Symptoms	Personality or behavioral changes, language impairment (mostly *PGRN*), parkinsonism (mostly *MAPT*), cognitive impairment, parkinsonism, corticobasal syndrome, amyotrophy, gaze palsy, motor neuron disease (rare)	
Treatment	Levodopa ineffective but may have a limited effect for some time	

Differential Diagnosis

The high clinical heterogeneity of FTLD makes it prone to clinical misdiagnosis, particularly in early stages. In most cases, the key is long-term follow-up of patients, as both sensitivity and specificity of diagnostic criteria improve with disease progression. Early behavioral changes may suggest psychiatric conditions. Behavioral and language impairment along with absence of severe memory loss usually allow differentiating FTLD from AD. However, clinico-pathological studies have shown that some patients display significant anterograde amnesia even in early stages of FTLD, often leading to a false AD diagnosis. In some patients, particularly those with a familial form of FTLD, the phenotype may suggest PD, although response to levodopa is poor or absent.

Diagnostic Work-up/Tests

Biological tests include standard dementia work-up to exclude metabolic, endocrine, immunologic, and paraneoplastic disorders. Imaging studies are crucial to establish a diagnosis of FTLD.

Morphologic imaging often shows mild or no atrophy in the early stages of the disease. However, as the disease progresses, atrophy becomes more apparent by standard CT and MRI scans (**Figure 2**). Atrophy usually predominates in the frontal and temporal lobes in FTD, in the left frontal lobe in PNFA, and in the left temporal lobe in SD, however with wide variability and overlap. Some studies have shown that patients with normal or borderline MRI scans had a longer survival than those with prominent frontotemporal atrophy.

Functional imaging shows hypometabolism on glucose positron-emission tomography (FDG-PET) and hypoperfusion on single photon-emission computed tomography (SPECT). FDG-PET studies have found hypometabolism in the lateral and medial prefrontal cortices, caudate nucleus, insula, and thalamus, with later involvement of temporal and parietal cortices. The severity of apathy and disinhibition has been correlated with the degree of hypometabolism/reduced blood flow in the posterior orbitofrontal, ventromedial prefrontal and temporal cortices. ^{18}F-Fluoro-dopa PET (FD-PET) has shown both pre and postsynaptic reduced tracer intake in patients with FTDP-17 due to a *MAPT* mutation, explaining the short-lasting response to levodopa seen in some patients. Presymptomatic FD-PET abnormalities have been reported in *MAPT* mutation carriers, showing this method may be used as a surrogate marker when studying the effect of putative neuroprotective interventions.

Management

No specific pharmacological treatment is currently approved for FTLD, and management is symptomatic. Off-label use of acetylcholinesterase inhibitors or memantine has been found useful in some patients, but no benefit has been established for cognitive symptoms. In patients displaying significant behavioral or mood alterations, atypical antipsychotics and antidepressants should be considered. Speech therapy may benefit patients with language impairment. Physical therapy is indicated for gait impairment and activities of daily living. Levodopa is usually not effective.

Prognosis

FTLD progression is faster than that of AD, and recent studies have found a median survival of 3 years after diagnosis, and of 6 years after initial symptoms. Absent or mild atrophy in early stages may be associated with a better prognosis. No strategy has been proven effective in preventing the disease or in halting its progression. Prognosis may even be poorer in some FTDP-17 patients with survival rates of less than 2 years.

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See also: Corticobasal Degeneration; Dementia with Lewy Bodies; Dementia, Movement Disorders; Progressive Supranuclear Palsy; Punding (PD); Tauopathies.

Further Reading

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Relevant Websites

http://geneclinics.org/ – GeneTests website.
http://www.ftd-picks.org/ – The Association for Frontotemporal Dementias.
http://www.molgen.ua.ac.be/ADMutations/ – Website with updated mutations that cause frontotemporal dementia.
http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id = 600274 – Online Mendelian Inheritance in Man (OMIM).
http://www.pdsg.org.uk – Pick's disease Support Group.
http://www.alz.org – Alzheimer's Association.
http://www.orpha.net – Orphanet.

Fumarase Deficiency

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Definition and History

Fumarase hydratase (FH) deficiency belongs to the group of inborn errors of metabolism of the tricarboxylic acid cycle. FH deficiency is also named fumaric aciduria, since it results in excessive urinary excretion of fumarate.

Fumarase deficiency was first described in 1983 by Whelan who reported fumaric aciduria in two adult sibs with mental retardation and speech impairment. The enzyme defect was discovered three years later by Zinn in 1986 in a patient with the clinical picture of an early-onset severe encephalopathy. The first molecular diagnosis was published in 1994 by Bourgeron. Generally, the disease is characterized by early-onset encephalopathy with seizures and hypotonia, associated with excessive fumaric acid excretion. Milder cases are also described. In 2002, heterozygous germline mutations of FH were described in patients with multiple cutaneous and uterine leiomyomas.

Pathogenesis and Metabolic Consequences

Human fumarate hydratase is a homotetramer with mitochondrial and cytosolic isoenzymes. It catalyzes the reversible conversion of fumarate and malate. No cofactors are required. The mitochondrial isoenzyme is involved in the tricarboxylic acid cycle in the mitochondria, and the function of the cytosolic isoenzyme is still unclear.

The pathogenesis of fumarase deficiency and other TCA cycle defects includes impaired energy production caused by interrupting the flow of the TCA cycle and secondary enzyme inhibition associated with accumulation of metabolites proximal to the primary enzyme deficiency. The first mechanism limits the number of enzymatic steps at which reducing equivalents can be generated and transferred to the ETC. In addition, this mechanism may lead to depletion of oxaloacetate, preventing continued influx of acetyl-CoA into the TCA cycle via citrate synthase. The second mechanism may involve other pathways of oxidative metabolism. Finally, the primary mechanism of how a metabolic enzyme can also work as a tumor supression has not yet been solved.

Epidemiology and Genetics

There is an unusually high incidence of fumarase deficiency in the southwestern United States among members of the Fundamentalist Church of Jesus Christ of Latter Day Saints (FLDS).

The genetic defect was traced to one of the community's founding patriarchs and the first of his plural wives, who had 14 children together.

The disease is usually very rare and is inherited as an autosomal recessive trait. The two isoforms of fumarase, mitochondrial and cytosolic, differing in electrophoretic mobility, are encoded by a single locus on chromosome 1. The same gene and the same mRNA encode both proteins, but the fumarase transcript is alternately translated to generate the two isoforms. The two peptides are identical after the latter initiation methionine; heterozygous carriers have about 50% of the fumarase hydratase activity of normal controls, while deficient patients have undetectable or less than 10% levels of activity of normal controls.

The fumarase gene has been mapped to chromosome 1q42.1. Bourgeron described the first mutation in a consanguineous family with two affected sibs A homozygous missense mutation was found. Different mutations have been demonstrated in several unrelated families. One paper describes a case with uniparental isodisomy. The unaffected father was found to be heterozygous for the mutation of the child who was homozygous, while the mother was found to be homozygous wild-type. Analysis of chromosome 1 markers showed that the patient inherited both paternal alleles with a complete absence of maternal alleles.

Most mutations are private mutations except for the 435insK mutation, which was described in several patients.

Heterozygous mutations in the FH gene are associated with a predisposition to cutaneous and uterine leiomyomas and to kidney cancers; later also to ovary adenocarcinomas, Leydig cell tumors, and cerebral cavernomas. The tumors are generated after somatic loss of the normal allele.

It has been proposed that the mutations cluster at the 5′end of the FH gene in patients with tumor predisposition, whereas mutations associated with FH deficiency tend to cluster in the 3′end of the gene.

Clinical Features and Diagnostic Criteria

Approximately, less than 40 patients with fumarase hydratase deficiency have been reported. The first biochemically proven case started at 3 weeks of age with vomiting and hypotonia. He developed microcephaly (associated with dilated lateral ventricles) and severe axial hypertonia and had no developmental progression. An EEG showed abnormal background rhythms and bitemporal spike-wave patterns. Elevated plasma lactate levels and urinary fumarate and other Krebs cycle intermediates in the organic acid analysis suggested the diagnosis, which was biochemically confirmed. Petrova-Benedict reported in 1987 a case of fumarase deficiency in a mentally retarded child with microcephaly of consanguineous parents. Using iso-electrofocusing, they could demonstrate that the enzyme in the cytosolic compartment appeared to be more severely affected. Bourgeron in 1994 described the first mutation in the fumarase hydratase gene in a consanguineous family with two affected sibs. The children presented with a severe encephalopathy and became microcephalic and quadraplegic. In these sibs, plasma lactate was normal, but CSF lactate was consistently elevated. A severe FH deficiency (<0.5% of control activity) was found in all tissues investigated and affected to the same degree as the cytosolic and the mitochondrial isoenzymes.

Until the publication of Kerrigan in 2000, only 13 patients were described, all presenting in infancy with a severe encephalopathy and seizures, with poor neurological outcome. Kerrigan reported on eight patients from a large consanguineous family. All the patients had a profound mental retardation and presented it as a static encephalopathy. Six out of the eight developed seizures. The seizures were of various types and of variable severity, but several patients experienced episodes of status epilepticus. All had a relative macrocephaly (in contrast to previous cases) and large ventricles. Dysmorphic features such as frontal bossing, hypertelorism, and depressed nasal bridge were noted.

Visual impairment, optic nerve hypoplasia, and areflexia have been clinical features in other patients. Infantile spasms have been commonly reported. Milder cases with developmental delay and epilepsy have been described, for example in a 5-year-old girl with a previous diagnosis of cerebral palsy, nonprogressive psychomotor retardation, and hypotonia. She was found to excrete excessive fumaric acid in urine. Fumarate hydratase activity in skin fibroblasts was 10% of the control value.

Maradein described a girl in whose case both the mother and grandmother had uterine myomas. She had been hypotonic since birth; walked by the age of 4 years; and started having epilepsy at the age of 7 years and was moderately to severely mentally delayed.

The diagnosis is made by organic acid analysis in urine revealing increased fumaric acid and increases of one or more of the Krebs cycle intermediates, such as succinic, α-ketoglutaric acid, citric, and malic acid. Metabolic acidosis can be absent. The diagnosis can be confirmed by measuring FH in cultured skin fibroblasts, in mononuclear blood leukocytes, skeletal muscle, or liver by monitoring the formation of fumarate from malate. Other diagnostic indicators are an increased lactate in CSF and a variable leucopenia and neutropenia.

Neuropathological changes include agenesis of the corpus callosum with communicating hydrocephalus as well as cerebral and cerebellar heterotopias. Periventricular cystes have also been described, as is seen in pyruvate carboxylase deficiency.

According to Kerrigan characteristic neuropathological abnormalities in fumarase deficiency are also polymicrogyria, open operculum, colpocephaly, and angulations of frontal horns, choroid plexus cysts, decreased white matter and a small brainstem.

Differential diagnosis should be made with other defects in Kreb's cycle, and in cases of a more static encephalopathy with mental retardation and speech delay, or developmental abnormalities of the brain, fumaric aciduria should be looked for.

Prenatal diagnosis is possible by measuring fumarase activity and/or mutational analysis in chorionic villi samples or cultured amniocytes.

Treatment and Prognosis

There is no specific treatment. In early-onset cases, prognosis is usually severe with no or little progress in psychomotor development.

See also: Dystonia, Secondary.

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GABA and Movement Disorders

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Glossary

Ataxia – Ataxia (from Greek 'lack of order'), gross incoordination of muscular action, is a nonspecific manifestation of dysfunction of any part of the nervous system that regulates movements.

GABA (γ-Amino-butyric acid) – GABA and glycine are the main inhibitory neurotransmitters in the vertebrate central nervous system (CNS). GABA is an omega amino-acid, produced from glutamate by the enzyme glutamate acid decarboxylase (GAD) specifically present in inhibitory neurons. GABA acts mainly through two types of receptors: $GABA_A$ and $GABA_B$ receptors. As ligand-gated anionic channels, permeable to chloride ions (Cl^-), $GABA_A$ receptors generate inhibitory postsynaptic potentials (IPSPs) that inhibit neurons by hyperpolarization and membrane shunting. $GABA_A$ receptors are found in all parts of the CNS. They are blocked by specific antagonists such as gabazine, bicuculline, and picrotoxin. Their activity can also be modified by ethanol and by allosteric modulators such as benzodiazepines, barbiturates, and some endogenous steroids. $GABA_A$ receptors form heteropentameric chloride channels assembled from a large family of subunits (α1–6, β1–3, γ1–3, δ, ε, π, and θ in mammalian brain). Like glycine receptors, most $GABA_A$ receptors are found at inhibitory postsynaptic sites where they are anchored by gephyrin to the cytoskeleton. By contrast, $GABA_B$ receptors have a dimeric structure with two heterologous subunits R1 and R2 and are metabotropic, being G protein-coupled to K^+ or Ca^{2+} channels: they are selectively activated by baclofen. They have a dual action: they reduce cell firing postsynaptically by opening K^+ channels; they inhibit transmitter release presynaptically (including GABA) by blocking Ca^{2+} channels.

Glycine (Gly) – Unlike GABA, glycine, the smallest amino acid, can form peptidergic bonds. Glycine is also a major inhibitory neurotransmitter in the CNS, especially in the spinal cord and brainstem. Like GABA, glycine activates Cl^- influx, causing an IPSP. Strychnine is a specific antagonist of glycine receptor. $GABA_A$ and glycine receptors are often colocalized. At low concentrations, glycine is also an essential coagonist at NMDA-type glutamatergic synapses.

Hypotonia and Spasticity – Insufficient or excessive tonic motor signals result in seriously disabling muscle weakness or overactivity, hypotonia or spasticity, respectively, which may interfere with motion, gait, and also speech.

Motoneuron (Mn) – Motoneurons are located in the ventral spinal cord and motor nuclei of the brainstem. Their axons innervate muscles. In vertebrates, all motoneurons are cholinergic: by releasing acetylcholine from their terminals, they initiate muscle excitation and contraction. Motoneurons are excited by glutamatergic and inhibited by GABAergic and/or glycinergic inputs.

Transmembrane anionic gradient and Potassium-Chloride Cotransporter (KCC) – The effect of a large increase in anionic conductance – produced by GABA or glycine – depends on the anionic electrochemical gradient, determined mainly by the cytosolic concentration of Cl^- ($[Cl^-]$). As a rule, in the mature CNS, a relatively low internal $[Cl^-]$ favors Cl^- influx: hence, GABA and glycine tend to hyperpolarize (inhibit) neurons. Internal $[Cl^-]$ homeostasis is maintained by several mechanisms, including the cation-chloride cotransporters (CCCs) and Cl^--HCO_3^- exchangers. Two dominant CCCs are especially relevant: the K^+-Cl^- cotransporter isoform 2 (KCC2), which extrudes Cl^-; and the Na^+-K^+-$2Cl^-$ cotransporter (NKCC1), which mediates Cl^- uptake. Note that in immature CNS, the

net Cl^- transport is inward, and both GABA and glycine tend to depolarize central neurons and can thus cause excitation. As HCO_3 ions also permeate these Cl^- channels (albeit less effectively), under some conditions, metabolic changes that affect tissue [HCO^-_3] can affect the inhibitory action of GABA and glycine.

Introduction

Both the initiation and the execution of movements depend on a fine balance between excitatory and inhibitory actions in the CNS: this is as true in the spinal cord, where specific neuronal networks called *central pattern generators (CPGs)* determine their execution, as in the motor cortex, basal ganglia, and cerebellum, where movements are initiated, the appropriate CPGs selected, and the overall performance continually monitored and optimized. At all levels, as the predominant inhibitory agent, GABA's role is crucial. It is not surprising that movement disorders are often caused by GABAergic dysfunction and that GABA receptors are key targets for drug design to treat various pathological conditions.

Motor Reflexes and Locomotion

Underlying most movements are spinal reflexes. Albeit regulated or initiated by supraspinal structures (**Figure 1**), movement patterns are generated in the spinal cord by the CPGs. As inhibitory neurotransmitters, GABA and glycine play a crucial role in the organization of CPGs and in movement synchronization. Pharmacological block of GABA or glycine receptors soon leads to an uncontrolled motor activity, such as epileptiform seizures.

As shown in **Figure 2**, some basic CPGs are propriospinal reflexes:

- In **Figure 2(a)**, groups of neurons with antagonistic motor functions (ex: flexion and extension) are *reciprocally inhibited* via GABAergic and/or glycinergic inhibitory Ia interneurons monosynaptically activated by low-threshold (Ia) afferents from muscle. Hence, antagonist muscles relax during the contraction of agonist muscles.
- *The flexion (withdrawal* or *nociceptive) reflex* (**Figure 2(b)**) quickly removes limb from a painful stimulus by contracting the appropriate muscles (usually flexors) and relaxing their antagonists.
- *The crossed-extension reflex* (**Figure 2(c)**): the contraction of flexor muscles on one side of the body is accompanied by the contraction of the contralateral extensors, which hold the body upright. The relevant CPG is also involved in gait.

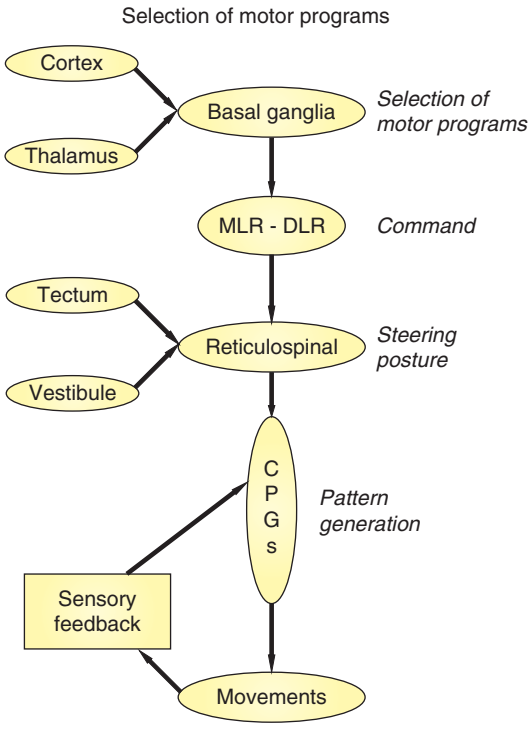

Figure 1 Supraspinal and spinal systems involved in the control of locomotion. Motor program is selected in basal ganglia which receive inputs from cerebral cortex and thalamus. At rest, basal ganglia inhibit command centers in mesopontine and diencephalic locomotor areas (MLR and DLR). Locomotion is initiated by controlled disinhibition which allows reticulospinal (RS) neurons to activate the spinal central pattern generator (CPG) for locomotion. Tectal (visual) and vestibular inputs to brainstem further control both steering and posture. In addition, spinal CPG network is modulated by local sensory feedback. Reproduced from **Figure 1** in Grillner S, Wallen P, Saitoh K, Kozlov A, and Robertson B (2008) Neural bases of goal-directed locomotion in vertebrates – An overview. *Brain Research Reviews* 57: 2–12, with permission from Elsevier.

- *Recurrent inhibition* by *Renshaw cells* auto-regulates firing of α-motoneurons (**Figure 2(d)**). These cells release both GABA and glycine. The excitation of Renshaw cells by specific sensory inputs, which reduces motoneuronal activity, is also important in gait.

Of clinical interest is that all inhibitory interneurons are targeted by tetanus toxin. From contaminated wounds, toxin travels to the spinal cord where it suppresses the release of GABA and glycine: the resulting motoneuronal hyperactivity leads to intense spasms (*tetanus*).

Complex patterns of motor activity, including locomotion, have been studied much in 'simpler' animals.

GABA and Animal Models of Locomotion

Nematodes (Caenorhabditis Elegans)

Although nematodes and vertebrates diverged >800 Mya, many proteins governing exocytosis and neurotransmitter functions remain conserved in vertebrate nervous

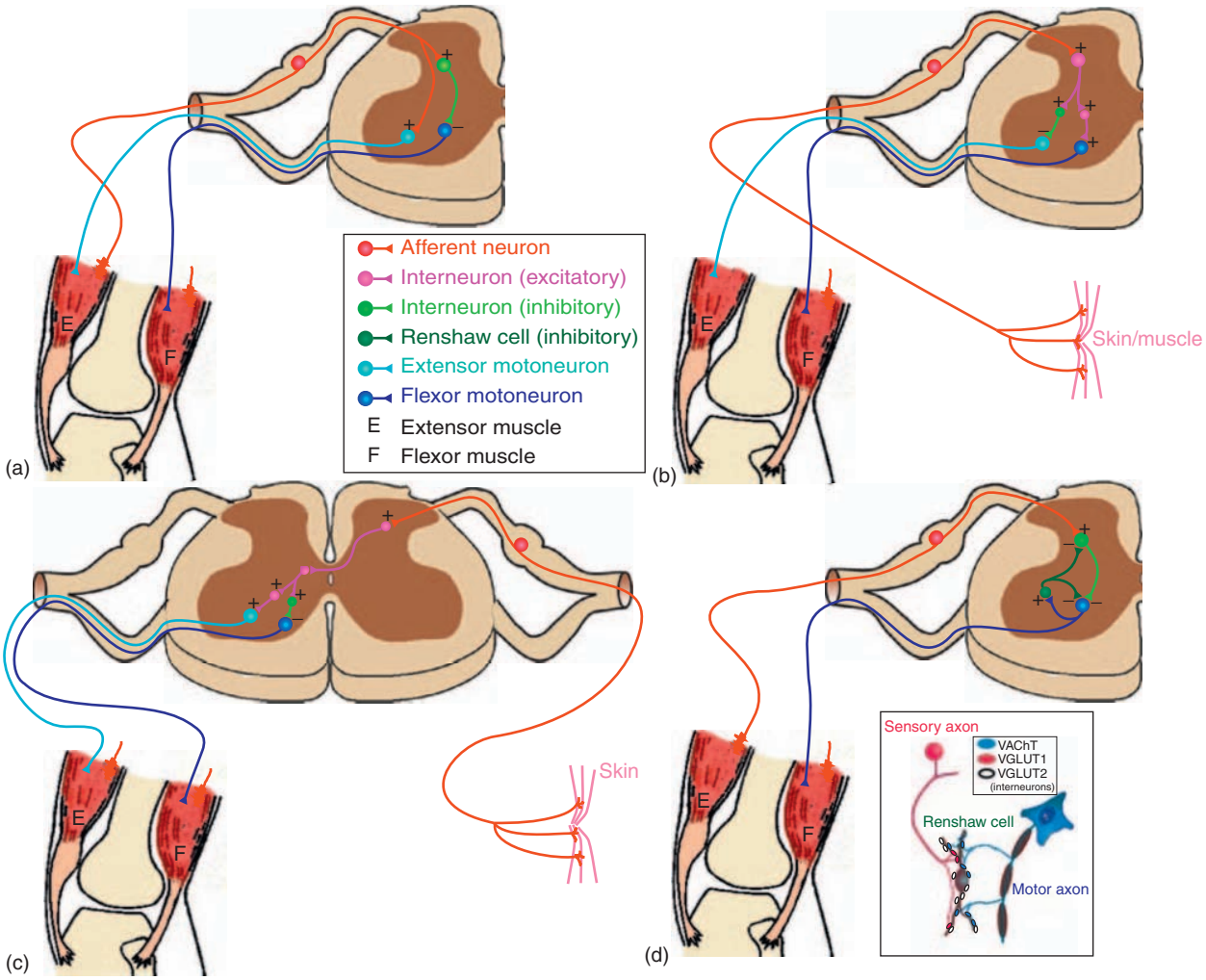

Figure 2 GABA and spinal reflexes. (a) Tendon jerk and reciprocal inhibition. The tendon jerk (myotatic reflex) is the simplest reflex and also the most rapid because it involves only two neurons (monosynaptic connection). Thus, a brief tap to the tendon of quadriceps (knee extensor) muscle excites primary muscle spindle ending of Ia-afferent axon which excites homonymous motoneuron by a glutamatergic synaptic connection. The cholinergic motor axon innervates the muscle from which the group Ia afferent fiber originated: the homonymous muscle thus contracts. The knee extension is facilitated by relaxation of knee flexors, mediated by Ia-afferent collateral excitation of Ia interneurons that inhibit the antagonist flexor motoneurons by releasing mostly glycine but also GABA. (b) Flexion reflex. This protective reflex withdraws limb from noxious stimulation. Strong excitation of peripheral sensory endings (typically in the skin) activates parallel excitatory and inhibitory polysynaptic pathways initiating contraction of the flexor muscles and relaxation of the antagonist extensors. (c) Crossed extension reflex. This 'mirror' reflex accompanies the flexion reflex by causing contraction of contralateral muscles. Operating in alternation from side to side, it is a part of the mechanism of locomotion; and, as an important component of nociceptive reflexes, contralateral extension helps to preserve the upright posture. (d) Recurrent inhibition. Renshaw inhibitory neurons are directly activated by intraspinal motor axon collaterals which release ACh. They are also excited by glutamatergic sensory axons; because these terminals accumulate glutamate in their presynaptic vesicles, they display the vesicular glutamate transporter type-1 (VGluT1). Various glutamatergic interneurons also excite Renshaw cells, but their terminals can be identified by a different vesicular glutamate transporter (VGluT2). Renshaw cells inhibit motoneurons, inhibitory Ia interneurons and even other Renshaw cells. Overall, Renshaw cells down-regulate motoneuronal activity. Framed scheme reproduced with permission from **Figure 2** Alvarez FJ and Fyffe RE (2007) The continuing case for the Renshaw cell. *The Journal of Physiology* 584: 31–45, with permission.

systems. In nematodes, as in crustacea, GABAergic inhibition relaxes body muscles during locomotion (**Figure 3(a)**). However, GABA causes enteric muscles to contract during defecation. Thus in nematodes, GABA inhibits or excites different muscles. Studies of GABA functions in worms greatly advanced genetic screening and the identification of the GABA biosynthetic enzyme, plasma membrane and vesicular transporters, inhibitory and excitatory receptors, and a transcription factor required for the differentiation of GABAergic cells (**Figure 3(b)**).

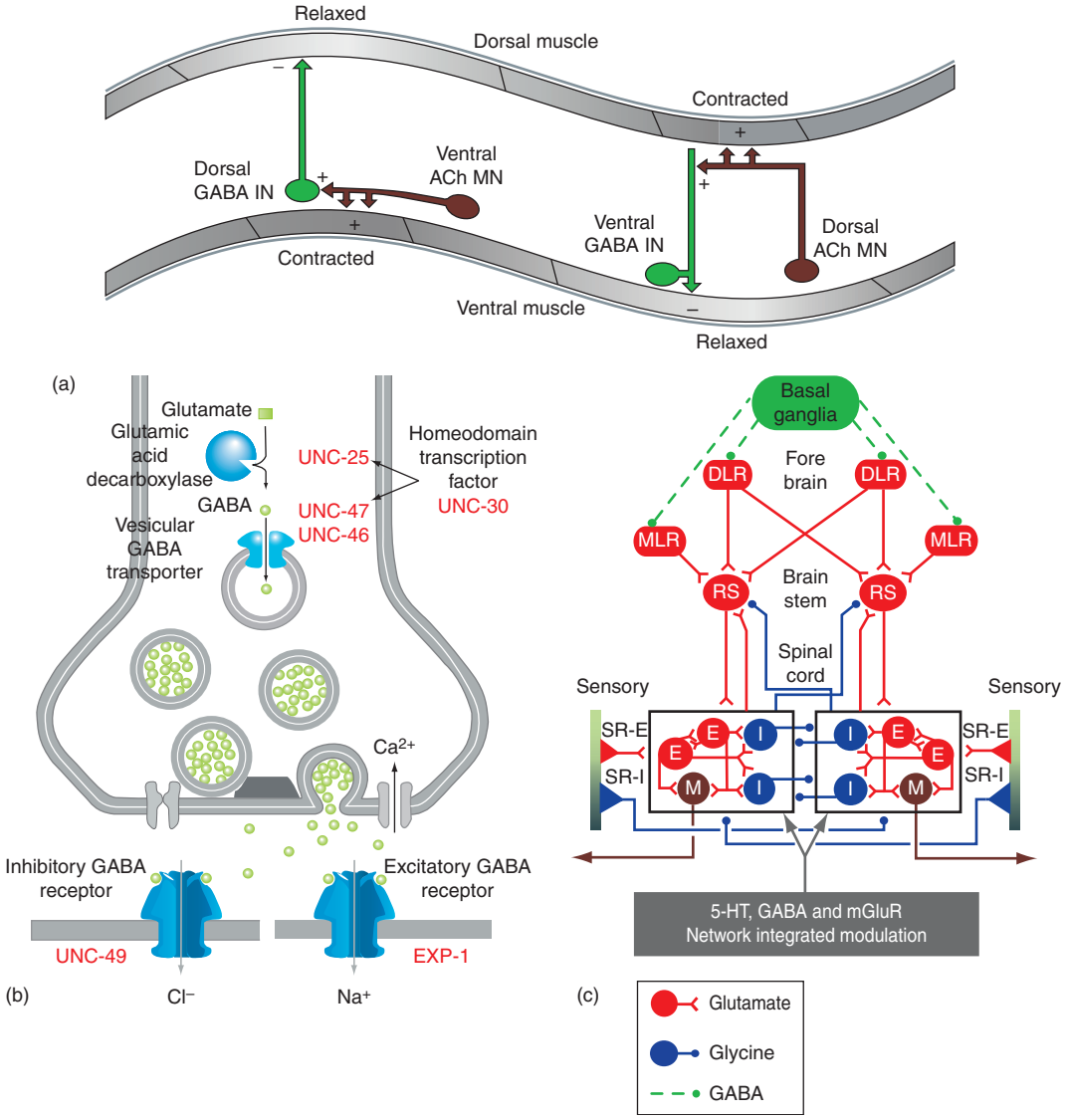

Figure 3 GABA in some 'simpler' motor systems. (a) *C. elegans* locomotor network. Neuronal cell bodies in ventral cord form synapses on dorsal and ventral body wall muscles. Cholinergic motor neurons (ACh MN in brown) send inputs to ventral and dorsal muscles, as well as to GABA interneurons (GABA IN in green). Release of ACh leads to contraction of muscle on one side and GABA release and relaxation of opposite muscle, causing body to bend. Coordinated waves of excitation and inhibition generate locomotion. Reproduced from **Figure 2** in Schuske K, Beg AA, and Jorgensen EM (2004) The GABA nervous system in *C. elegans*. *Trends in Neurosciences* 27: 407–414, with permission. (b) Genes and proteins involved in the *C. elegans* GABAergic synapses. In presynaptic terminal, GABA is synthesized from glutamate by glutamic acid decarboxylase (GAD), which is encoded by the unc-25 gene. GABA is then transported into synaptic vesicles by the vesicular GABA transporter (VGAT), encoded by the unc-47 gene. UNC-46 probably modulates vesicular GABA loading. The UNC-30 transcription factor is required for UNC-25 and UNC-47 expression in GABA neurons. Reproduced from **Figure 4** in Schuske K, Beg AA, and Jorgensen EM (2004) The GABA nervous system in *C. elegans*. *Trends in Neurosciences* 27: 407–414, with permission. After release, by acting on postsynaptic $GABA_A$-type UNC-49 receptor, GABA promotes hyperpolarization by Cl^- influx, thus causing muscles to relax. In the gut, GABA release from another type of motor neuron activates novel excitatory EXP-1 GABA receptors; Na^+ influx-mediated depolarization causes contraction of the enteric muscles. Reproduced from **Figure 4** in Schuske K, Beg AA, and Jorgensen EM (2004) The GABA nervous system in *C. elegans*. *Trends in Neurosciences* 27: 407–414, with permission. (c) Lamprey locomotor network. Schematic representation of forebrain, brainstem, and spinal neural circuitry that generates locomotor activity. Dashed lines from GABAergic basal ganglia illustrate indirect connections. All symbols represent cell populations. The reticulospinal (RS) projection and excitatory spinal interneurons (E) are all glutamatergic. Axons of spinal glycinergic inhibitory interneurons (I) cross the midline to inhibit contralateral interneurons and motoneurons (M). The stretch receptor neurons either excitate (SR-E) ipsilateral spinal neurons, or inhibit (SR-I) contralateral neurons. RS neurons are excited by signals from the diencephalic and mesopontine locomotor regions (DLR and MLR, respectively), which are under GABAergic control from the basal ganglia and receive visual and olfactory inputs. Activation of metabotropic receptors (5-HT, $GABA_B$ and mGluR) is also an integral part of locomotion. Reproduced from **Figure 6** in Grillner S, Wallen P, Saitoh K, Kozlov A, and Robertson B (2008) Neural bases of goal-directed locomotion in vertebrates – An overview. Brain Research Reviews 57: 2–12, with permission.

Cyclostomes (Lamprey)

The CNS of this primitive vertebrate offers many advantages for research: it can be studied in vitro, for several days, without the need of dissection. Overall, the motor control system is very much as in higher vertebrates (**Figure 3**(**c**)). Under cortical and thalamic influence, motor programs are selected in basal ganglia and then transmitted via brainstem and reticulospinal neurons to the spinal cord. The core of the spinal locomotor network consists of ipsilateral glutamatergic neurons and glycinergic neurons projecting contralaterally. This spinal network can generate autonomous motor activity driven by coordinated patterns of firing. Such CPGs are triggered by the descending glutamatergic reticulospinal axons. The crossed glycinergic axons are indispensable for burst generation, alternating between the two sides, and thus for correct locomotion. By contrast with mammals, in the lamprey's spinal network, only glycinergic neurons play a major role.

GABA and Transgenic Mice

The effects of targeted deletion of the gene encoding $GABA_A$ receptor α subunits has been studied, for example, in the cerebellum of $\alpha^{-/-}$ mice. Recently, knock-in mice have much advanced our understanding of the function of different $GABA_A$ receptor subtypes. In transgenics, with a point mutation in the gene encoding $GABA_A$ receptor α subunits, the corresponding receptor was still sensitive to GABA but not to benzodiazepines. Combining increasing doses of diazepam with behavioral tests revealed the physiological role of the knocked-in α subunit (insensitive to benzodiazepines). Such differential studies have clarified the respective functions of different benzodiazepine-sensitive α subunits in sedation, motor impairment, myorelaxation, anxiety, and pain. Behavioral tests clearly demonstrated that the $\alpha 1$ subunit mediates sedation, but other α subunits (**Figure 4**) may be involved in myorelaxation or motor impairment.

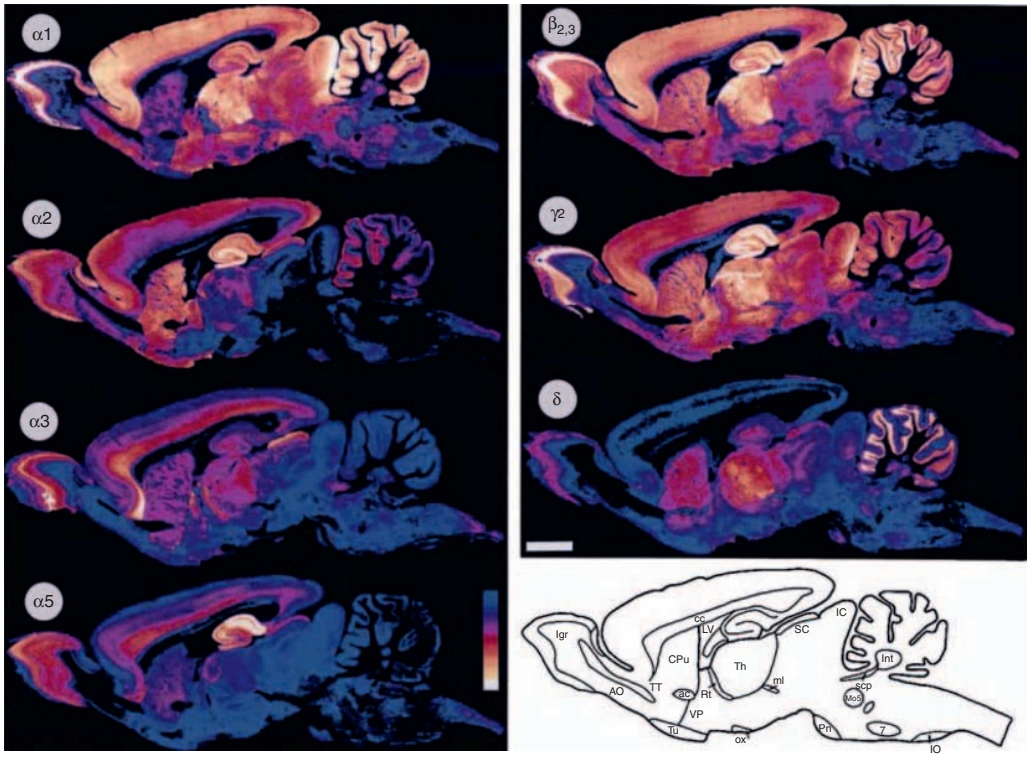

Figure 4 Distribution of various $GABA_A$ subunits in the rat brain: α-benzodiazepine-sensitive subunits, $\beta 2$–3, $\gamma 2$, and δ subunits. Color-coded images of regional variations in immunohistochemical staining of seven $GABA_A$-receptor subunits. Parasagittal sections of adult rat brain, processed for immunoperoxidase staining with subunit-specific antibodies, were digitized by high-resolution computer-based image analysis system. For each subunit, intensity of pixels was color-coded by a normalized scale (strongest signals in white and background in dark blue). Note minimal signal in white matter: regions rich in fiber bundles (e.g., brainstem reticular formation) are only lightly stained for each subunit. Cytoarchitectonic landmarks are indicated in the schematic drawing. Scale bar = 2 mm. Igr, internal granular layer of olfactory bulb; AO, anterior olfactory nucleus; TT, tenia tecta; CPu, caudate putamen (striatum); ac, anterior commissure; Tu, olfactory tubercle; cc, central canal; LV, lateral ventricle; VP, ventral posterior thalamic nucleus; Rt, reticular thalamic nucleus; Th, Thalamus; ox, optic chiasm; ml, medial lemniscus; SC, superior colliculus; IC, inferior colliculus, Pn, pontine nuclei; Mo5, motor trigeminal nucleus; scp, superior cerebellar peduncle; Int, intercalated cerebellar nucleus; 7, facial nucleus; 10, dorsal motor nucleus of vagus. Reproduced, with permission, from **Figure 1** in Fritschy JM and Möhler H (1995) $GABA_A$-receptor heterogeneity in the adult rat brain: Differential regional and cellular distribution of seven major subunits. *The Journal of Comparative Neurology* 359: 154–194, with permission.

GABA in Basal Ganglia and Associated Neurodegenerative Diseases

The basal ganglia (or *basal nuclei*), the major components of the 'reptilian brain,' are situated deep in the forebrain (**Figure 5**). They consist of the *striatum*, which includes the *putamen* and the *caudate nucleus*; the *external globus pallidus (GPe)*, the *internal globus pallidus (GPi)*, the *caudal subthalamic nucleus (STN)*, and *the substantia nigra pars compacta (SNc) pars reticulata (SNr) pars lateralis (SNl)*. The basal ganglia are involved in cognitive functions such as learning, and especially in motor control. The main input is from the *cerebral cortex* to the *striatum*. The striatum is regulated by dopaminergic input from the *SNc* acting on D1 and D2 types of dopamine receptors. *The basal ganglia* operate through two pathways: one excitatory (direct pathway, on left in **Figure 5**) and one inhibitory (indirect pathway, on right in **Figure 5**). Working together, they process corticofugal information and respond with appropriate output signals. From the main output nuclei, *SNr* and *GPi*, signals are sent to the *ventral nuclei of the thalamus*, and from there back to *motor cortex*. By disinhibiting cortical motor neurons, the excitatory pathway initiates a movement that is modulated by the inhibitory pathway. In this system, GABAergic neurons are crucial for the maintenance of a good equilibrium between excitation and inhibition. In basal ganglia disorders, this equilibrium is disturbed owing to degeneration of specific neuronal groups – as illustrated by some well-known neurological diseases.

Huntington's Disease

Huntington's disease, a well-characterized genetic disorder, causes defective inhibition in supraspinal structures of the motor network (**Figure 6(a)**). Early selective degeneration of striatal enkephalin-containing GABA neurons projecting to GPe diminishes the moderating striatal influence on motor cortex mediated via the indirect pathway and thalamus. In spite of compensatory upregulation of GPe postsynaptic $GABA_A$ receptors,

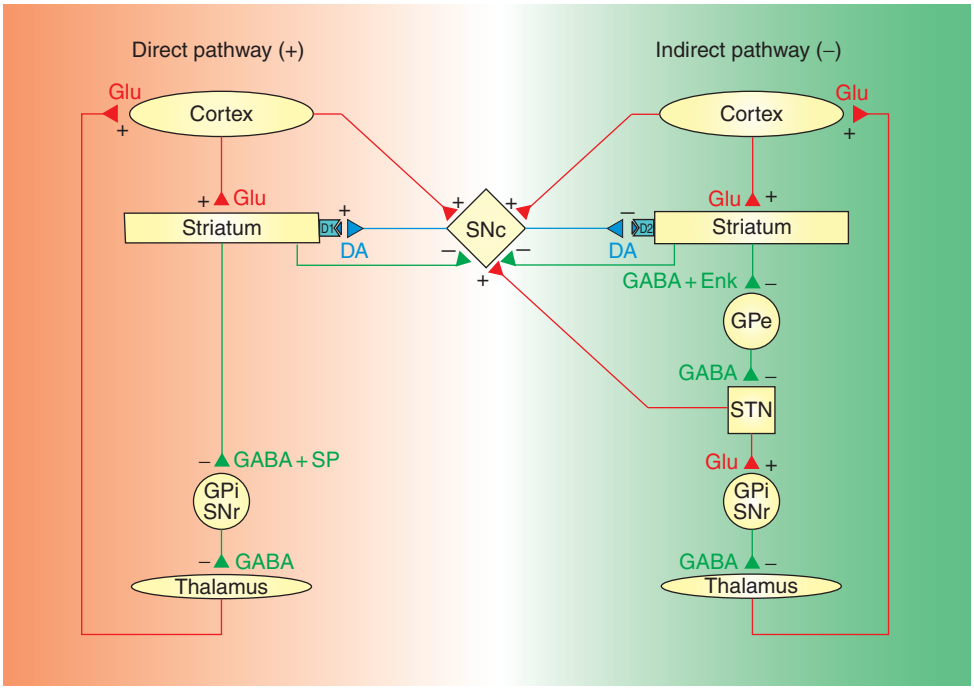

Figure 5 Internal architecture of mammalian basal ganglia. In the two main pathways, excitatory glutamatergic connections are in red, inhibitory GABAergic ones in green. The major excitatory projections to striatal neurons come from the motor and prefrontal cortex (prefrontal insular cortex, cingulate sensory motor area, supplementary motor and premotor areas). The direct pathway (at left) relays two successive inhibitions (to GPi–SNr and then to thalamus) that make its overall output to thalamus excitatory (by disinhibition). The indirect pathway (at right) includes three inhibitory relays that make its overall output to thalamus inhibitory. Note that striatal inhibitory neurons in the direct pathway contain substance P (SP) as well as GABA, whereas enkephalin (ENK) is present in the striatal GABAergic neurons of the indirect pathway. These different peptides may modulate the postsynaptic inhibitory action of GABA. The two types of striatal neurons also express different dopamine (DA) receptors (D1 for the direct pathway and D2 for the indirect one). Because D1 receptors are excitatory and D2 receptors inhibitory, DA from the SNc tends to activate the direct pathway and inhibit the indirect pathway, thus enhancing signals to the thalamus–which in turn activates the motor cortex. Note that SNc is also activated by axons from the cortex and the STN, and inhibited by negative feedback from striatal neurons. Glu, Glutamate; D1 and D2, dopaminergic receptors D1 and D2; GPi and GPe, internal and external globus pallidus; STN, subthalamic nucleus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulate.

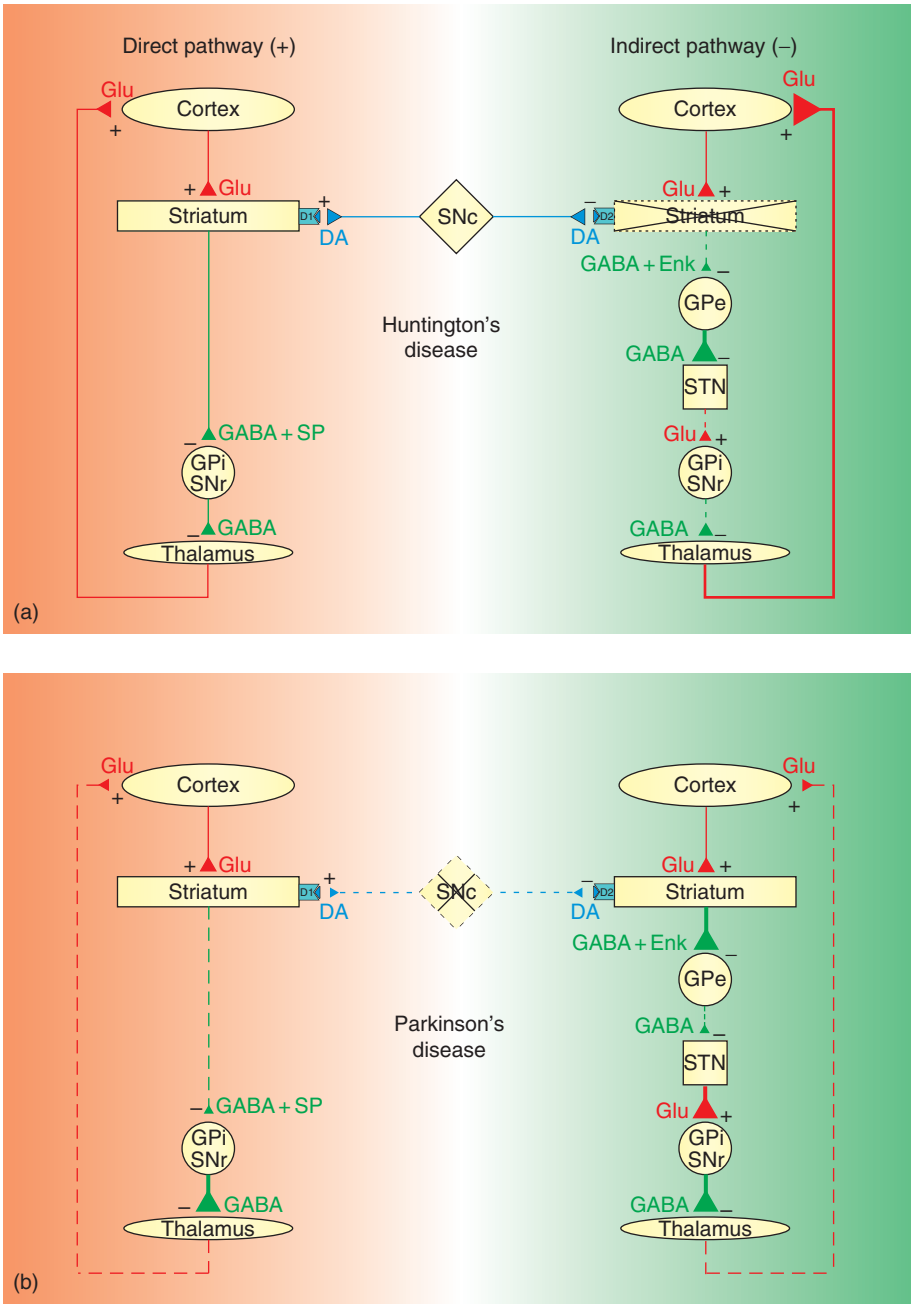

Figure 6 Involvement of GABAergic transmission in Huntington's and Parkinson's diseases. (a) Huntington's disease is characterized by selective degeneration of striatal GABAergic neurons which contain enkephalin and are inhibited by SNc via D2 receptors. Consequently the inhibition of thalamus by the indirect pathway is much weakened, resulting in over-excitation of cortical neurons involved in motor control. (b) In Parkinson's disease, the dopaminergic substantia nigra pars compacta (SNc) degenerates, with opposite consequences for the direct and indirect pathways: reduced dopaminergic inhibition of striatal neurons of the indirect pathway and reduced excitation of striatal neurons of the direct pathway. Overall, diminished activation of thalamus has a depressant effect on cortical motor neurons, making movement initiation more difficult. Abbreviations as in **Figure 5**.

deregulated thalamic activity overexcites cortical motor areas, leading to characteristic motor symptoms. In Sydenham's chorea – a more benign condition, seen most often in children as a temporary after-effect of infections such as rheumatic fever – Valproate has proved useful for the treatment of choreic manifestations.

Parkinson's Disease

The selective degeneration of dopaminergic neurons in pars compacta of *substantia nigra* (**Figure 6(b)**) leads to tremor and increasing rigidity, at later stages progressing to a drastic reduction (bradykinesia) or complete absence

of movements (akinesia). Albeit not directly involved in the primary neuronal degeneration, GABAergic neurons are essential components of the neural circuits that generate the typical movement disorders. In healthy individuals, by opposite actions on striatal neurons of the direct and indirect pathways, the nigrostriatal projections facilitate cortical initiation of movements. When this dopaminergic track degenerates in Parkinson patients, the direct pathway, which is excitatory, receives less D1 receptor-mediated stimulation, whereas the inhibitory indirect pathway is less inhibited via D2 receptors. As a result of the stronger GABAergic action, the overinhibited thalamus no longer activates motor cortical neurons. Consequently, the generation of movements is seriously impaired.

The most effective treatment of Parkinson disease is pharmacological: the loss of dopamine production is compensated for by the administration of the dopamine precursor L-dopa and dopaminergic agonists and by the inhibitors of dopamine breakdown. When drug therapy becomes less effective, Parkinsonism can be alleviated surgically by direct thalamotomy and pallidotomy. More recently, deep brain stimulation, by an electrode implanted in *the thalamus, the subthalamic nuclei* or *the GPi,* has proved quite effective. The electrode for deep brain stimulation is connected to a pacemaker-like electrical stimulator, implanted under the skin. Unlike lesional surgery, this approach minimally damages the brain; the stimulation can even be automatic, the deep electrode applying suitable stimulation whenever it senses aberrant neuronal activity.

Tourette Syndrome

Like Huntington's and Parkinson's diseases, Tourette syndrome is caused by dysfunction of the thalamus, basal ganglia, and frontal cortex. It is an inherited neuropsychiatric and movement disorder, associated with uncontrolled speech and motor tics. Tourette syndrome is probably a multigenic disease. Underlying mechanisms enhance dopaminergic function. Through multiple connections with the striatal pathways, dopaminergic hyperactivity could lead to overall circuit *disinhibition.*

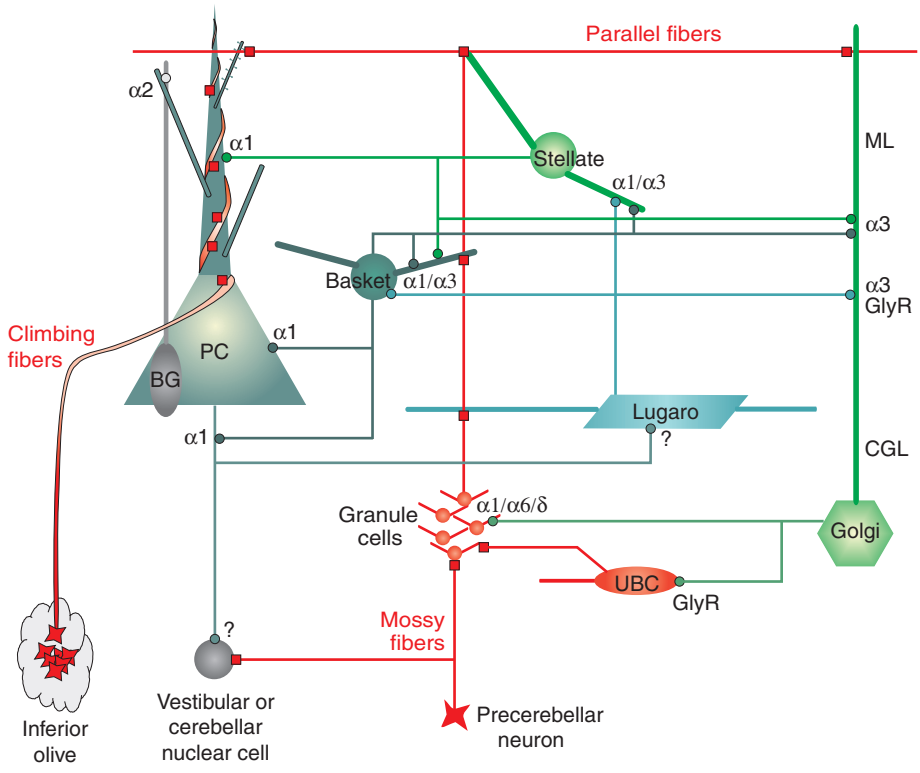

Figure 7 GABAergic networks of the cerebellar cortex. Excitatory neurons are red; inhibitory ones in different types of green. Thick lines are dendrites and thin lines axons. At inhibitory synapses (green circles) the main postsynaptic $GABA_A$ receptor ($GABA_AR$) subtype(s) or glycine receptors (GlyR) are indicated. Glutamatergic synapses are denoted by red squares. Note that Lugaro cells inhibit all cell types in molecular layer except Purkinje cells (PC). In turn, their only inhibitory input comes from PCs; the subtype(s) of GABARs on Lugaro cells is not known. Basket/stellate cells express both α1- and α3-$GABA_ARs$. Bergman glia (BG) express an unusual $GABA_AR$ subtype, containing the α2 and γ1 subunit, which is enriched at sites of contact with PC. PC, Purkinje cell; BG, Bergman Glial Cell; GCL, granule cell layer; ML, molecular layer; UBC, unipolar brush cell. Adapted from **Figure 1** in Fritschy JM and Panzanelli P (2006) Molecular and synaptic organization of $GABA_ARs$ in the cerebellum: Effects of targeted subunit gene deletions. *Cerebellum* 5: 275–285, with permission.

GABA and Cerebellar Disorders

Through reciprocal links to both motor cortex and spinal cord, the cerebellum exerts an important control over patterns of motor signals initiated in the cortex and their spinal execution. As in the basal ganglia, $GABA_A$ receptor-mediated inhibition is predominant in the internal organization and the output of the cerebellum (**Figure 7**). Hence, many symptoms of cerebellar ataxia arise from GABAergic deficits. For example, *the stiff-person syndrome*, associated with cerebellar ataxia, can result from an autoimmune disease targeting GAD, the enzyme necessary for GABA synthesis. In this kind of progressive cerebellar ataxia, a high anti-GAD antibody titer in the cerebrospinal fluid (CSF) is an early indication of decreased GABAergic transmission and deregulation of the output signals of the cerebellum. In the same vein, deficiency of a GABA transporter (GAT1) causes tremor, ataxia, and increased GABA-induced tonic conductance in cerebellar neurons. Another cerebellar pathology, *Angelman's syndrome*, is characterized by mental retardation and motor symptoms, including ataxia, as well as a genetic abnormality of the maternal chromosome 15q11–13. This gene encodes the β3 $GABA_A$ receptor subunit: albeit important constituents of $GABA_A$ receptors, β subunits, unlike α subunits, have no role in Cl^- conductance.

In the internal network of the cerebellum, $GABA_A$ receptors are differentially segregated as a function of cell types and synaptic circuits (**Figure 7**). Compared with the strong effects of acute pharmacological blockage or stimulation of $GABA_A$ receptors, some mutants with profound loss of cerebellar $GABA_A$ receptors paradoxically have only minor impairments in motor function, presumably owing to compensatory changes during development.

Spasticity

Painful muscle spasms are a feature of a variety of neurological disorders, notably multiple sclerosis and spinal injury or degenerative changes (as in amyotrophic lateral sclerosis). Such spasms, caused by spinal hyperreflexia, can be prevented by the $GABA_B$ selective agonist Baclofen; as a lipophilic agent (unlike GABA), Baclofen can be given orally, or most effectively, intrathecally.

Acknowledgments

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See also: Ataxia; Basal Ganglia; Huntington's Disease; Parkinson's Disease: Definition, Diagnosis, and Management; Tourette Syndrome.

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Gait Disturbances in Parkinsonism

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Glossary

Cueing – Providing external stimuli as a movement target or reference to initiate or facilitate walking.
Fall – An event that results in a person coming to rest unintentionally on the ground or other lower level and not as the result of a major intrinsic event or overwhelming hazard.
Freezing of gait (FOG) – An episodic inability to generate effective stepping at the onset of or during ongoing walking and turning.
Gait – Alternating steps of left and right lower limbs, that leads to forward progression while being in an upright position.

Introduction

Parkinsonian gait is classified as a hypokinetic, rigid type of gait disorder within the wider spectrum of neurological gait disorders (**Table 1**). The underlying mechanisms responsible for gait disturbance in Parkinson's disease (PD) are heterogeneous and complex. Gait is affected by muscle rigidity, hypokinesia, and bradykinesia. Several additional or underlying factors influence gait disturbance, such as: decreased force generation, dysrhythmicity, left/right dyssynchrony, abnormal scaling of step size, abnormal preparation and execution of motor set, as well as frontal dysexecutive syndrome. In addition, the ability to initiate and maintain locomotion is heavily dependent on postural reflexes, which are frequently abnormal in PD. The contribution of each dysfunction to the clinically observed 'parkinsonian gait' differs from one patient to another and in the same individual at different times of the day ('On'–'Off') or stage of the disease.

The Evolution of Gait Disturbance

Clinically significant gait disturbance is rare at the time of diagnosis, but more common among patients with motor symptoms onset in older age. If important gait disturbance or postural instability (early falls) are the presenting symptoms or early problems, atypical parkinsonism or Parkinsonism-plus syndrome should be suspected. The main differential diagnosis in such early fallers is: progressive supranuclear palsy (PSP), multiple-system atrophy (MSA), normal-pressure hydrocephalus (NPH), higher level gait disorder (HLGD), or vascular parkinsonism, while PD is less likely to be the final diagnosis. As PD progresses, gait disturbances are very common and constitute 'the leading edge of disability.' Eventually, most patients will experience gait disturbances, dependency, and significant fall risk (Hoehn & Yahr stages 3–5). Loss of independent walking may lead to partial use of a wheelchair, but some limited ability to walk will nearly always remain. In the advanced stages of parkinsonism, wheelchair use may be the last resort to avoid falls and all their devastating consequences.

Since the introduction of levodopa, the relationship between PD progression and deterioration of gait has become more complex. Because of recent therapeutic advances, patients can often walk in the 'On' state, even in the advanced stages of the disease, whereas akinesia can be seen throughout the course of the disease as part of the 'Off' state. Furthermore, the beneficial effects of levodopa treatment have created new types of gait disturbances, such as choreic or dystonic (dyskinetic) gait and 'On'-freezing. Moreover, levodopa therapy and functional neurosurgery have increased the PD patient's life expectancy and years of mobility. Consequently, disturbed postural reflexes, orthostatic hypotension, severely distorted posture, as well as cognitive disturbances have become major contributory factors to gait disturbance in the advanced stages of PD.

Parkinsonian Gait: Special Features

Parkinsonian gait is slow, with reduced stride length, decreased cadence (steps per minute), and an increased proportion of the gait cycle spent in the double limb support phase of stance. Decreased arm swing can also be considered as a hypokinetic and bradykinetic gait feature, partially influenced by rigidity as well. Asymmetrically decreased arm swing while walking is commonly observed by the spouse as a very early or even as a presenting motor symptom of parkinsonism.

Probably, the most fundamental gait disturbance indicative of underlying basal ganglia dysfunction is impaired stride length regulation. However, the basal ganglia regulate not only the automatic maintenance of the scale of movement (motor set) but also the running of each

Table 1 System-oriented classification of gait syndromes

Peripherally originating gait syndromes
Musculoskeletal
• Joints, bones, ligaments, tendons or muscles, peripheral nerves, neuromuscular junction
Sensory
• Proprioceptive, vestibular, visual
Centrally originating gait syndromes
Spinal
• Spastic paraparetic
• Sensory ataxic
Pyramidal
• Spastic
• Paretic
Cerebellar
• Ataxic
Extrapyramidal
• Bradykinetic/hypokinetic
• Rigid
• Dyskinetic
• Episodic
Frontal
• Dysequilibrium
• 'Apractic'
Unclassified
• Cautious

Table 2 Locomotion gait disturbances in parkinsonism

Continuous	*Episodic*
• Shortened stride with increased cadence gait	• Freezing of gait
• Bradykinetic gait/ turning	– Start/turning hesitation
• Shuffling gait/ turning	– Tight quarters hesitation
• Dysequilibrium gait	– Hesitation while reaching destination
• Fear of falling gait/ turning	– Hesitation during mental over-load or stressful situations
• Dysrhythmic gait	• Festinating gait
• Dyskinetic gait	
• Stiff gait/turning	

component of the motor plan in a timely manner (internal cue production). Recent findings of higher step-to-step variability of stride duration and increased variability of leg muscle activation in PD bear evidence of this fact. Stride length is normalized by the use of visual cues or strategies that increase attention to gait performance. In contrast, tasks that compete for the individual's attention while walking (dual task distraction) decrease gait speed, increase stride-to-stride variability (dysrhythmicity) and decrease left/right swing synchronization. Normal locomotion in PD is a motor task influenced by cognition. Furthermore, the vulnerability of locomotion to dual tasking is directly correlated with the performance of executive function and attention. In summary, parkinsonian gait is primarily the result of abnormal scaling of stride length (motor set) but variable timing of dynamic stepping may also reflect the basal ganglia deficit, and rely on allocation of extra cognitive resources (**Table 2**).

Freezing of Gait

Freezing of gait (FOG) is a typical episodic gait disturbance, which may occur suddenly against the background of relatively good and fluent locomotion. Recently a clinical definition for FOG was proposed by Giladi and Nieuwboer: 'an episodic inability (lasting seconds) to generate effective stepping in the absence of any known cause other than parkinsonism or high level gait disorders. It is most commonly experienced during turning and step initiation but also when faced with spatial constraint, stress, and distraction. Focused attention and external stimuli (cues) can overcome the episode.'

Patients struggle with FOG most frequently in their home and as part of the 'Off' period, demonstrating that FOG is primarily a consequence of hypodopaminergic state. Freezing episodes are difficult to observe in the doctor's office or the gait laboratory, situations which may evoke higher levels of arousal. In contrast, FOG is negatively influenced by dysfunction of the frontal executive system, anxiety or depressed mood.

The severity of freezing seems not correlated with other cardinal features of parkinsonism, supporting its unique and independent pathophysiology. FOG can be classified according to the response to levodopa or apomorphine ('On' vs. 'Off' freezing) or based on the motor state during the episode itself. There are three classical motor response strategies that can be observed during a freezing episode: (1) no movement-akinesia (the patient is not making any observed effort to overcome the block), (2) trembling in place (rapid, 3–6 Hz, synchronized movement of both legs as part of an attempt to overcome the block but no significant movement forward is seen), and (3) shuffling forward (the patient makes an effort to overcome the block and is partially successful). Stepping is abnormally small and rapid and no effective step is taken.

Patterns of leg muscle activation in relation to freezing sometimes show reciprocal and sometimes simultaneous EMG activity in flexors and extensors. EMG activity during the steps preceding freezing indicate a premature timing in the lower limb muscles with overall preservation of reciprocity, pointing to a disturbance of central gait cycle timing as a trigger for FOG. Recent work has associated the development of FOG also with abnormal synchronization between left and right leg stepping as well as with the deterioration in executive functions.

The risk of developing freezing in PD is increased with disease progression, but is generally more common among patients who have abnormal gait and postural instability with only little tremor. FOG also often occurs in other parkinsonian syndromes. It is frequent and disabling in PSP, multiple-system atrophy parkinsonian type (MSA-P), vascular parkinsonism and HLGD.

As PD progresses, FOG becomes a major cause of disability and falls with subsequent loss of independency. FOG has been shown to have a major effect on quality of life, over and above its effect on gait and mobility. Therefore, it deserves special attention and aggressive treatment.

Festinating Gait

Festinating gait is another episodic disturbance of locomotion in parkinsonism. It may be part of the onset or termination of freezing, as described above, but can be observed by itself. Its frequency is undetermined, but it is known to be more common in older patients and in those with more advanced PD. It consists of rapid small steps taken in an attempt to keep the center of gravity (COG) above the feet while the trunk leans forward involuntarily and shifts the COG forward. Festination and freezing are related phenomena and may also share a common etiology.

Assessment of Gait

The importance of gait deficits in PD warrants a thorough gait assessment as part of the basic clinical evaluation. Two timed tests of gait can be used: (1) the 10-m walk test and (2) the timed 'up-and-go' (TUG) test. In the 10-m walk test the patient is asked to perform straight-line walking, enabling the measurement of gait speed, step length, and step frequency. For the TUG, the patient is asked to get up from a chair, walk for 3 m in a comfortable speed, turn around, walk back to the chair and return to a sitting position. These are two informative bed side tests, providing an opportunity to evaluate general motor function, comprehension as well as the quality of gait initiation, locomotion, turning, and gait termination. In both tests the patient should be asked to walk at whatever speed feels most comfortable. Such an examination should be performed in an open space free of obstacles to allow for the patient's best performance. If the patient is complaining about freezing, the examiner should try to provoke freezing episodes by testing the patient 'Off' drugs and asking to perform turns, walk through narrow spaces, and step up and down stairs to differentiate between freezing (locomotion gait disturbance only) and akinesia (which also effects stairs climbing in addition to walking). Also, for assessment of gait in general it is of special importance to distinguish between performance in 'On' or 'Off' state. Various instrumental gait assessment systems allow for measuring cadence, stride length, velocity, and double limb support phase objectively. For the assessment of the dynamic aspects of gait, like stride-to-stride variation, left/right leg synchronization, the use of cues and the effect of dual tasking, locomotion should be assessed over a longer period of time (2–6 m) and over multiple steps. Ambulatory monitors are now used for quantifying walking and general mobility over 24-h period in daily life.

The clinical evaluation and quantification of FOG is difficult because of the highly variable and transitory nature of this motor disturbance. Two FOG questionnaires (FOG-Qs) have been validated; the original one which assesses FOG but also general mobility; and the New FOG-Q which includes a video to ensure uniformity, has a screening part to define freezers, assesses FOG severity and disability separately and is validated against care givers perception.

Treatment of Parkinsonian Gait

Levodopa, the most effective and commonly used antiparkinsonian drug, has significant and long-lasting effects on parkinsonian gait. Its use leads to improvements in stride length, velocity, and synchronization of movements, double-support time, and control of foot landing. The addition of external cueing to enhance motivational or arousal processes will yield further improvements in stride length. The effect of levodopa on locomotion occurs mainly through mechanisms involved in control of force and amplitude, as it has smaller effects on stride-to-stride time variation. The symptomatic benefit of levodopa is greater in younger patients, suggesting that gait disturbances in the older PD population are more profoundly related to nondopaminergic mechanisms. However, the motor complications of long-term treatment with levodopa also have to be considered. Especially dyskinesias (dystonia and chorea) have serious implications with regard to gait. These hyperkinetic complications are much more common in younger patients. Severe painful foot or leg dystonia as well as violent generalized or crural chorea/ballism, frequently aggravated by walking, can form a major problem in advanced PD patients. Patients often have to choose between an akinetic 'Off' state with freezing or an 'On' state with disabling dyskinesias.

Dopamine agonists, amantadine, monoamine oxidase type B(MAO-B) inhibitors, and C-*O*-methyltransferase (COMT) inhibitors are all known for their symptomatic benefits on almost all parkinsonian parameters, including gait disturbances. However, there have been no prospective, double blind, placebo-controlled studies

to assess the effect of any of these drugs on parkinsonian gait as the primary outcome. In addition to medication, it is generally agreed that nonpharmacologic treatment and, in particular, physiotherapy can improve parkinsonian gait disturbances.

Treatment of FOG

Freezing is considered to be among the more therapy-resistant symptoms in PD. 'Off' freezing may respond to dopaminergic treatment, whereas 'On' freezing sometimes improves by lowering the dosage of dopaminergic medications.

One of the most characteristic features of freezing is its response to cueing. Cueing may heighten attention to the motor task and can be used in addition to a variety of behavioral and attentional strategies. These strategies are of immediate help to overcome a freezing episode and because of their effectiveness, noninvasiveness and availability can be recommended. However, whether training with such strategies is also effective in reducing the occurrence of freezing episodes needs further investigation.

Levodopa and MAO-B inhibitors are the two classes of drugs which have been shown to have special effects on FOG in prospective double blind, placebo controlled studies. However, any dopaminomimetic treatment that will decrease the severity or duration of the 'Off' phase will decrease FOG. The effect of dopamine agonist drugs on FOG is not clear, but it has been suggested that they might increase its prevalence. In contrast, apomorphine injections have been reported to produce a good symptomatic effect on severe freezing episodes where other antiparkinsonian agents failed. L-Threo-3,4-dihydroxyphenylserine (DOPS) (a chemical precursor of norepinephrine) has been proposed to have a unique symptomatic effect on FOG especially in the 'Pure freezing syndrome' but further studies are needed.

Rehabilitation Treatments of Gait Disturbances

Physiotherapy for gait disorders in PD can be of benefit, especially by improving the speed of walking through a variety of training methods. Treadmill training has been shown to have symptomatic benefit on gait speed, especially after intensive practice. In addition, walking on a treadmill can be used as an external pacemaker, improving the timing variability of gait.

To overcome the typical problem of automatic maintenance of the appropriate scale and timing of gait, cues have been used for immediate gait correction and as a training method with demonstrated benefits. As stated before, external cues (temporal or spatial stimuli) as well as attentional strategies have been successful in overcoming episodic gait disturbances.

Functional Neurosurgery for Gait Disturbances

Stereotactic neurosurgery is an increasingly common approach for treating patients with advanced PD. Bilateral high-frequency, deep brain stimulation (DBS) of the globus pallidus internus (GPi) or the subthalamic nucleus (STN) have shown significant beneficial effects on parkinsonian gait. It is most effective for patients with a clear response to levodopa even if short lasting. STN stimulation improves levodopa-responsive FOG in most patients but less consistently than levodopa itself and in some cases it may aggravate gait disturbance. Preliminary data suggests that unilateral or bilateral stimulation of the pedunculopontine nucleus (PPN) in the upper brainstem can be an alternative approach for the treatment of levodopa-resistant gait and postural disturbances.

See also: Akinetic-Rigid Syndrome; Freezing of Gait; Gait Ignition Failure; Parkinson's Disease: Definition, Diagnosis, and Management; Parkinsonism: Genetics; Parkinsonism: Vascular; Parkinson's Disease: Genetics.

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Gait Ignition Failure

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Glossary

Gait pattern – The cadence, base of support, and limb and body trajectories that characterize a patient's walking pattern while starting to walk, walking in a straight line, turning, and tandem walking. Gait patterns are neurological signs that generate a differential diagnosis as no gait pattern is pathognomonic of a single disease.
Locomotor networks – The spinal and brainstem neural circuits that can generate stepping adequate for walking forward without input from the brain hemispheres.

Definition and History

Gait ignition failure was a term invented by Professor David Marsden to describe freezing of gait. The term captured the apparent impairment of engaging the lower locomotor networks of the brainstem and the spinal cord crucial for stepping that characterize freezing of gait. Gait ignition failure was first used in a paper describing higher-level gait disorders, gait patterns that could not be explained by motor, and sensory and coordination signs that are elicited by the neurological examination.

Freezing of gait is a dramatic neurological sign that has caught the attention of many clinicians who have used a variety of terms for the clinical phenomenon. It has been described with various terms that (1) describe the phenomena such as freezing, primary progressive freezing, gait ignition failure, trepidant abasia, or magnetic gait; (2) imply types of neurological dysfunction such as gait apraxia; or (3) describe pathology with which freezing is associated such as vascular parkinsonism or lower-half parkinsonism.

Freezing of gait is the most widely accepted term for describing the difficulties in initiating gait or maintaining gait. Freezing is not a perfect term for the phenomenon, as it implies no movement, while freezing of gait is often associated with the trembling of the legs. However, until we understand the origin of this neurological sign, it seems that this term should be used in preference to gait ignition failure and the other synonyms described earlier.

See also: Freezing of Gait; Gait Disturbances in Parkinsonism; Primary Progressive Freezing Gait.

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Gaucher's Disease

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Glossary

Gaucer's disease – The most common lysosomal storage disease.
GBA associated parkinsonism – Mutations in the GBA gene have been associated with the late development of parkinsonism.
***GBA* gene** – The gene located on chromosome 1q21 and is coding the synthesis of glucocerebrosidase.
Glucocerebrosidase (GBA) – The enzyme responsible for the degradation of the Glucocerebroside (a glycolipid component of the cell membrane) which is affected in Gaucher's disease due to mutation in the *GBA* gene.

Pathogenesis/Epidemiology

Glucocerebroside is a basic glycolipid component of the cell membrane, which is degraded by the enzyme glucocerebrosidase (GBA) to glucose and lipid, with saposin c acting as a cofactor protein in the reaction. The gene responsible for the synthesis of GBA is 7 kb in size and is sited on chromosome 1q21. More than 200 mutations have been described in the GBA gene; however, the mutations N370S (the commonest one), L444P, and 84GG are found in about 80% of mutation carriers. Among Ashkenazi Jews, the prevalence of those three mutations is even higher, reaching over 90%.

Gaucher's disease (GD) has a diverse dispersion worldwide with a carrier prevalence of 1% or about 1 out of 40 000 births in western countries. The frequency is lower in Asian countries: for example, the incidence is 1 out of 330 000 births in Japan. There are several ethnic groups with higher prevalence in the general population, among them Ashkenazi Jews who have a carrier frequency of 1 out of 15 people and an incidence of 1 out of 450–500 people. The second ethnic group with especially high frequency lives in the Norrbotten region of northern Sweden, with a higher frequency of Type 3 GD (see below) and an incidence of 1 out of 50 000 people.

Clinical Presentation

GD is a lysosomal storage disease. Because of mutations in the GBA gene, the activity of the enzyme is reduced or absent and glucocerebroside accumulates in the macrophages which constitute the Gaucher cell. The main areas where glucocerebroside accumulations are found in the senescent leukocytes and erythrocytes that are phagocytized and degraded by macrophages. Other areas where glucocerebrosides accumulate are the bone marrow, liver, spleen, lungs, and brain, all of which are classically involved in the clinical picture.

There are three forms of the clinical expression of GD:

Type 1 – nonneuronopathic
Type 2 – acute neuronopathic
Type 3 – chronic neuronopathic

All three forms are inherited in a recessive mode. There are several typical clinical features which are seen in most GD cases. Splenomegaly, hepatomegaly, anemia, thrombocytopenia, osteopenia, bone pain, and pathologic fractures can be observed in most Type 1 and in some of Types 2 and 3 cases. Neurological involvement is responsible for the clinical manifestations in Types 2 and 3.

Type 1 GD

This is the most common form of GD, with a prevalence of 1 out of 40 000 among the general Caucasian population. There is significant diversity in the age at diagnosis of patients with Type 1 GD, but two-thirds of the patients will have been diagnosed by 20 years of age. The most prevalent sign detected on clinical examination is splenomegaly, which can be an incidental finding on a medical examination in asymptomatic people or the cause of abdominal discomfort that motivates the individual to seek medical counseling. There are several symptoms associated with splenomegaly, including excessive energy expenditure and growth delay, as well as the trapping of thrombocytes in the spleen, which result in easy bruising. Hepatomegaly with different degrees of liver dysfunction is the next most common clinical presentation of GD Type 1. Another common clinical presentation is skeletal changes which can manifest as painful episodes that are the result of bone ischemia. Other skeletal changes include a lower than the average level of bone mineral density and pathological fractures or progression into avascular necrosis. The cortical thinning and widening of the medullary cavity of the metaphysis and adjacent diaphysis is a typical radiological finding of Erlenmeyer flask deformity of the distal femur. Other less common features include puberty delay, interstitial lung disease,

malignancies in the hematopoietic system (especially multiple myeloma) and a high level of angiotensin-converting enzyme (ACE) in the blood.

The natural history of GD is varies greatly, from the individual's being able to live a normal life in the milder form to death within the first decade of life in the severe form if untreated. Death is the result of complications such as severe thrombocytopenia with bleeding, severe asthenia and complications of infections due to splenectomy or from severe bone disease. With currently available treatment, Type 1 GD patients can expect to live an almost normal life with a life expectancy of 60–90 years.

Type 2 GD

The second type of GD has a very poor prognosis, with no clinical benefit of the new treatment on the disease course. The acute neuronopathic form is characterized by a rapidly progressive, early onset disease with severe neuroectodermal manifestation and death in the first few years of life. The clinical syndrome includes ichthyosis, disruption of the epidermal layers, oculomotor dysfunction, disruption of saccadic eye movements, bulbar palsy, hypertonia, rigidity, swallowing disturbance, seizures, strabismus, and eventually a failure to thrive, progressive psychomotor deterioration and death.

Type 2 GD can also be manifested in the uterus, affecting the embryo by causing nonimmune hydrops with or without ichthyosis. Pathologic examination of the brains of those embryos demonstrated extensive neuronal loss, especially in the frontal cortex, thalamus, cerebellum, the basal ganglia, and pons.

Type 3 GD

The third type of GD has a diverse course but most of the patients die in their second decade of life because of progressive neurological manifestations. The only available long-term prospective follow-up study was conducted in the Norrbotten region of Sweden: the mean life expectancy was 11 years before the advent of modern enzyme replacement therapy, but has now been extended to the third and even to the fifth decade of life.

The chronic neuronopathic form has slower rate of progression compared to the galloping form. There are two major types: the one typically reported from the Norrbotten region of Sweden has a mutation at L444P location and is associated with extensive involvement of visceral organs, oculomotor disturbance, seizures, and cognitive impairment. The second type is associated with mutation at D409H location with the development of early corneal opacities and calcifications of the aortic and mitral valves.

The Gaucher Gene and Parkinsonism

The last 10 years have witnessed an increasing interest in GD and several lines of evidence for an association between Type 1 GD and parkinsonism have recently emerged. Some GD patients manifest the disease very late in the form of parkinsonism of the akinetic-rigid type with manifestation of the first symptoms during the fifth or sixth decade of life. However, the introduction of genetic screening of patients with Parkinson's disease (PD) for mutations in the Gaucher gene has revealed cases of typical PD who were found to be homozygote or compound heterozygote for the Gaucher mutations. The relationships between GD and PD have a third potential level of association. Recent studies have demonstrated that healthy people who are heterozygotes, that is, carrying only one of the GD-related mutations, are at higher risk to develop classical PD. About 17% of Ashkenazi Jews with PD carry mutations on the GD gene, and being heterozygote for the Gaucher's mutations, significantly increases the risk of developing classical PD between the fifth and seventh decade of life. The exact mechanism that links those two diseases is still unclear but an association was observed between the presence of mutations which are known to cause more sever GD and an earlier age of PD onset as well as higher risk to develop PD among asymptomatic carriers.

Diagnosing GD

The first steps in diagnosing GD depend on the clinical history of the patient, the physical examination and the laboratory results (including cell blood count, ACE, and liver function enzyme). The appropriate imaging studies include abdominal ultrasound for evaluation of organomegaly, magnetic resonance imaging for evaluation of the involvement of the bone marrow, radiography for identification of skeletal manifestations, and diagnostic bone marrow aspiration for the demonstration of Gaucher cells. The results of a biochemical assessment of the GBA activity in peripheral leukocytes and DNA analysis for the common mutations in the Gaucher gene can strongly support the diagnosis, but both should be considered with the clinical syndrome.

Treatment

The most important therapeutic modality is enzyme replacement therapy with a recombinant GBA that replaces the production of the enzyme from the human placenta. This treatment has led to a revolution in the way patients with GD live and develop. The main disadvantage of this treatment is the high production cost which

Table 1 Gaucher Types

	Type 1 – nonneuronopathic form	*Type 2 – acute neuronopathic form*	*Type 3 – chronic neuronopathic form*	
Common mutation	*N370S*	L444P	*L444P*	*D409H*
Ethnic predilection	Ashkenazi Jews	None	Norrbottenians (Northern Sweden)	Palestinian Arabs, Japanese
Prevalence	1/40 000	1/100 000	1/50 000–100 000	Rare
Clinical manifestation	Organomegaly, easily bruising bone pain	Neuroectodermal manifestation	CNS involvement	CNS involvement
Special feature	None	None	None	Corneal opacities and calcifications of the aortic and mitral valves
CNS involvement	Parkinsonism	Oculomotor dysfunction, bulbar palsy, hypertonia, rigidity, strabismus	Oculomotor disturbance, seizures, and cognitive impairment	Oculomotor disturbance
Enzyme replacement therapy	Indicated for symptomatic patients	Not indicated	Indicated for visceral involvement	Indicated for visceral involvement
Life expectancy	60–90 years	2 years	20–40 years	Adolescence

limits its use for the symptomatic nonneuronopathic type as well as the use for patients with Type 3 GD who have severe manifestation of skeletal disease and a significantly abnormal blood count or organomegaly.

The recommended dose of the recombinant enzyme ranges between 30 and 60 unit kg^{-1}, with the first signs of improvement being seen in the laboratory results followed by decrease in the organomegaly and then improvement in skeletal disturbances. This pattern of recovery can last several years and a gradual decrease in dosages can be considered but only when there is a significant improvement in all measures.

This treatment has a disadvantage in the neuronopathic types (Types 2 and 3) because of the very low penetrance of the recombinant enzyme through the blood–brain barrier. As a result, the effect of the treatment and the damage to the CNS are inconclusive.

If enzyme replacement therapy is not effective or available, the next option is a substrate reduction therapy that involves inhibiting glucosylceramide synthase, which has a limited negative effect on glucocerebroside production and has a main influence with improvement on the blood count as well as on organomegaly.

Other treatments, which are less medically accepted include splenectomy. Due to the serious negative effects associated with this procedure, it is limited to cases of uncontrolled thrombocytopenia, severe pulmonary disease, and inferior vena cava syndrome.

Bone marrow transplants have a high mortality rate and are used sparingly for the severe neurological form before the onset of disease manifestation.

There is a wide difference in therapeutic results between each of the three forms of GD. While the acute neuronopathic form has a gloomy outcome, we can be optimistic about the final outcome of the other types as a result of the continuously improving treatment modalities.

See also: Parkinson's Disease: Definition, Diagnosis, and Management.

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GDNF (including Nurturin)

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Glossary

AAV2 – Adeno-associated virus serotype 2; a viral vector used to deliver genetic material into the brain by transfecting the host cells.
GDNF – Glial cell line-derived neurotrophic factor, the first discovered member of a novel family of neurotrophic factors composing a subgroup of the transforming growth factor β superfamily.
GFRα-1 – GDNF family receptor α-1, the preferred cell surface receptor for GDNF. It can also be activated by NTRN.
GFRα-2 – GDNF family receptor α-2, the preferred cell surface receptor for NTRN. It can also be activated by GDNF.
NTRN – Neurturin, a member of the GDNF family of neurotrophic factors composing a subgroup of the transforming growth factor β superfamily.
RET – A component of a cell surface receptor complex for GDNF family trophic factors. RET is a receptor tyrosine kinase activated by binding to GDNF (and other family members) in combination with GDNF family receptors like GFRα-1 and GFRα-2.

Definition and History

Glial cell line-derived neurotrophic factor (GDNF) and the related proteins neurturin (NTRN), persephin, and artemin define a novel family of neurotrophic factors composing a subgroup of the transforming growth factor β superfamily. Both GDNF and NTRN have undergone testing in clinical trials for treating Parkinson's disease and are being actively studied for possible use in treating movement disorders. The receptors for GDNF and NTRN are also promising candidates for drug therapy.

GDNF, the first member of this family, was described in 1993 by a research team working at Synergen (a Biotechnology Company in Boulder, CO) searching for trophic factors for dopamine neurons. They identified a 211 amino acid protein proGDNF, which is processed by endoproteolytic enzymes into the 134 amino acid mature trophic factor. This biologically active form of GDNF is composed of two monomers (a homodimer) that migrate in gels with an apparent molecular weight in the 33–45 kDa range. Two additional splice variants of GDNF have been identified, the biological importance of which have not been determined.

NTRN, a related protein with a 42% amino acid homology with GDNF and conserved GDNF-like molecular structural features, was discovered by an academic research team at Washington University, St Louis, in 1996, while searching for other members of the GDNF family. Human PreproNTRN is a 197 amino acid protein that is also processed by endoproteolytic enzymes into a 102 amino acid mature protein.

Unlike other members of the TGFβ superfamily, which signal through the receptor serine–threonine kinases, GDNF family ligands activate intracellular signaling cascades via receptor tyrosine kinases. The receptors of the GDNF family ligands have multiple components. They include a signaling unit, the membrane-spanning receptor tyrosine kinase (RET) and a high-affinity GDNF family receptor (GFR) ligand-binding protein. It is posited that ligand–receptor interactions begin when the dimer binds to its preferred receptor, in the case of GDNF to GFRα-1. Then, the ligand–GFRα-1 complex binds to and stimulates autophosphorylation of RET. The preferred receptor for NTRN is GFRα-2, but both GDNF and NTRN can bind to and activate the other's receptors. Evidence has emerged for another multicomponent receptor complex consisting of GFRα-1 and neural cell adhesion molecule (NCAM), that can be activated by GDNF and NTRN.

Trophic Effects

GDNF exerts both short-term (minutes to hours) and long-term effects (weeks to months) on dopamine

neurons that that have the potential to slow the progression of Parkinson's disease and promote the regeneration of injured neurons. If this therapeutic potential is realized, it would represent an important advance in Parkinson's disease treatment. Consistent results from a number of laboratories suggest that GDNF exerts at least three general trophic actions on dopamine neurons in the substantia nigra: pharmacological, restorative, and neuroprotective.

Pharmacological

GDNF can increase the phosphorylation of tyrosine hydroxylase (TH), the rate-limiting enzyme in dopamine synthesis. Increased invoked release of dopamine is also found. These actions can effectively increase neuronal levels of dopamine and increase dopamine metabolism in the nigrostriatal pathway that undergoes degeneration in Parkinson's disease and the synaptic release of dopamine in the normal, aged, and parkinsonian brain.

Restoration

A long-term effect of GDNF that can last for over a month following a single administration is to increase the number of neurons expressing the dopamine markers TH and the dopamine transporter in the substantia nigra. This suggests that one trophic action is to stimulate recovery of injured/quiescent nigral neurons. Supporting this interpretation is the consistent observation that GDNF promotes increases in dopamine neuron perikaryal size and the number of neurites. In addition, intraputamenal (IP) GDNF administration promotes restoration of dopamine axons in the nigrostriatal pathway of parkinsonian nonhuman primates and, based on increased [^{18}F] dopamine uptake in PET scans, in patients with Parkinson's disease.

Neuroprotection

Nigrostriatal administration of GDNF either shortly before or following a neurotoxic challenge (e.g., 6-hydroxydopamine, MPTP, or methamphetamine) protects dopamine neurons from injury in rodents and nonhuman primates. In part, this action appears to be related to its effects on modulating cell signaling pathways. While the pharmacological effects of NTRN on dopamine neurons are not clear, treatment with NTRN is neuroprotective and restorative for dopamine neurons in rodent and nonhuman primate models of Parkinson's disease.

GDNF and NTRN Therapy for Parkinson's Disease

Following its discovery as the first member of the GDNF family, intensive efforts by a number of research groups were focused on developing GDNF for the clinical treatment of Parkinson's disease. More recently, patent issues have dictated that the other members of the GDNF family also be considered. NTRN, like GDNF, is also a ligand for the GFRα-1 receptor. As mentioned earlier, in animal models of parkinsonism, NTRN shows neuroprotective and neurorestorative actions similar to GDNF. Because GDNF and NTRN demonstrated safe toxicological profiles (with exceptions that will be discussed later) and consistent efficacy in animal models, five clinical trials have been conducted to evaluate their safety and efficacy in treating Parkinson's disease (see **Table 1**).

Efficacy

Significant functional improvements were reported in three of the five clinical trials: Bristol Phase 1 GDNF Trial, Kentucky Phase 1 GDNF Trial, and the Ceregene Phase 1 AAV2-NTRN Trial. In the first year of treatment, all three trials reported significant improvements averaging from 36% to 45% in the off medication motor subscore (Part III) on the Unified Parkinson's Disease Rating Scale (UPDRS), the gold standard for judging efficacy. The two GDNF Phase 1 studies also showed significant improvements in total UPDRS scores both on and off medication.

In contrast to open label Phase 1 trials, Phase 2 trials have a vehicle control arm and are double-blinded. Thus, a placebo component to the striking differences between the Phase 1 and Phase 2 trials cannot be ruled out. However, the placebo effects are typically sporadic and longitudinally inconsistent for individual patients. The consistent improvements in the UPDRS III off medication in the Bristol and Kentucky GDNF trials and the Ceregene NTRN trial strongly suggests that efficacious trophic factor effects in patients are possibly matching those demonstrated in animal models.

Why did the two Phase 2 trials fail? Insuring adequate trophic factor availability to dopamine neurons in the substantia nigra and their axons and synapses in the putamen is critical for achieving the efficacy. There is evidence that the delivery systems used in both Phase 2 studies failed to do this. The first Phase 2 trial used an implanted intracerebroventricular catheter to deliver bolus injections of GDNF monthly. In all likelihood, sufficient GDNF failed to penetrate through the ventricular wall into the parenchyma of the target tissue, the principal components of the nigrostriatal dopaminergic system consisting of the putamen and substantia nigra. The second Phase 2 trial used a catheter implanted in the putamen to continuously infuse GDNF. However, a different catheter and infusion parameters were used than those utilized in the Phase 1 studies. It has been calculated that GDNF bioavailability was limited to only 2–9% of the human putamen with the point source Phase 2 IP catheter.

Table 1 GDNF and neurturin clinical trials

Study/phase	*Start date*	*Delivery*	*Dose range*	*Patient number*	*Treatment duration*	*Results*
Amgen ICV GDNF/ Phase 1/2	1996	Monthly bolus ICV	25–4000 μg per month	50	Up to 28 months	Side effects, not efficacious
Bristol IP GDNF/ Phase 1	2001	Continuous IP infusion	14.4–42.4 μg day per putamen	5	Up to 42 months	Safe, efficacious
Kentucky IP GDNF/ Phase 1	2002	Continuous IP infusion	3–30 μg day per putamen	10	Up to 26 months	Safe, efficacious
Amgen IP GDNF/ Phase 2	2003	Continuous IP infusion	15μg day per putamen	34	6 months	Safe (?), not efficacious
Ceregene AAV2 NRTN/Phase 1	2005	AAV2-NRTN IP injection	$1{\cdot}3\times10^{11} - 5{\cdot}4\times10^{11}$ Vector genomes	12	12 months	Safe, efficacious

Four clinical trials have been conducted testing GDNF. The first employed an implanted intracerebroventricular (ICV) catheter and subcutaneous access port to deliver bolus GDNF injections monthly. Significant side effects were found and the treatment regime was not efficacious. The next two studies (Bristol and Kentucky) used subcutaneously implanted programmable pumps connected to intraputamenal (IP)-implanted catheters to continuously deliver GDNF into the putamen. Both studies reported that the procedures were safe and promoted significant functional improvements. The Phase 2 Amgen IP GDNF trial that followed did not achieve its primary endpoint of a statistically significant improvement in the UPDRS III off medication score. There were also two safety issues raised during the trial: cerebellar toxicity was seen in high-dose GDNF-treated rhesus monkeys and some patients developed binding antibodies to GDNF. The most recent clinical trial tested the safety and efficacy of using adeno-associated virus serotype 2 (AAV2) to transfect cells in the putamen with a hybrid gene construct consisting of the prepro sequence of Nerve Growth Factor linked to the gene sequence for mature NTRN. The initial report from the trial indicated that both the low and high doses were safe, with functional improvements in four of six patients in both treatment groups.

Side Effects

The most significant side effects were noted following intracerebroventricular delivery of GDNF in the first Amgen Phase 1/2 trial. Hyponatremia, weight loss, paresthesias, and nausea were the most common problems. The two Phase 1 GDNF IP infusion studies and the Phase 1 NTRN trial have not reported serious clinical side effects. Surgical complications with the delivery system were encountered in three patients in the Amgen Phase 2 IP GDNF study, requiring surgical intervention in all three individuals, and in one case the device removal.

Safety Issues

Two significant safety concerns have arisen with IP infusion of GDNF. The first, seen in 6 of 32 patients receiving GDNF and 46 of 52 nonhuman primates in a toxicology study, is the expression of binding antibodies to GDNF. It is not atypical to find in patients antibodies to endogenous proteins used therapeutically (e.g., β-interferon and insulin): this does not prohibit continued use of the drug. To date, there have not been any clinical consequences in humans or animals that have developed GDNF antibodies.

The second safety issue, cerebellar toxicity, has only been found in one study in nonhuman primates receiving high doses (100 μg per day) of continuous GDNF infusion into the putamen. Four monkeys were found to have multifocal lesions involving the loss of cerebellar Purkinje cells, and in some instances, associated loss of underlying granule cells. GDNF-associated cerebellar toxicity has not been seen in other toxicology studies in rodents or nonhuman primates, nor is there any evidence that GDNF therapy has induced cerebellar injury in patients. Autopsies on patients who participated in the clinical trials may help to resolve this question, but high-resolution MRI scans conducted on 10 patients and the one published autopsy report conducted to date are negative. The apparent restriction of cerebellar toxicity to one animal study, raises the possibility that it was idiosyncratic, due to some peculiar combination of physiology, surgery, anesthesia, or other treatment in that group of nonhuman primates.

While the published reports on AAV2-NTRN indicate that this approach is safe, there remains a concern that there is no way to control the expression of NTRN in transfected cells in the brain. Overexpression of NTRN eventually causing serious side-effects from leakage into the ventricular system (see below) or leading to the accumulation of large deposits of protein in brain regions would prove challenging to manage medically in patients. Another possible side-effect could be aberrant sprouting and TH downregulation of the nigrostriatal dopaminergic pathway, which has been reported in rats exposed to high GDNF levels from viral vector gene transfer.

Effective Therapy: The Challenges are Delivery and Regulation

Analysis of the clinical trials conducted to date and supporting studies in animal models strongly indicate that successful GDNF or NTRN therapy requires site-specific delivery. Oral delivery of either trophic factor

or a mimetic drug would produce side-effects from actions on the GDNF-responsive neurons composing the enteric nervous system. In addition, the blood–brain barrier effectively blocks entry of blood-borne proteins and many drugs preventing systemic delivery. In addition to focal delivery into the appropriate site, distribution of GDNF or NTRN must be tightly regulated regardless of the method used (e.g., direct infusion, stem cells, encapsulated cells, gene therapy). This is because allowing either trophic factor to persist in brain sites outside of the target area significantly increases the risk for major side effects, such as the hyponatremia, anorexia, nausea, and paresthesias seen with GDNF infusion into the cerebrospinal fluid in the first Phase 1/2 trial. Both GDNF and NTRN have strong heparin-binding domains, which help to control their distribution by limiting their free diffusion in brain parenchyma.

The two leading methods for delivering GDNF and NTRN into the brain are by direct infusion through catheters connected to programmable pumps and via gene therapy. As previously discussed, both methods have been tested clinically; both approaches are well suited for site-specific delivery. Regulation of drug delivery is straightforward using programmable pumps where the flow is adjustable and dosing can be varied as needed. If necessary, the pump can be turned off, stopping drug infusion. The challenge with programmable pump/implanted catheter delivery is with optimizing target tissue distribution of the trophic factor. High concentrations of the infused protein build up at the catheter tip and drug concentration can drop precipitously with increasing distance from the catheter site. Convection-enhanced delivery can partially correct this problem by increasing the bulk flow rate of large molecules promoting tissue penetration and distribution over larger volumes of the brain. In contrast, tissue distribution using gene therapy is easily managed, while regulation of trophic factor levels is problematic. Creative approaches for regulating transfected genes are currently in preclinical testing including drug-dependent regulatory systems to induce transient gene expression. However, none has reached a level of safety and reliability suitable for clinical use.

Summary

GDNF and NTRN therapies have the potential to revolutionize the treatment of Parkinson's disease and other neurodegenerative disorders. The field is now in a challenging era, where three Phase 1 clinical trials have yielded encouraging results, while two Phase 2 studies have been disappointing. Analysis of the differences between the successful and unsuccessful trials strongly suggests that efficacious therapeutic approaches require controlled, site-specific delivery of trophic factors using methodology to optimize the target tissue distribution. The next generation of clinical and preclinical studies is underway to understand and build upon the hard-won lessons from the five clinical trials conducted to date. Achieving efficacy will depend upon the progress made in regulating trophic factor delivery and distribution.

See also: Parkinson's Disease: Definition, Diagnosis, and Management; Surgery for Movement Disorders, Overview, Including History.

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Gene Microarrays

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Introduction

Analytical and experimental developments in high-throughput genomic methods enable the assessment of dozens to hundreds to thousands of genes simultaneously in a coordinated manner. Expression data is increasingly available for many diverse organs and tissues throughout the body, allowing for exciting hypothesis testing of critical concepts such as normative function, development, senescence, and ultimately, disease pathogenesis. For example, microarray analysis has been performed from RNA extracted from the midbrain and discretely within the substantia nigra pars compacta (SNPC) using animal models of Parkinson's disease (PD) as well as human brains obtained postmortem from subjects with PD and age-matched normal controls. Expression profiling studies have revealed downregulation of genes critical to mitochondrial function and energetic homeostasis, suggesting that experimental perturbations such as mitochondrial poisons and complex I inhibitors of the respiratory chain result in a PD-like pathology in the SNPC. Moreover, microarray analysis of postmortem SNPC tissue from PD patients identified increases within the ubiquitin–proteosomal system compared to age-matched controls. These observations suggest that a final common pathway for neutralizing and removing misfolded proteins contributing to the electron transport chain may be dysfunctional in PD.

CNS Expression Profiling

Microarray analysis is a useful, reproducible, and fairly cost-effective tool to assess transcript levels in a wide variety of experimental paradigms. A disadvantage is a requirement for high-quality and abundant input sources of RNA. Whole organism studies can generate significant input amounts of RNA, but do not allow regional or cellular specificity. Regional gene expression analysis is used widely with RNA extracted from cultured cells, animal model tissues, as well as postmortem human brain tissues. However, expression profiles garnered from regional dissections cannot discriminate molecular signatures from admixed neuronal and nonneuronal populations within the region of interest.

Microaspiration

Several techniques are used to aspirate individual cells or populations of cells (termed population cell analysis), including single-cell microaspiration and laser capture microdissection (LCM). Single-cell microaspiration entails visualizing and manually removing an individual cell (or cells) using an inverted microscope connected to a micromanipulator, vacuum source, and an imaging workstation on an air table. This method yields very precise accrual of cells, but can be labor intensive and is dependent on the experience level of the end user. LCM enables rapid accession of single cells and homogeneous populations, and is generally available at genomics core facilities and some individual functional genomics laboratories. Positive LCM extraction entails pulsing an infrared laser source onto thermoplastic film embedded in a specialized microfuge cap, effectively adhering the matrix to target cells. Lifting the thermoplastic cap separates targeted cells from surrounding undisturbed tissue. Negative LCM extraction (or noncontact laser extraction) procedures employ a near-infrared laser source to cut around the area of interest within a tissue section, and the microdissected material is catapulted into a microfuge tube. RNA, DNA, and protein extraction methods can be performed on microdissected cells for downstream genomic and proteomic applications.

Microarray Platforms

Microarrays can be considered as a nanotechnology derivative of conventional dot blots, as they are effectively miniaturized probe–target platforms that exploit the complementary hybridization between nucleic acids. Synthesis of cDNA microarrays entails adhering cDNAs or expressed sequence-tagged cDNAs (ESTs) to a material support such as glass slides or nylon membranes. Similarly, photolithography can be employed to synthesize oligonucleotides directly onto a desired array media. The anchored sequence is commonly called the microarray target. Target length varies from short oligonucleotides to large chromosomal fragments. Probe generation is typically performed via reverse transcription, and a detection moiety is incorporated directly into the transcribed strand. If input RNA is amplified through an RNA amplification methodology, then the amplified material is labeled and used to probe a microarray. Arrays are washed to remove nonspecific hybridization, and imaged using a laser scanner for biotinylated/fluorescently labeled probes a phosphor imager for radioactively labeled probes. A target-labeled probe complex emits a quantifiable signal that is proportional to the abundance of the labeled probe in the sample. Quantification of hybridization signal

intensity is performed to evaluate relative expression levels of each cDNA, EST, or oligonucleotide feature on the array platform. Gene expression is then assessed using informatics software. Computational analysis is a key aspect for adequate array quantitation due to the massive number of data points that can be generated from a single assay.

RNA Amplification Strategies

An RNA amplification technique is often required when using small sample inputs as starting material. PCR-based amplification methods are not optimal, as exponential amplification can skew the original quantitative relationships between genes. Linear RNA amplification is another approach used to generate input RNA for microarrays. For example, the amplified antisense (aRNA) amplification method utilizes a T7 RNA polymerase-based amplification procedure. aRNA maintains a proportional representation of the size and complexity of the initial mRNAs. Modifications of the initial aRNA procedure have been utilized, and several aRNA-based kits are available commercially. A new RNA amplification procedure has been developed in our laboratory that utilizes a method of terminal continuation (TC). Specifically, synthesis of the first strand cDNA complementary to template mRNA is performed by two oligonucleotide primers, a poly d(T) primer and a TC primer. RNA is then amplified via in vitro transcription procedure using the newly formed cDNA as template. The poly d(T) primer is similar to conventional primers that anneal to the poly(A)+ sequence present on most mRNAs. Therefore, transcript orientation can be in an antisense orientation (similar to conventional aRNA methods) when the bacteriophage promoter sequence is placed on the poly d(T) primer or in a sense orientation when the promoter sequence is attached to the TC primer, depending upon the experimental design. TC RNA amplification enables quantitative assessment of a large proportion of genes as evidenced by bioanalysis and microarray analysis in animal model and human postmortem brain tissues, including single cells and populations of homogeneous neurons.

Microarray Considerations

The application of microarray technology towards understanding the pathophysiology of PD and related movement disorders is in its early stages. There are many concerns regarding the actual handling of tissues, fixation, and cutting of sections for RNA accession, especially in the case of human postmortem material. The decision to microdissect specific cell type(s) of interest via LCM or a related technology still depends on the skill level of the operator and the availability of expensive equipment that requires significant maintenance. Moreover, the choice of microarray platforms (i.e., high-density versus moderate density; single use glass arrays versus reusable nylon membrane arrays), probe labeling procedures (e.g., direct or indirect fluorochrome incorporation and radioactive labeling), and amplification procedures (including PCR-based amplification, T7-based RNA amplification, isothermal amplification, and microRNA amplification), and a dizzying array of hybridization procedures make standardization a significant issue. Each of these procedural and technical variables may have substantial effects on the subsequent microarray datasets. As a result of these potential pitfalls, negative findings on any array platform must be interpreted cautiously. Importantly, independent validation methods of transcript analysis (including real-time quantitative PCR (qPCR), Northern hybridization, RNase protection assay, and in situ hybridization, among others) are essential components to a rigorous study that employs high-throughput transcription profiling technologies. Another caveat of microarray analysis is that coordinate changes in respective proteins encoded by the genes of interest are often found, but are not an absolute feature.

Conclusions

Functional genomics advances have led to the development of high-throughput techniques that enable expression profiling within discrete brain regions and specific cell types. These exciting technologies, when combined with solid experimental design and validation using alternative molecular- and cellular-based strategies, comprise a paradigm that is useful for assessing mechanisms underlying the pathophysiology of PD. Specifically, individual genes and classes of transcripts that comprise discrete signaling pathways can be evaluated in vitro as well as in the midbrain, SNPC, and/or striatum of relevant animal models of PD and human postmortem brains of subjects afflicted with PD.

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Generalized Primary Torsion Dystonia

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Definition and Classification

Dystonia is a syndrome characterized by sustained, twisting involuntary contractions of muscles, producing abnormal postures and movements. The movements are usually directional in nature, and may be action specific. Dystonia is classified in several ways: (1) by etiology, (2) by age of onset, (3) by the site in the body where dystonia begins, or (4) by the final distribution of the body parts affected by dystonia. These classifications are not mutually exclusive, as most early onset dystonia starts on a limb, and most leg-onset dystonia is early onset.

When separated by etiology, dystonia is classified as primary or secondary, with an intermediary form, dystonia-plus, which straddles both categories, but usually considered as a form of secondary dystonia. Primary torsion dystonia (PTD) is defined when dystonia is the only abnormality on neurological exam, with the exception of tremor, and when there is no known metabolic, structural, or toxic etiology and a dramatic and sustained response to levodopa is absent. When an etiology is identified, such as an exposure to dopamine-blocking medications (tardive syndromes), perinatal brain injury (germinal matrix hemorrhage, hypoxic brain injury, kernicterus) or dystonia is a component of heredodegenerative diseases (Parkinson disease, Wilson disease) or when brain imaging abnormalities are present, the dystonia is then considered secondary. Primary dystonias were previously labeled 'idiopathic,' but as genetic etiologies for some forms of 'idiopathic' dystonias have been elucidated, they have been renamed as 'primary.'

There are three genetic disorders where dystonia is not the sole neurological feature, but in which no imaging or structural abnormalities are identified, and these are classified as dystonia-plus syndromes. They include dopa-responsive dystonia (DRD), myoclonus-dystonia (M-D), and rapid-onset dystonia parkinsonism (RDP). Parkinsonism and hyperreflexia may be present in DRD, myoclonus is prominent in M-D, and parkinsonism and spasticity are features of RDP. Particularly in DRD and MD, some family members may present with isolated primary appearing dystonia; therefore, these conditions should be considered in the differential.

Dystonia may also be defined by the age at onset, with <27 or <22 usually being the cut-off for early onset dystonia. Age of onset may be helpful in determining the etiology; almost all DYT1 dystonia, for example, is early onset. In contrast, in other conditions such as DYT6, there is a mixed age of onset disorder with the majority of cases starting before the age of 25 (earliest age 5 years), but some starting as late as 49 years of age.

Dystonia may also be separated into the muscles involved first, such as leg or neck, and this has utility in predicting spread, as rostral onset dystonia (such as blepharospasm) is much less likely to spread to other sites than more caudal onset dystonia such as leg onset. The most useful clinical classification is by the distribution of sites involved at last exam in combination with and the etiology and the age at onset. Focal dystonias present in specific body regions (such as the arm in writer's cramp, and the muscles of eye closure in blepharospasm). Segmental dystonias affect adjacent areas of the body (e.g., blepharospasm with other lower cranial involvement in segmental cranial dystonia, and cervical dystonia with writer's cramp in segmental cervical-brachial). Generalized dystonia involves multiple body regions, usually defined as one or both legs, the trunk, and one other part of the body.

This section focuses on dystonias which are primary in etiology and which are generalized in distribution.

History

Some of the first reports of primary generalized dystonia were from Schwalbe and Oppenheim in 1908 and 1911, respectively. Schwalbe described generalized PTD in his essay "*Tonic Cramps with Hysterical Symptoms*" and his reference to hysteria led to the misunderstanding that dystonia was a psychiatric disorder. This is probably based in the misinterpretation of the unusual and sometimes bizarre abnormal postures of dystonia, and the fact that the postures can be action specific, as well as the Freudian influence in Europe at the time. Oppenheim described classic primary generalized dystonia in his treatise in 1911 entitled "About an unusual cramping syndrome in children and adolescents" which he named dystonia musculorum deformans. In hindsight, because the cases Oppenheim described were of Jewish background, it is likely that they had mutations in the first dystonia gene to be identified, DYT1. However, it took over 70 years to understand that although DYT1 is familial, and may skip generations, it is an autosomal dominant disorder with reduced penetrance (and not autosomal recessive), and that even though there is a founder effect in the Ashkenazi population, it occurs worldwide, and in people of varied ethnicities.

While ethnic background plays a role in determining the likelihood that generalized PTD is due to certain mutations, not all cases of primary generalized dystonia in the Ashkenazim can be attributed to DYT1 mutations, and not all cases of primary generalized dystonia in the Amish-Mennonites can be attributed to DYT6 mutations. In individuals of Ashkenazi background, DYT1 mutations account for 80–90% of early onset PTD; however, in those not of Ashkenazi descent, DYT1 mutations only account for approximately 30–60% of early onset PTD. Recently, the DYT6 gene was cloned, and while a founder was initially demonstrated in the Amish-Mennonites, mutations in this gene are responsible for PTD in people of other backgrounds as well. Conversely, a de novo DYT1 mutation was reported in a Mennonite man with early onset generalized PTD.

Unlike DYT1, DYT6 less classically begins as leg-onset dystonia, although onset in the arm is common. While DYT6 may be an important cause of PTD, it is unlikely to account for most of the generalized PTD in non-Ashkenazim or in the Ashkenazim without DYT1 mutations. Another gene, DYT13, has been reported to cause generalized dystonia, but the gene has not yet been identified. Further, it has been seen in only one Italian family, and infrequently causes generalized dystonia.

Therefore, while this entry will focus on the three identified etiologies of generalized PTD, *there is still a large amount of generalized PTD whose etiology must be elucidated*. We will discuss overall features of primary generalized dystonia, followed by the specific genetic etiologies, DYT1, DYT6 and DYT13, differential diagnosis, genetic counseling and testing and treatment.

Epidemiology

Primary generalized dystonias occur with a reported prevalence of 34–50 per 1 million persons of the population in the United States and Western Europe, although the prevalence may be much higher in certain ethnic groups. Early-onset primary generalized dystonia in the Ashkenazi Jewish population occurs with a prevalence of more than 100 per 1 million persons.

Clinical Features

During normal muscular activity, antagonist muscles relax when the agonist muscles contract, and vice versa. Dystonic patients often experience simultaneous contraction of the agonist and antagonist muscles. Usually one set of muscles will dominate; this often produces movements with a dominant directional vector. The directionality of the movements can help distinguish cervical and brachial dystonias from essential tremor of the head or arm, for example. Careful examination and positioning of an affected limb will often reveal a null point, at which the dystonic movement is minimized, again differentiating this disorder from other tremors, myoclonus, or tics. Movements in dystonia are often task specific and usually show kinetic exacerbation or overflow, for example, muscles of the hand and forearm will display little activity at rest, but contract dramatically with handwriting in the patient with writer's cramp. In generalized PTD, the task specific phenomenon may be observed when patients may have pronounced dystonia walking forward, but not walking backwards or running. Dystonic movements disappear during sleep and anesthesia, although over time contractures may appear which then do not abate.

One of the most intriguing characteristics of dystonias is the sensory 'trick' or *geste antagoniste*. Tactile stimulation of a specific site within the dystonic region of the body can ameliorate the abnormal movement; for example, touching the chin or the back of the head may temporarily straighten the neck of the patient with cervical dystonia, and holding a toothpick or orthodontic device within the mouth may provide relief from oral movements. In certain patients, simply visualizing the 'trick' may also provide relief. The effect of sensory afferent input on dystonic movements provided some of the first clues that the disorder encompasses abnormal sensory processing as well as abnormal movements; more recent investigations with functional and detailed anatomical imaging, as well

as studies of motor learning have confirmed the complex pathophysiology of the disease.

Primary generalized dystonias often present with focal onset during childhood, usually in the foot or leg in the cases of DYT1 or in an arm in cases of DYT6. Spread to the other leg and trunk then occurs. The "dromedary gait" described by Oppenheim with trunk flexion and hip elevation during walking is classic for generalized PTD. There is tremendous heterogeneity among generalized PTD with regards to the disability associated with the dystonia, and this depends on the severity of the trunk and leg posturing. As discussed below, not all cases of DYT1 and DYT6 dystonia will spread to become generalized.

DYT1 Dystonia

DYT1 dystonia, also known as Oppenheim dystonia, or dystonia musculorum deformans is the most common known genetic etiology of generalized PTD. It is caused by a three base pair (GAG) deletion in exon 5 of the *DYT1* gene on chromosome 9q34. This common deletion is found in almost all patients with this disease regardless of ethnic background, and the relevance of other reported mutations is not yet clear. Therefore genetic screening is limited to screening for the GAG deletion.

Pathophysiology

DYT1 encodes a nuclear envelope heat shock protein in the AAA+ family of ATPases known as torsinA. The protein is widely expressed in the brain, including in the basal ganglia, cerebral cortex, hippocampus, and cerebellum. The intracellular localization of torsinA changes as a result of the GAG deletion, and the mutant form of the human protein shows decreased ATPase activity when expressed in bacterial cultures. Animal and cell culture models have also demonstrated a redistribution of the mutant protein from the endoplasmic reticulum to the nuclear envelope. A single copy of the gene can cause this redistribution; hence the mutation acts in a dominant negative fashion. The role of torsinA in cellular functioning remains unknown, but it may play a role in interactions between the nucleus and the cytoskeleton, trafficking of vesicles along the microtubular components of the cytoskeleton, extension of neurites during development, or regulated exocytosis of synaptic vesicles. The possible link to exocytosis of vesicles containing neurotransmitters is particularly intriguing in light of other evidence demonstrating increased dopamine turnover in the striatum in transgenic mice expressing mutant human DYT1. Transgenic mice also manifest dopamine D2 receptor abnormalities associated with altered GABAergic neurotransmission, as well as abnormal responses of cholinergic interneurons to dopaminergic afferent activity.

Genetics, Penetrance, and Expression

The higher frequency of disease in patients of known Ashkenazi ancestry is attributed to a founder mutation that likely occurred in Byelorussia over 400 years ago. The disorder occurs in 1 out of 3000–9000 Ashkenazi Jews and in 1 out of 9000–27 000 non-Jews. About 90% of primary generalized dystonia in the Ashkenazi group results from the DYT1 founder mutation, and about 50% of the primary generalized dystonia in non-Jewish populations can be attributed to DYT1. The mutation is dominant, but there is both reduced penetrance and variable expression. Only approximately 30–40% of individuals who harbor the mutation will ever develop disease, and the type of disease they develop (expression) may vary from severe generalized to mild focal even among family members. Opal et al. reported a family with one member with severe dystonic storm and another with mild writer's cramp. A polymorphism at residue 216 of the codon has been demonstrated to decrease penetrance of the mutation; however, as it is rare, it only accounts for a small proportion of the reduced penetrance. As this is an early onset disorder, there is a window of vulnerability, with most individuals developing symptoms by the age of 26 or not at all. Late onset cases (up to the age of 64 with oromandibular dystonia) are rare. Among carriers of the DYT1 mutation who have not developed dystonia, there may be an endophenotype with functional imaging abnormalities as well as slowness in motor learning tests, and a higher prevalence of affective disorders than control subjects without the mutation.

Clinical Features

DYT1 dystonia almost always (95%) involves a limb initially, and two-thirds of cases will progress to generalized or multifocal dystonia, usually within 5–10 years. Onset is almost always by age of 26. A minority of cases will remain as focal or segmental dystonias, usually writer's cramp or bibrachial dystonia. Focal neck or cranial muscle involvement is rare. A study of early onset cervical dystonia did not identify any DYT1 cases, and it is highly unusual for DYT1 to be the cause of adult onset focal dystonia, overall the most common form of dystonia. Early involvement of the cranial structures in patients with DYT1 dystonia is unusual; this distinguishes these patients from other forms of primary generalized dystonia that may show early (younger than 21 years of age) cranial symptoms, particularly DYT6 dystonia where cranial features are common and usually more disabling than leg dystonia. Later in the disease, about 15–20% of individuals may have cranial muscle involvement. The trunk and cervical muscles may also be involved in 25–35% of cases. As the dystonia may be jerky, or myoclonic, it is infrequently mistaken for essential tremor (ET) or

myoclonus-dystonia. DYT1 dystonia can be distinguished from ET by the directionality and posturing of the limbs in certain movements, and often a null-point of the tremor. Further, unlike myoclonus-dystonia where there are separate jerks of myoclonus, the myoclonic jerks superimposed on the dystonia in DYT1 are usually slightly slower.

As alluded to, unusual cases of DYT1 dystonia have been documented with clinical presentations as late as seventh decade of life, although most older onset cases do not present for medical attention and are usually identified through an affected family member. Because writer's cramp may never come to medical attention, in some individuals dating the onset of the dystonia may be difficult.

Imaging and Neurophysiology

Although clinical magnetic resonance imaging of the brains of patients with DYT1 dystonia is usually normal, multiple studies have found abnormalities on positron emission tomography (PET) scanning, functional MRI, and specific sequences of (e.g., diffusion tensor imaging/DTI) of MRI scans. Fluorodeoxyglucose PET scanning of persons with DYT1 dystonia, as well as of nonmanifesting carriers of the mutation, shows increased glucose metabolism in the putamen, globus pallidus, cerebellum, supplementary motor area, and parietal cortex association regions. Similar patterns have been noted across variable clinical phenotypes of dystonia: regional metabolic patterns are distinct between manifesting and nonmanifesting carriers of DYT1 and DYT6 mutations. During the performance of a motor task, differences in metabolic activity emerge on glucose PET scans of manifesting carriers of the DYT1 mutation and nonmanifesting carriers or control subjects. All carriers of the DYT1 mutation showed increased metabolic activity in primary motor cortex, whereas manifesting carriers showed greater activation in sensorimotor cortex, supplementary motor area, parietal association regions, and the cerebellum; nonmanifesting carriers showed increased activity compared to controls, but not as great as the levels seen in manifesting carriers. As a functional correlate, both manifesting and nonmanifesting carriers of the DYT1 deletion show impairment in learning sequential motor tasks. Further, DTI scans of the brains of manifesting and nonmanifesting carriers of DYT1 show abnormalities in white matter tracts in primary sensorimotor cortex and in the lentiform nucleus, suggesting structural abnormalities.

Imaging with the dopamine D2 receptor ligand, raclopride, shows decreased binding in carriers of the DYT1 and DYT6 mutations in the caudate and putamen. These abnormalities in striatal dopaminergic tone occur both in manifesting and in nonmanifesting carriers of the mutations. The well-known occurrence of acute-onset of focal dystonias after exposure to D2 receptor blocking agents (metaclopramide, haloperidol), and development of dystonia as a result of a number of mutations in the biosynthetic pathway for dopamine, illustrate the clinical relevance of this finding.

Transcranial magnetic stimulation (TMS) of the cortex in manifesting and non-manifesting carriers of DYT1 reveals abnormal cortical electrical activity; specifically intracortical inhibition is decreased in carriers of the DYT1 deletion. Transgenic mouse models of DYT1 dystonia show abnormal inhibition in the globus pallidus externa (GPE) and interna (GPI) after stimulation of the cortex.

Possible Affective and Cognitive Features

Nonmotor symptoms have emerged as possible features of primary generalized dystonias. In one study, major depression occurred more commonly in carriers of DYT1 mutations, even if they did not have motor manifestations of the disease, than in family members who did not carry the mutation. Further supporting that the depression was related to the gene, the age of onset for major depression in the nonmanifesting carriers was younger than that seen in family members with depression who did not carry the mutation. Interestingly, patients with DYT1 dystonia perform better on tests of semantic verbal fluency than age-matched controls. This occurs in spite of retroactive memory interference (the adverse effect of learning new material on the retention of material learned in the past) seen in patients with DYT1 dystonia.

DYT6

Until recently, only one gene for primary dystonia, DYT1, had been discovered. There is now a second gene, DYT6, which causes a phenotype deemed 'mixed' due to its overlap with both early onset generalized dystonia and late onset localized cervical or cranial dystonia. Like DYT1, DYT6 dystonia tends to begin early and to spread to multiple body regions. On the other hand, DYT6 is more likely than DYT1 to involve cervical or cranial muscles, with less disabling leg and gait abnormalities.

The DYT6 gene was originally mapped to chromosome 8p21–q22 in two Amish-Mennonite families who shared a haplotype of marker alleles across a 40 cM linked region, and common ancestral pairs were later identified through genealogical records. In these families, dystonia was characterized by a relatively early but broad age at onset (mean 18 years, with range 5–38 years). The body regions first affected included the cranial muscles, neck, arm, and rarely the leg; almost all had some degree of progression of dystonia to other body regions, but this varied widely. More recently, three additional dystonia families of Amish-Mennonite ancestry have been identified. In one of them, the DYT6 haplotype was identified but it was excluded in the other two, suggesting genetic

heterogeneity in the etiology of PTD in the Amish-Mennonite population. In early 2009, a mutation in the THAP1 gene was identified as responsible for DYT6 dystonia in the above mentioned families carrying the common haplotype. Since then, mutations in DYT6 have been shown to be responsible for mixed age onset PTD in non-Amish-Mennonite families as well.

Genetics, Pathogenesis, and Pathophysiology

DYT6 is inherited in an autosomal dominant manner with reduced penetrance (~60%) and variable expressivity. Although more cases of DYT6 mutations in women are reported, initial penetrance studies have not demonstrated that gender affects penetrance.

The founder mutation found in the three initial families of Amish-Mennonite origin and the subsequent one represented a 5 bp insertion/3 bp deletion resulting in premature termination of the THAP1 protein. A different mutation, representing a missense mutation in exon 2 of the *THAP1* gene was identified in a German family without Amish-Mennonite ancestry.

The mechanism for which mutations in *THAP1* result in primary dystonia is not clear. THAP1 regulates endothelial cell proliferation through its DNA binding domain. Both known mutations are likely to be sufficient to abolish its DNA binding activity and this loss it is hypothesized to potentially cause transcriptional dysregulation effecting downstream targets. An alternative pathway involving programmed cell death has also been proposed as a possible etiologic mechanism, as THAP1 is known to function also as a proapoptotic factor.

Clinical Features and Diagnostic Criteria

From the families described, it is known that the disease onset is broad; however, in more than of half of the affected members, PTD began in midadolescence. The most common site of onset was the arm, followed by cranial muscles and neck. Most affected individuals had some but varying degree of progression to other body regions. It is notable that in contrast to DYT1, very few patients required assistive aids for ambulation despite involvement of leg in half of the affected subjects. Most had arm involvement and more than half had speech impairment. The greatest source of disability was cervical and lower cranial dystonia.

The phenotype of DYT6 may expand in the near future as we learn that DYT6 mutations are present in pedigrees of non-Amish-Mennonite descent and other mutations are described in *THAP1*.

DYT13

Generalized PTD has also been identified in a single Italian family, although leg involvement was present in only 2 of 11 family members with dystonia, supporting that generalized dystonia may be present, but is not the predominant phenotype. Dystonia was mapped to the DYT13 locus on chromosome 1p, although the gene has not yet been identified. Age of onset in DYT13 is early (mean age 15.6 years, range 5–43) with a range that is strikingly similar age range to DYT6 (5–58 years). Body regions first affected in DYT13 include the neck, cranial muscles, and arms. Only 2 out of 11 individuals developed leg dystonia, but like DYT6, the disability from leg dystonia was relatively mild.

Diagnostic Work-up/Tests and Differential Diagnosis

First, as is the case for other types of dystonia, a careful and detailed history and examination should be performed to determine whether the dystonia is primary or secondary. This includes a careful medication history, including current and past exposure to neuroleptics and antiemetics to elucidate medication induced tardive dystonia. Imaging of the brain with MRI should be considered in cases without DYT1 mutations (see Genetic Testing section). The differential diagnosis for primary generalized dystonia includes DYT1 dystonia, DYT6 dystonia, DYT13 dystonia, dopa-responsive-dystonia and myoclonus-dystonia. Secondary causes of dystonia are less likely in dystonia without other neurological features and normal imaging; however, Wilson disease should always be considered in the differential as it is a highly treatable disorder. Evaluation for Wilson includes serum ceruloplasmin and slit lamp examination, and may include 24 h urine collection for copper levels. Incomplete history-taking or unfamiliarity with the diagnosis may result in the misdiagnosis of 'cerebral palsy' in these children or even in young adults. Dopa-responsive-dystonia is an early onset dystonia plus disorder, which usually presents in childhood with generalized dystonia. This may be accompanied by spasticity, toe walking, hyperreflexia, and or parkinsonian features. However, dystonia may be the sole presenting finding; therefore, a diagnostic and therapeutic trial of levodopa-dopa should be considered in all patients presenting with primary generalized dystonia who do not harbor a DYT1 mutation, or whose status is unknown.

DYT1 and DYT6 differ in their overall clinical presentation, although in individual cases there may be overlap: in DYT6 there is a prominence of cervical and cranial muscle involvement and high frequency of speech abnormalities compared to the greater leg and gait abnormalities characteristic of DYT1. Also, in contrast to most early onset dystonia, there is a high preponderance of cervical and cranial onset disease in DYT6. Even when DYT6 dystonia is generalized, the walking disability is usually less severe than in DYT1 dystonia. However, as noted, DYT1 may also be mild. In the case of the Mennonite man with de novo DYT1 dystonia, the

clinical picture was suggestive of DYT1 rather than DYT6 because of the crural, trunk, bibrachial, and cervical involvement with prominent gait impairment. He did not have cranial dystonia or speech impairment.

Further, while the DYT6 phenotype also shares many features with DYT13, there is more prominent cranial and laryngeal dystonia in DYT6 than DYT13. The differential for DYT6 dystonia also includes inherited dystonia with prominent cervical involvement (DYT13, DYT7), as well as focal cervical dystonia and focal and segmental cranial dystonia.

Genetic Testing

In patients younger than 26 years of age who present with idiopathic generalized dystonia, genetic counseling should be offered together with DYT1 mutation testing. Genetic counseling serves a particularly important function with this disease because the inheritance pattern is complex and patients and family members need to be educated that even if a DYT1 mutation is found, there is only 30–40% chance that symptoms will develop, and even then the phenotype is variable. Presymptomatic testing is available in adults, as is preimplantation diagnostic testing. At this time there is no clinical testing to assess for the polymorphism associated with decreased risk of disease. As the DYT6 gene was recently elucidated, no commercial clinical genetic testing is yet available; however, it is anticipated that it will be available soon. In contrast to DYT1 where one mutation, the GAG deletion is responsible for dystonia, many different DYT6 mutations across the three exons are likely to cause DYT6. Therefore interpretation of a negative result will be more difficult, as until complete screening for all mutations and deletions is available, one cannot definitively state that an individual is not a DYT6 carrier. Genetic testing for DRD is discussed in the section on dopa-responsive-dystonia.

Treatment

Treatment of primary generalized dystonias currently involves a combination of medical (either oral or injectable with botulinum toxin), and/or surgical and nonpharmacological strategies. Current dilemmas in treatment of generalized PTD revolve around whether and when to refer individuals for deep brain stimulation (DBS) surgery. This decision must include weighing risks and benefits of surgery compared to the ones of medical therapies. Important factors in consideration of surgery include whether the genetic form of dystonia plays a role in (a) responsiveness to surgery, for example, DYT1 patients have dramatic improvement in DBS in the GPi, although some have argued that response depends more on duration to timing of surgery than the genetic etiology, and (b) the targets chosen, as pallidal DBS appears ideal for DYT1 but may not necessarily be for other genetic etiologies of generalized PTD.

Medical treatment of dystonia often involves a combination of oral medications and injections of botulinum toxin. Primary oral treatment options include: anticholinergics (e.g., trihexyphenidyl), benzodiazepines (e.g., clonazepam), baclofen or tizanidine. Others include levodopa, tetrabenazine, topiramate, gabapentin and pregabalin, and levetiracetam.

Anticholinergic medications have long been a mainstay of medical treatment for dystonia, and often are the initial medication employed. Trihexyphenidyl is probably the most commonly used anticholinergic drug; others include benztropine, biperiden, and ethopropazine. The anithistaminergic drug, diphenhydramine, also has significant anticholinergic actions, which may account for its mild benefit to some patients. Anticholinergic drugs may prove effective when generalized dystonias first manifest, and the effects may be dramatic in some individuals, although others may be refractory. If patients require higher doses of the agent, side effects may prevent further dose escalations. Side effects include pupillary dilation and blurred vision, dry mouth and eyes, urinary retention, decreased gastric motility, and cognitive impairment; children tend to tolerate higher doses of anticholinergic agents better than adults, but impaired eyesight and memory can affect academic performance. Simultaneous administration of pyridostigmine may ameliorate the ophthalmologic side and other peripheral side effects and enable the patient to tolerate higher doses of these drugs.

Benzodiazepines likely ameliorate dystonia directly through GABAergic effects on the impaired cortical inhibition found in the dystonic brain, and secondarily by their anxiolytic benefit. Doses are again limited by side effects, notably sedation and amnesia, although children may paradoxically become agitated or irritable. Clonazepam is the commonly used agent in this class, due to its relatively long half-life and somewhat lower sedating capability. Diazepam may be used as well. Shorter-acting agents, such as alprazolam and lorazepam are usually less helpful.

Oral baclofen may benefit patients with generalized and focal dystonias, most likely by increasing GABAergic tone. Side effects include sedation, and in the elderly, hallucinations or other psychotic symptoms. Intrathecal baclofen pumps allow delivery of the drug directly into the cerebrospinal fluid, and may provide higher effective doses to reach the brain directly, with fewer systemic side effects. However, baclofen pumps carry considerably morbidity and have been most useful in cases of secondary dystonia with associated spasticity. Currently, if a baclofen pump is considered, the patient is usually considered a surgical candidate for deep brain stimulation.

Other drugs with significant GABAergic properties, such as gabapentin and pregabalin, are generally well-tolerated, but less efficacious in the treatment of primary

generalized dystonia. They may lessen pain, however, and can play an important role in adjunctive therapy. The anticonvulsant topiramate, commonly used in the treatment of essential tremor and migraine, may also improve symptoms in dystonia. Cognitive impairment may preclude the use of high doses.

Most patients with primary generalized dystonia will not respond dramatically to levodopa therapy, but small doses of the drug are well-tolerated and have been reported to produce improvement in a minority of patients, even those with genetically proven DYT1 disease. Significant response to especially low doses of levodopa should immediately raise the diagnostic possibility of dopa-responsive dystonia, or a secondary dystonia due to an underlying disorder such as Parkinson disease.

Conversely, the dopa-depleting agents (tetrabenazine, reserpine, and α-methyl-para-tyrosine), which are often effective oral agents for treating tardive dystonias, have also been reported to improve symptoms in primary generalized dystonia, particularly in combination with anticholinergics and benzodiazepines. The occurrence of severe depression in patients on dopa-depleting drugs necessitates vigilant monitoring of mood. If severe depression occurs, the dopa-depleting agent usually must be withdrawn; if this is required, the depression will often improve within days if due to tetrabenazine, but may persist for weeks in patients treated with reserpine.

Injections of botulinum toxin are the treatment of choice for isolated blepharospasm or cervical dystonia, and can greatly improve either of these symptoms in patients with primary generalized dystonia, sometimes reducing the need for higher doses of oral medications. Injections to the limbs may also improve dystonic movements, but great care must be exercised, especially in children. Deaths have occurred in children with cerebral palsy who received large doses of botulinum toxin for relief of spasticity in the limbs. Limb and cervical injections are often done with electromyographic guidance in order to target affected muscles more accurately and lessen the chance of side effects.

Botulinum toxin type A inhibits the release of vesicles containing acetylcholine in motor neurons, by binding and cleaving the protein SNAP-25 at the presynaptic site of neurotransmitter vesicle docking. This results in a failure of neuromuscular transmission and weakens muscle contraction. Botulinum toxin also inhibits the release of neuropeptide transmitters, such as substance P and calcitonin gene-related peptide in sensory neurons; it may also modulate the activity of vanilloid receptors in patients with chronic pain. This antinociceptive property may explain why the toxin may lessen pain in patients with dystonia even more significantly than it improves the dystonic posture or movement.

Three formulations of botulinum toxin A are available for therapeutic use (Botox, Dysport, and Xeomin), although only Botox is currently available in the United States. Myobloc is the only commercially available form of botulinum toxin B, and is available in the United States and other countries. The remaining serotypes of the toxin (C-G) are not used clinically.

Surgical Treatment

Deep Brain Stimulation

Deep brain stimulation (DBS) has replaced earlier neurosurgical practices of lesioning the brain by freezing or chemical ablation; the placement of electrodes into the globus pallidus interna (GPi) allows delivery of electrical stimulation of precisely controlled amplitude and frequency into an area of the brain responsible for a major motor efferent pathway from the basal ganglia. Patients with primary generalized dystonia also show abnormal inhibition within the globus pallidus, and the GPI is the target for electrode placement in the treatment of DYT1 dystonia with deep brain stimulation. Current theory holds that DBS blocks abnormal electrical overactivity in this pathway and symptomatically improves dystonia. For the treatment of primary generalized dystonia, electrodes are usually implanted bilaterally. Programming of the stimulators must be done by a neurologist with experience in the field, and parameters such as amplitude, pulse width, and frequency must be adjusted for individual patients. Improvement of dystonic tremor may occur relatively quickly (in hours to days), but sustained dystonic postures may not improve for weeks or even months. DYT1 dystonia may respond particularly well to DBS, and children who show rapid progression of their symptoms, or who develop intolerable side effects from oral medications or from botulinum toxin should undergo evaluation by a neurologist and neurosurgeon with expertise in this therapy. Although the neurostimulator can be turned off completely, and the electrodes may be removed surgically if necessary, some patients have experienced irreversible dysarthria after the procedure. Reports of cognitive impairment and impulsivity after the procedure also reinforce the value of careful neuropsychological testing before surgery.

Denervation

Selective denervation has been employed for focal dystonias, such as blepharospasm or cervical dystonia. If these sites represent the major location of disability or pain in a patient with generalized dystonia, and the patient fails to respond to botulinum toxin and oral medications, denervation may be considered. However, clinical improvement after denervation has been inconsistent, and significant, non-reversible side effects may occur. For generalized dystonia, DBS is usually considered before denervation treatment.

Nonpharmacological Treatment

Nonpharmacological treatment includes physical therapy to retain range of motion, and support in the school and at work, with accommodations not only for assistive devices, but also in allowing people to sit/stand in positions that accommodate their particular postures, and having a scribe or personal computer in the classroom or workplace. Psychological stress exacerbates dystonia, and stress-reduction techniques can therefore form an important therapeutic function. Proposed entities include acupuncture, massage, relaxation techniques, yoga, and tai ji quan. Although the effect of these therapies on the underlying disease is not well-known, many patients report subjective improvement, reduction in pain, and better quality of life. Finally, affective disorders are known to occur at higher rates both in patients with DYT-1 dystonia and in nonmanifesting carriers, when compared to control groups. Effective treatment of these symptoms can improve psychiatric health as well as the severity of the involuntary movements and pain. If anxiety or depression emerges as a disabling symptom, the expertise of a psychiatrist familiar with movement disorders will benefit the patient, and may avoid complications of psychopharmacotherapy, such as tardive syndromes.

See also: DYT5; DYT6, Mixed Phenotype Primary Dystonia; DYT13, Cranio-Cervical-Brachial.

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Geste Antagonistique

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Glossary

Geste antagoniste – A maneuver that can temporarily improve dystonia.

Introduction

Gestes antagonistes, also called 'sensory tricks,' are maneuvers that can temporarily ameliorate dystonic postures and spasm. Gestes are especially likely in idiopathic dystonia and are particularly characteristic of cervical dystonia.

Clinical Features

Typical gestes in cervical dystonia (CD) include touching the cheek, face, back of the head or chin. Gestes can be effective whether applied contralaterally or ipsilaterally to the direction of the dystonia. Other maneuvers include resting the back of the head, shoulders, or neck against a support, bending the trunk forward, or yawning.

The duration of relief of symptoms from a geste varies widely. In 42% of patients reported by Muller, the effect on head position lasted less than a minute, sometimes only seconds. However, in 1/3 of patients, normal head posture could be sustained as long as the touch or geste was maintained. About half of patients have several geste

techniques that vary by either using the other hand or touching different areas of the face.

Gestes do not rely on simple pressure to push the head to a normal position, and often do not even require touch or contact. In many patients, the head begins moving towards a neutral position before contact is made and some patients can elicit dystonic relief by simply thinking about or imagining the geste. In CD, relief of dystonia is not elicited as effectively by passive maneuvers such as having someone else manipulate the arm or touch the face.

The prevalence of effective gestes appears to vary with CD pattern. While 64–89% of CD patients overall report having a geste, they are present in 85% of those with rotational torticollis and in 55% of those with retrocollis, but only in 36–38% of those with laterocollis or complex CD.

The utility of gestes is not affected by sex, age, the severity of dystonia, presence of pain, or presence of coexistent tremor, although there may be a relationship to the age at dystonia onset and the duration of dystonia. Gestes may be more likely in those with a younger age of dystonia onset and in those who have had dystonia for a shorter period of time. Most patients cannot describe how they discovered their geste, but some patients uncover the geste while actively seeking a way to obtain relief or when questioned about gestes by a clinician.

Patients consider gestes that maintain relief for long periods of time more beneficial than those that bring the head closer to midline but are not sustained. 82% of CD patients have at least 30% improvement in head posture with geste. With the most effective geste, dystonic head deviation can be reduced by 60–100%. However, an individual geste may not be consistently effective every time it is applied. Gestes are usually more effective in correcting abnormal head position than in reducing abnormal movements or in relief of pain. While the degree of benefit from the geste can be greater than that obtained by botulinum toxin injection, the brief nature of relief makes gestes less useful therapeutically.

Gestes remain effective for years in some patients, but many others lose benefit over the years with a shorter duration of geste effect and a need for more forceful sensory stimulation. In some cases, gestes entirely lose efficacy. Interestingly, three patients reported by Muller whose gestes ceased being effective, regained benefit from the gestes for 4–6 weeks following botulinum toxin treatment, although Filipovic reported patients whose gestes became weaker or disappeared after starting botulinum toxin injections.

Sensory tricks can also relieve blepharospasm and oromandibular dystonia. In blepharospasm, a light touch to the cheek or near the eyes is commonly used. Gestes reported for oromandibular include a light touch to the face, humming, singing, yawning, pulling an eyelid, pinching the neck, chewing gum, sucking on candies, bending the neck forward or talking. Although external supports and devices are not generally helpful in cervical dystonia, placing objects in the mouth or between the teeth often ameliorates oromandibular dystonia. Thus, various reports describe relief from custom dental or oral prosthetics. Similar to cervical dystonia, oromandibular dystonia in some patients can be relieved by thinking about the geste.

EMG has been used to characterize the modulation of dystonic muscle activity by gestes. Two distinct patterns of neck muscle surface EMG during performance of an effective geste have been reported. Two-thirds of patients have a decrease in EMG amplitude and in recruitment in at least one dystonic muscle. One-third of patients, and only those with phasic CD, have an increase in tonic muscle activation in at least one dystonic muscle. Four percent of subjects have no change in EMG pattern during the geste. Gestes can suppress burst, tremorous, and continuous dystonic EMG activity. Wissel et al. confirmed that touch is not necessary to elicit dystonia relief. They found a decrease in EMG activity that was movement related, starting before the finger actually made contact with the face, in 52% of patients. EMG activity decreased again when the geste was released. In 28% of patients, the EMG activity did not decrease until contact was made. Decreased EMG activity was not sustained during touch in all cases, and outlasted the touch in 28% of patients. The role of the geste itself in mediating a decrease in muscle activity is not certain since moving towards and maintaining the head in midposition causes a similar decrease in cervical muscle EMG activity in patients without gestes.

On PET scanning, Naumann et al. demonstrated increased activation of the postcentral gyrus and other parietal areas ipsilateral to the direction of head rotation with a decrease in the activity of the contralateral supplementary motor area and primary sensorimotor cortex during performance of an effective geste. Clinical observation and physiological studies thus suggest that the mechanism by which geste maneuvers decrease dystonic posture involves somatosensory or proprioceptive feedback modulating neuronal activity in the basal ganglia-thalamo-cortical circuits implicated in the generation of dystonia.

Thus, when present, gestes provide temporary dystonic relief for some individuals and can provide insight into the pathophysiology of dystonia.

See also: Basal Ganglia; Blepharospasm; Botulinum Toxin; Cervical Dystonia; Dystonia; Dystonia in Amish-Mennonite and Mennonite Families; Dystonia, Drug-induced (Acute); Dystonia, Secondary; Dystonia, Task-specific; Dystonia, Traumatic; Dystonic Storm; DYT1; DYT2, Autosomal Recessive Generalized Dystonia; DYT4, Autosomal Dominant Type Dystonia or Whispering Dysphonia; DYT5; DYT6, Mixed Phenotype Primary Dystonia; DYT7, Autosomal Dominant Focal Dystonia;

DYT11, DYT15, Myoclonus-dystonia; DYT12, Rapid Onset Dystonia-parkinsonism; DYT13, Cranio-Cervical-Brachial; Electromyography (EMG); Generalized Primary Torsion Dystonia; Meige's Syndrome; Tardive Dystonia.

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Glabellar Reflex

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Glossary

Glabellar reflex – A primitive reflex elicited by tapping a person's forehead (between the nose and eyebrows) with an index finger and observing that the eyes blink.

Habituation – A decrease in a response to a stimulus after exposure to repeated stimuli over a duration of time.

Myerson's sign – The lack of habituation of the glabellar reflex.

Primitive reflex – Reflex originating from the central nervous system normally present in infancy and early childhood that disappears in the mature brain. Presence of a primitive reflex in adulthood is viewed as a physical finding associated with brain pathology.

The glabellar reflex is one of the primitive reflexes. Primitive reflexes originate in the central nervous system, are present in infancy and early childhood, and disappear as the brain matures. If they are present in a neurologically intact adult, they are felt to represent central nervous system pathology.

The glabellar reflex is elicited by tapping the forehead in between the eyebrows and nose (known as the glabella) with the index finger of the examiner. While the subject will blink in response to the first several taps, blinking ceases with additional taps. If the blinking persists in an adult (sometimes termed Myerson's sign), the finding is considered abnormal.

Physiologically, the glabellar reflex occurs via transmission of afferent sensory signals by the trigeminal nerve to the brainstem bulbopontine level. The efferent signals conducted by the facial nerve cause contraction of the orbicularis oculi muscle and result in the blinking of the eyes. Influences on the reflex come mainly from the cerebral cortex and basal ganglia. In a study of children from ages 2 days to 18 years and adults from 18 to 50 years, the mean number of glabellar taps required for habituation of the blink reflex increased from ~3 at 0–2 months of age to a peak of 13 at ages 3–4 and remained at more than 10 until age 6. Then, a rapid decline occurred reaching an adult level of 2–5 blinks to habituation by age 12.

The abnormal glabellar reflex has been examined as a diagnostic sign in many conditions, especially in older persons. While an abnormal glabellar reflex may be present in the pediatric population with conditions such as mental retardation, it commonly has been examined in

geriatric populations as a sign of cognitive and/or movement disorders.

Some of the difficulty in associating an abnormal glabellar reflex with a specific age-related condition lies in the fact that the abnormal glabellar reflex increases in prevalence with aging. In normal aging Dutch individuals from age 25 to 75, the prevalence of the glabellar reflex increased from about 10% between ages 25 and 45 to 22% between ages 66 and 82 with no significant difference between men and women. In a Japanese brain imaging study of 68 normal aged volunteers, 50% of all subjects had one primitive reflex (glabellar, snout, or palmomental). Individuals with a primitive reflex had more incidental cerebral lesions with no differences in mean regional blood flow and brain atrophy.

In the limited prospective studies examining the relationship between an abnormal glabellar reflex and cognition, an abnormal glabellar reflex was not found to be a marker of cognitive decline in older persons. However, a higher prevalence of an abnormal glabellar reflexes in individuals with dementia (including Alzheimer's disease) and with movement disorders (mainly Parkinson's disease) has been noted in longitudinal cohort studies and in case-control studies.

While the finding of an abnormal glabellar sign may not be a sensitive or specific physical exam finding for dementia and/or a movement disorder, it may be a more useful marker of disease severity, especially if it is present with other primitive reflexes. Also, habituation to the glabellar reflex may change in response to therapy. In Parkinson's disease, small studies have pointed to reduction of the abnormal glabellar reflex during the 'on' period of treatment with dopamine replacement agents. However, at least one study has found that the presence of the glabellar reflex in Parkinson's disease did not vary with plasma dopamine levels and that the presence of the glabellar reflex may reflect extrapyramidal disease.

In conclusion, while an abnormal glabellar reflex is common in older persons, it may be a better sign of severity of a given disease entity (such as dementia or a movement disorder) rather than as a diagnostic sign. Further work is needed to elucidate the underlying pathways resulting in the abnormal habituation of the glabellar reflex in the context of certain neurodegenerative diseases.

See also: Akinetic-Rigid Syndrome; Corticobasal Degeneration; Dementia, Movement Disorders; Multiple System Atrophy; Parkinson's Disease: Definition, Diagnosis, and Management; Progressive Supranuclear Palsy.

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Glial Cell Activation in PD

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Glossary

6-Hydroxydopamine – A dopaminergic neurotoxin inducing parkinsonism in rodents.

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) – A dopaminergic neurotoxin inducing parkinsonism in humans, nonhuman primate, and

other species of animals. MPTP is oxidized by monoamine oxidase to produce 1-methyl-4-phenylpyridinium ion (MPP^+), which is a more potent and true neurotoxin than MPTP itself.
Rotenone – A lipophilic pesticide causing highly selective nigrostriatal dopaminergic degeneration in rodents.
α-Synuclein – A presynaptic nerve terminal protein originally identified as the precursor protein of the non-Aβ component of Alzheimer's disease amyloid. α-synuclein is now known to be a major component of Lewy bodies.

Definition and History

Microglia, the antigen presenting immune cells in the brain, were discovered independently by Nissl (1899) and Robertson 1900, and first studied in detail by Rio-Hortega. Regarding the origin of microglia, the most widely accepted hypothesis is that they are bone marrow-derived cells. Microglia constitute ~10% of all glial cells. Under normal conditions, microglia display a ramified morphology, but rapidly transform into an activated state displaying a plastic ameboid morphology in response to invading pathogens, the presence of foreign substances, or neuronal injuries inflicted by trauma, ischemia, or neurodegeneration. Activation of microglia begins within minutes after the insult and precedes the morphologically detectable neuronal damage. Activated microglia can destroy invading microorganisms and remove potentially deleterious debris by phagocytosis.

Pathogenesis/Pathophysiology

Markers of neuroinflammation, including activated microglia and increased levels of circulating proinflammatory cytokines, have been observed in the brains and cerebrospinal fluid of patients with Parkinson's disease (PD). Activated microglia and reactive astrocytes are prominent in the substantia nigra in PD. The presence of activated microglia in the substantia nigra is also observed in animal models of PD. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), rotenone, and 6-hydroxydopamine (6-OHDA) all cause selective degeneration of nigrostriatal system.

In addition to the dramatic morphological changes, activation of microglia results in the upregulation of surface molecules. Furthermore, activation of microglia leads to an increase in the production of cytokines such as tumor necrosis factor-α (TNFα), interleukin-1β (IL-1β), IL-2, IL-4, IL-6, interferon-γ (IFNγ), the induction of inducible nitric oxide synthase (iNOS), cyclooxygenase-1 (COX-1), COX-2, and the activation of enzymes such as NADPH oxidase. These proinflammatory and neurotoxic factors and related enzymes are upregulated in human PD brains and experimental animal models of PD. Furthermore, studies of postmortem of PD brains and various cellular and animal models of PD strongly suggest that the generation of proinflammatory and neurotoxic factors by microglia plays a prominent role in mediating the progressive neurodegenerative process. The proinflammatory cytokines TNFα and IL-1β can trigger direct toxicity in neurons and potentiate an ongoing inflammatory response by enhancing microglial NO production. Mice deficient in TNFα receptors are completely resistant to MPTP toxicity. Several groups have shown an association of IL-1β gene polymorphism with increased risk of PD. IFNγ has been demonstrated to induce the expression of major histocompatibility complex class II molecules in microglia in vitro. Mice lacking *iNOS* gene are less sensitive to MPTP-induced loss of dopaminergic neurons in the substantia nigra. Microglia upregulate the levels of COX-2, a key enzyme responsible for the synthesis of inflammation-related prostaglandins. The prostaglandins can be directly toxic to neurons through activation of caspase 3, or indirectly through the release of glutamate by astrocytes leading to excitotoxicity. Mice lacking COX-2 gene, but not COX-1 gene, are significantly less vulnerable to MPTP-induced nigral degeneration. NADPH oxidase is one of the major sources for production of reactive oxygen species or related reactive nitric species in activated microglia. In mice lacking a functional NADPH oxidase, significant protection against MPTP-induced nigral degeneration is observed. Thus, activation of microglia is associated with the induction of neuronal cell death in PD, causing the vicious cycle of neurodegeneration. This is in line with the autopsy finding that activated microglia were present in the substantia nigra in human subjects decades after MPTP exposure, suggesting that even a brief pathogenic insult can induce an ongoing inflammatory response.

Astrocytes can produce various proinflammatory and neurotoxic factors, and may play a role in modulating microglial activity. Intercellular adhesion molecule-1 (ICAM-1) is overexpressed in reactive astrocytes in the substantia nigra in PD cases. Additionally, its counter receptor lymphocyte function-associated antigen 1 (LFA-1) is overexpressed in activated microglia. Astrocytes also secrete a number of neurotrophic factors. These include glial cell line-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), and mesencephalic astrocyte-derived neurotrophic factor (MANF). Overexpression of NF-E2-related factor 2 (Nrf2) in astrocytes is also reported to protect against 6-OHDA damage in mice. Furthermore, astrocytes may suppress microglial activation by releasing transforming growth factor-β or IL-10. Astrocytes may play dual roles in neurodegeneration in PD.

Pathological Feature

The discovery of point mutations of the α-synuclein gene and amplification of the gene in some familial forms of PD, and the identification of α-synuclein protein as a major component of Lewy bodies, the histological hallmark of PD, in sporadic and familial PD, have emphasized interest in the role of α-synuclein in the pathomechanisms in PD. Lewy body formation has been considered to be a marker for neuronal degeneration, because neuronal loss is found in the predilection sites for Lewy bodies. To date, more than 70 molecules have been identified in Lewy bodies, in which α-synuclein is a major constituent of the inclusions. α-Synuclein is a potent activator of microglia and induces microglial expression of both IL-1 and TNFα. Microglia stimulated by a combination of α-synuclein and IFNγ are neurotoxic in vitro. Aggregated extracellular α-synuclein activates microglia in culture. This α-synuclein-induced microglial activation leads to dopaminergic neurotoxicity in a midbrain neuron/microglia mixed cell culture. However, the α-synuclein treatment does not produce the neurotoxic affect in the absence of microglia. α-Synuclein can stimulate the expression of ICAM-1 and the secretion of IL-6 in human astrocytes in vitro. Nigral neuronal damage may release aggregated α-synuclein that activates microglia with the production of proinflammatory mediators, thereby, leading to persistent and progressive nigral neurodegeneration in PD. Although α-synuclein is concentrated in the presynaptic nerve terminals in the normal brain, in vitro studies have shown that α-synuclein mRNA and protein are also expressed in both astrocytes and oligodendrocytes. Fibrillary aggregates of α-synuclein have been reported in astrocytes in PD. α-Synuclein expression in astrocytes increases in response to stimulation with the proinflammatory cytokine IL-1β. Although α-synuclein inclusions have also been reported in oligodendrocytes, they do not seem to play a role in promoting inflammation. Conversely, α-synuclein inclusions have never been described in microglia.

Epidemiology/Management

Nonsteroidal antiinflammatory drugs are effective inhibitors of COX enzymes that block the production of prostaglandins. Epidemiological studies suggest that chronic use of nonsteroidal antiinflammatory drugs such as aspirin and ibuprofen reduce the risk of PD. Evidence is accumulating that anti-inflammatory agents may have a place in PD therapy.

Prognosis

Activation of microglia is a double-edged sword in PD pathogenesis. Microglia produce several protective factors including antioxidants, growth factors, and signals to astrocytes that can secrete neuroprotective factors. Microglia also play an important role in the disposal of extracellular α-synuclein aggregates. However, microglial activation induces cell death in the substantia nigra through increasing oxidative stress and through producing noxious compounds including proinflammatory cytokines.

See also: Alpha-synuclein; Inflammation and Parkinson's Disease; MPTP; PARK1, Alpha Synuclein; Parkinson's Disease: Animal Models; Parkinson's Disease: Definition, Diagnosis, and Management.

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Glial Cytoplasmic Inclusions

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Glossary

αB-crystallin – A lens protein which has homology with the small heat-shock proteins and is also expressed in nonlenticular tissues.

α-Synuclein – A presynaptic nerve terminal protein originally identified as the precursor protein of the non-Aβ component of Alzheimer's disease amyloid. α-Synuclein is now known to be a major component of Lewy bodies and glial cytoplasmic inclusions.

Definition and History

Glial cytoplasmic inclusion (GCI) is a histopathological hallmark of multiple system atrophy (MSA), a sporadic neurodegenerative disorder characterized clinically by combinations of parkinsonism, cerebellar signs, autonomic failure, and pyramidal signs. MSA was previously thought to be three separate diseases known as striatonigral degeneration, olivopontocerebellar atrophy, and Shy–Drager syndrome. Graham and Oppenheimer (1969) first proposed the term MSA based on the finding that sporadic striatonigral degeneration, olivopontocerebellar atrophy and Shy-Drager syndrome can coexist both clinically and pathologically. GCIs are consistently found in the brain of patients with MSA regardless of clinical presentation. The discovery of GCIs confirmed that MSA is a single clinicopathological entity.

Cellular Pathology

GCIs are argyrophilic and oligodendroglial in origin. They are triangular, sickle, half-moon, oval, or conical in shape. The nuclei of the GCI-bearing cells appear to be slightly larger and lighter than those of normal-looking oligodendrocytes. Immunohistochemical studies have shown that GCIs contain many substances, including α-synuclein, ubiquitin, tubulin, and αB-crystallin. The cells containing GCIs also give positive staining with oligodendroglial markers, including carbonic anhydrase isoenzyme II, transferrin, Leu-7, and heat-stable tubulin polymerization promoting protein. Gallyas-Braak impregnation method and α-synuclein immunohistochemistry are the most sensitive techniques to demonstrate GCIs. Ultrastructurally, GCIs consist of randomly arranged, loosely packed, granule-coated fibrils ~25–40 nm in diameter. Filamentous inclusions are also found in the nuclei of GCI-bearing oligodendrocytes.

Distribution

GCIs are widely distributed throughout the central nervous system. Although GCIs are more numerous in the areas showing neuronal loss and gliosis, as well as their targets, they are distributed even in regions in which neuropathological changes (neuronal depletion, loss of myelin and axons, or reactive astrocytosis) seem minimal or negligible. High GCI density is seen in the motor and supplementary motor cortical areas, white matter subjacent to the motor cortical areas, caudate nucleus, putamen, globus pallidus, internal capsule, external capsule, pontine base, middle cerebellar peduncle, cerebellar white matter, and reticular formation of the brainstem. GCIs are also present in the spinal cord and olfactory bulbs.

Pathogenesis/Pathophysiology

The most important recent development in the characterization of GCIs has been the discovery of α-synuclein in MSA. α-Synuclein was originally identified as a presynaptic nerve terminal protein. In Parkinson's disease and dementia with Lewy bodies, α-synuclein is deposited in neuronal cell bodies and processes as Lewy bodies and Lewy neurites, whereas filamentous aggregates of α-synuclein are predominantly found in oligodendrocytes as GCIs in MSA. α-synuclein deposited in α-synucleinopathy lesions was phosphorylated at Serine129; anti-phosphorylated α-synuclein antibody intensely immunolabeled Lewy bodies and Lewy neurites in Parkinson's disease and dementia with Lewy bodies, as well as GCIs in MSA. Moreover, the phosphorylated α-synuclein is ubiquitinated. Lewy bodies and GCIs are also immunopositive for synphilin-1, an α-synuclein-associated protein.

Although α-synuclein is abundantly expressed in neurons, α-synuclein mRNA and protein have been reported to be expressed by cultured rat oligodendrocytes. α-synuclein immunoreactivity has been detected in the neuronal perikarya and axons as well as in the cytoplasm of oligodendrocytes in proteinase K- or formic acid-treated

sections of normal human brain. Therefore, it is possible to consider that overexpression of α-synuclein in oligodendrocytes can cause GCI formation.

In addition to GCIs, neuronal inclusions have also been observed in MSA. Neuronal cytoplasmic inclusions (NCIs) were first described in the pontine and arcuate nuclei of patients with olivopontocerebellar atrophy, using silver impregnation techniques such as Bielschowsky and Bodian staining. Subsequently, several investigators revealed that NCIs were also found in the putamen, substantia nigra, inferior olivary nucleus, motor cortex, and dentate gyrus. The NCIs in the pontine nucleus are visible as round or ovoid inclusions, whereas those in the inferior olivary nucleus are reniform, crescent-shaped, or coarse granular in shape. The NCIs in the dentate granule cells are ring-like or C-shaped inclusions. Moreover, neuronal nuclear inclusions are found in the same populations as the NCIs. The neuronal nuclear inclusions consist of fibrillary or thread-like structures, irregularly arranged near to the nuclear membrane, and are occasionally seen to fill the whole karyoplasm.

The occurrence of GCIs precedes neuronal degeneration in MSA. This notion is supported by some cases of 'minimal change' MSA in which neuronal loss was restricted to the striatonigral and olivopontocerebellar systems, but GCIs were widely distributed in the central nervous system. The incidence of GCIs is correlated with the severity of neuronal loss in the olivopontocerebellar system as well as in the striatonigral system. Apoptosis occurs almost exclusively in oligodendrocytes, and extensive myelin damage is present in the MSA brain. Moreover, loss of myelin is much more severe than that of axons in the pontine base (transverse fibers), suggesting that loss of myelin precedes loss of axons in the disease process of MSA. Thus, widespread occurrence of GCIs may cause oligodendroglia–myelin degeneration (oligodendrogliopathy) in the central nervous system in MSA.

Since the discovery of α-synuclein as a major component of glial and neuronal inclusions in MSA, two neurodegenerative processes have been considered in this disease; one is due to the widespread occurrence of GCIs associated with oligodendrogliopathy in the central nervous system, and the other is due to the filamentous aggregation of α-synuclein in neurons in several brain regions. These two degenerative processes might synergistically cause neuronal depletion in MSA.

Animal Models

In order to study the consequence of α-synuclein expression in oligodendrocytes, transgenic mouse models were generated in which human α-synuclein was driven by oligodendrocyte-specific promoters. MSA-like pathology has been reported in transgenic mice with oligodendroglial α-synuclein overexpression combined with mitochondrial inhibition by 3-nitropropionic acid. In a transgenic mouse model that expresses human wild-type α-synuclein in oligodendrocytes of the mouse central nervous system under the control of the 2′,3′-cyclic nucleotide 3′-phosphodiesterase promoter, they developed slowly progressive motor impairments, filamentous aggregates of human α-synuclein in oligodendrocytes, but not in neurons, linked to the autophagocytosis of myelin, and loss of oligodendrocytes and neurons. Several investigators have generated transgenic mouse lines expressing human α-synuclein under the control of the murine myelin basic protein promoter. These mice displayed severe neurological alterations, accumulation of phosphorylated human α-synuclein in oligodendrocytes, loss of dopaminergic fibers in the basal ganglia, and myelin pallor in the white matte. These findings suggest that oligodendrocytic degeneration is a consequence of α-synuclein aggregates and that GCIs cause secondary neuronal degeneration.

See also: Multiple System Atrophy; Multiple System Atrophy: Animal Models; PARK1, Alpha Synuclein; Striatonigral Degeneration; Synucleinopathies.

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Glucocerebrosidase Gene Mutations and Parkinsonism

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Glossary

Glycosphingolipids – A subtype of glycolipids (carbohydrate-attached lipids whose role is to provide energy and serve as markers for cellular recognition) containing the amino alcohol sphingosine. In Gaucher's disease, glucocerebroside (a type of glycosphingolipid) accumulates in lysosomes and macrophages resulting in multiorgan involvement.

Lewy body – An eosinophilic cytoplasmic inclusion whose primary structural component is α-synuclein; considered the pathological hallmark of Parkinson's disease.

Lewy body dementia, Lewy body disease, dementia with Lewy bodies – A disease characterized by dementia and parkinsonism.

Lipid (fats) storage disorders – A group of inherited metabolic disorders in which abnormal lipids accumulate in some of the body's cells resulting in cellular and organ failure. People with these disorders either do not produce enough of one of the enzymes needed to metabolize lipids or they produce enzymes that do not work properly. The nervous system, spleen, and bone marrow are usually affected.

LRRK2 – A gene that encodes a cytoplasmatic protein. Mutations in this gene have been associated with autosomal dominant Parkinson's disease, previously known as *PARK8,* but also with sporadic cases.

Lysosomes – Intracellular organelles that contain digestive enzymes (acid hydrolases), and digest excess or worn-out organelles, misfolded proteins, food particles, and engulfed viruses or bacteria.

Ubiquitin–proteosome system – An intracellular system by which misfolded proteins are tagged with polymeric ubiquitin for subsequent degradation by the proteasome.

α-Synuclein – α-Synuclein is a soluble protein that can aggregate to form insoluble fibrils in pathological conditions characterized by Lewy bodies such as in Parkinson's disease, dementia with Lewy bodies and multiple system atrophy.

Definition and History

The Glucocerebrosidase Gene and Gaucher Disease

The glucocerebrosidase gene, located on 1q21, encodes for the lysosomal enzyme glucocerebrosidase, which normally hydrolyzes glucocerebroside to glucose and ceramide. Deficiency of the glucocerebrosidase enzyme leads to the accumulation of glucocerebroside in lysosomes and macrophages resulting in multiorgan involvement. The ensuing clinical condition, named Gaucher disease, is the most prevalent, recessively inherited lysosomal lipid storage disease. The clinical manifestations include hepatosplenomegaly, anemia, thrombocytopenia, and easy bleeding. Bone and pulmonary involvement may also be present. Gaucher disease is classified into three subtypes based on the absence (type 1), presence of neurological involvement during childhood (type 2), or adolescence (type 3). Type 1 Gaucher disease, the most common form, is not associated with neurological manifestations, by definition. Type 1 is panethnic, but is especially prevalent among individuals of Ashkenazi Jewish descent. The carrier frequency for the glucocerebrosidase gene mutation is estimated at 0.0343 in the Ashkenazi Jewish population, and at 0.006 in the general population. In recent years, a subset of type 1 Gaucher patients who developed parkinsonism has been described.

Parkinsonism in Gaucher Type 1 Patients

Initial case reports indicating the existence of an association between Gaucher disease and parkinsonism described Gaucher patients with early onset, treatment refractory parkinsonism. Subsequently, Gaucher patients manifesting parkinsonism characterized by asymmetric onset of rigidity, resting tremor, bradykinesia, and favorable response to levodopa, as well as atypical, levodopa resistant disease were reported. Furthermore, an increased incidence of parkinsonism was reported in obligate heterozygotes, relatives of patients with Gaucher disease.

Epidemiology

Glucocerebrosidase Gene Mutations in Patients with Parkinson's Disease

Glucocerebrosidase gene mutations have been described in pathological samples and in clinical cohorts of patients with Parkinson's disease and Lewy body dementia. Sequencing of the glucocerebrosidase gene from 57 DNA samples

collected from brain bank material of patients diagnosed pathologically with idiopathic Parkinson's disease identified mutant glucocerebrosidase in 14% versus 4.6% mutant glucocerebrosidase in brain samples without pathological evidence of Parkinson's disease. In clinically diagnosed Parkinson's patients, mutant glucocerebrosidase was repeatedly detected more often than expected, in patients from various ethnic groups, with frequencies varying several folds among studies, and even within cohorts of similar ancestry. In a clinic based Ashkenazi cohort from Israel, 31% of 99 Parkinson's disease patients carried a mutant glucocerebrosidase as compared to 4.1% of 74 Alzheimer's patients and 6.2% of 1543 controls composed of healthy individuals undergoing testing to identify recessive disorders. An additional Israeli cohort identified a glucocerebrosidase carrier frequency of 17.9% in patients with Parkinson's disease versus 4.2% in elderly and 6.35% in young controls. A study in New York City revealed that 13.7% of 278 Parkinson's patients carried a glucocerebrosidase gene mutation compared to 4.5% of controls. The frequency of the glucocerebrosidase gene mutations was higher in a subset of 178 patients of Ashkenazi descent (16.9%). In Toronto, Canada, investigators reported a glucocerebrosidase gene mutation frequency of 5.6% of 88 Caucasian Parkinson's patients with early age of onset parkinsonism compared to 0.8% of controls. An increased number of Parkinson's disease patients presenting a mutation in the glucocerebrosidase gene as compared to controls was reported in Portugal (6.1% vs. 0.7%), Taiwan (12.9% of patients with early onset parkinsonism vs. 1.8% of controls), Brazil (3% of patients with early onset parkinsonism vs. 0% of controls), Venezuela (12% of patients with early onset parkinsonism vs. 3.2% of controls), Singapore (3% vs. o%), and Southern Italy (2.8% vs. 0.2%), but not in patients of Norwegian descent. The number of the glucocerebrosidase gene mutations studied varied among studies, from only two (N370S and L444P, the two most prevalent mutations) to comprehensive screening of the entire coding region. Parkinsonism was found to be associated with multiple allelic variants of the glucocerebrosidase gene.

The glucocerebrosidase mutations were not found to be associated with the G2019S mutation in the leucine-rich repeat kinase 2 gene which encodes the protein dardarin, and has been associated with autosomal dominant, late onset Parkinson's disease in both Askhenazi Jewish and non-Jewish subjects.

Clinical Features

Phenotypic Spectrum of Parkinson's Patients Carrying Glucocerebrosidase Mutations

The clinical features encountered among subjects with parkinsonism and glucocerebrosidase mutations include a wide spectrum of clinical manifestations. Patients with early age of onset, and refractory to levodopa therapy have been described along with patients with a classic presentation, including asymmetric onset of rigidity, tremor, and bradykinesia, favorable response to levodopa and clinical course that does not differ from patients with Parkinson's disease without glucocerebrosidase mutations. Recent analyses have suggested a high incidence of glucocerebrosidase mutations in patients diagnosed clinically and pathologically with Lewy body dementia. Treatment trials in a few subjects with Gaucher disease and parkinsonism with enzyme replacement therapy using recombinant human glucocerebrosidase did not show improvement or slowing of the parkinsonian symptoms.

Pathogenesis/Pathophysiology

Neuropathology

The neuropathological characteristics of the glucocerebrosidase related parkinsonism include loss of dopaminergic neurons in the substatnia nigra, synuclein positive Lewy bodies in the CA2–4 layers of the hippocampus or distributed all over the cortex and in the substantia nigra, and focal regions of gliosis especially in the hippocampal CA2–4 region and calcarine cortex. Biochemical cerebrospinal fluid studies show a decreased activity in several lysosomal hydrolases, beyond the expected decreased activity of β-glucocerebrosidase. The parkinsonism may be caused by a presynaptic dopaminergic dysfunction as substantiated in a [^{11}C] CFT and [^{11}C] raclopride PET study of a type 3 Gaucher patient and his heterozygous father, both presenting with treatment responsive parkinsonism. Nevertheless, as numerous studies report levodopa resistant parkinsonism, it would be premature to assume that all glucocerebrosidase related cases of parkinsonism represent a presynaptic hypodopaminergic state.

Pathogenic Mechanisms

The pathogenic mechanism causing parkinsonism in glucocerebrosidase gene mutation carriers remains elusive. Several hypotheses have been suggested. Since processing of α-synuclein occurs in lysosomes, glucocerebrosidase mutations might cause lysosomal dysfunction or interfere with the binding of α-synuclein at the lysosomal membrane. In addition, the aggregation of proteins in Lewy bodies suggests protein mishandling and subsequent proteolytic stress that might overwhelm the ability of the ubiquitin–proteasome system to degrade abnormally accumulated proteins, including α-synuclein. The functional form of α-synuclein is a lipid-bound state, and involves an interaction with lipid membranes. Glucocerebroside accumulation may perturb the affinity of the α-synuclein to lipid surfaces. The recent observation that α-synuclein binds to glucocerebroside-containing glycosphingolipids

which are elevated in glucocerebrosidase gene mutation carriers, supports this scenario.

Thus, a possible Parkinson–Gaucher intersection would involve a toxic gain of function related to aberrant α-synuclein accumulation, degradation, or a combination of both processes.

Summary

The association between Parkinson's disease and the glucocerebrosidase gene indicates that glucocerebrosidase mutations increase susceptibility to parkinsonism in heterozygotes from diverse ethnicities. Carriage of mutant glucocerebrosidase is one of the most significant risk factors for parkinsonism, identified to date. However, since the vast majority of patients with Gaucher disease never develop Parkinson's disease, it is likely that additional genetic and environmental factors interact with the glucocerebrosidase gene mutation's impact, resulting in the variety of clinical manifestations and responsiveness to levodopa therapy.

See also: Alpha-synuclein; Dementia with Lewy Bodies; Lick-force Rhythm Test; PARK1, Alpha Synuclein; *PARK8, LRRK2* (Dardarin); Parkinson's Disease: Animal Models; Parkinson's Disease: Genetics; Paroxysmal Movement Disorders; Pelizaeus-Merzbacher Disease; Proteasome Function in Movement Disorders.

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Gluten Ataxia

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Glossary

Ataxia – Disorder of coordination and balance that frequently affects limb movement, gait, eye movements, speech, and swallowing.

Autoimmunity – Lack of recognition by an organism of its own constituent parts as self, may result in an immune response against the organism's own cells and tissues; autoimmune diseases include celiac disease, systemic lupus erythematosus, Hashimoto's thyroiditis, rheumatoid arthritis among others.

Celiac disease (CD) – Celiac disease or gluten sensitive enteropathy, classically a disease characterized by gastrointestinal signs and symptoms.

Gluten ataxia (GA) – An immune-mediated disease triggered by dietary intake of gluten, associated with cerebellar signs and symptoms, often related to genetic susceptibility.

Definition and History

Celiac disease (CD) was first described in 100 AD. Classic CD (also known as gluten-sensitive enteropathy), was thought to be exclusively a disease of the small bowel and characterized by weight loss, diarrhea, abdominal bloating, and malabsorption. Gluten sensitivity (GS) refers to the whole spectrum of clinical manifestations,

including extraintestinal ones. Such manifestations can occur independently of the presence of the classic small bowel enteropathy. Cerebellar involvement, in the context of GS, also known as gluten ataxia (GA), is one of such extraintestinal manifestations that have only been recognized in the last decade. Currently-GA is defined as sporadic cerebellar ataxia associated with the presence of serological evidence of GS.

Pathogenesis/Pathophysiology

Postmortem examination from patients with GA demonstrates patchy loss of Purkinje cells throughout the cerebellar cortex. There is marked perivascular cuffing with inflammatory cells, mainly T lymphocytes within the cerebellar white matter. These findings are in favor of an immune-mediated pathogenesis.

Experimental evidence suggests that there is antibody cross-reactivity between antigenic epitopes on Purkinje cells and gluten peptides as well as tissue transglutaminase (the autoantigen in CD). Support for an antibody-mediated pathogenesis comes from the fact that intraventricular injection of serum from patients with GA can induce ataxia in mice. The role of transglutaminases in GA appears to be very important. Immune response targeting different types of transglutaminases (TG2 in CD, TG3 in dermatitis herpetiformis, TG6 in GA) may dictate the primary manifestation (e.g., bowel vs. skin vs. cerebellum involvement, respectively). The structural similarity among these transglutaminases may also explain the considerable overlap of these manifestations.

Epidemiology/Risk Factors

GA is probably one of the commonest causes of idiopathic sporadic ataxia (10–45%). A number of studies looking at the prevalence of antigliadin antibodies in patients with ataxia have been published. The common finding in all of these studies is the consistently high prevalence of these antibodies in sporadic ataxias when compared to healthy controls. Some have found a high prevalence of these antibodies in patients with genetically determined ataxias and in patients with Huntington's disease. This finding, if confirmed by larger studies, should not necessarily challenge the existence of GA as a disease entity, but rather should stimulate interest on the possible mechanism by which a genetically determined ataxia or other neurodegenerative process can result in the generation of antibodies against gluten. Variations in prevalence may relate to differences in the antigliadin assays used, geographical differences, and methodology including inadequate population size to extract meaningful prevalence information. Like CD, GA is associated with the HLA DQ2 and DQ8, which represent risk factors for the development of both CD and GA.

Clinical Features

There are no unique features that distinguish GA from other ataxias. The following clinical characteristics are based on 160 patients diagnosed and followed over the last 12 years. GA is characterized by insidious onset of predominantly gait ataxia, often associated with symptoms and signs suggestive of peripheral neuropathy (60%). The mean age at onset is 53 years. It affects both sexes equally. Evidence of limb ataxia is seen in up to 90% of patients with lower limbs more often affected than upper limbs. Gaze-evoked nystagmus and other ocular signs of cerebellar dysfunction are seen in up to 80% of cases. Additional movement disorders encountered in GA include myoclonus, chorea, palatal tremor, and opsoclonus myoclonus. As with CD, patients with GA are often found to have an increased prevalence of additional autoimmune diseases. Gastrointestinal symptoms are seldom seen and are not a reliable indicator of the presence or absence of enteropathy. In this respect, GA resembles dermatitis herpetiformis where gastrointestinal symptoms are not prominent despite the presence of an enteropathy.

Differential Diagnosis

The differential diagnosis includes all late onset acquired sporadic ataxias: cerebellar variant of multiple system atrophy (often associated with autonomic dysfunction), paraneoplastic cerebellar degeneration (usually a rapidly progressive course), immune-mediated cerebellar ataxia (organ-specific autoimmune disease), and idiopathic sporadic ataxia.

Diagnostic Work-up/Tests

By definition, all patients will have positive IgG and/or IgA antigliadin antibodies. Antiendomysium antibodies are present in only 22% of patients. Tissue transglutaminase antibodies are positive in up to 56% of patients with GA, often at lower titers than those seen in patients with CD. The HLA type DQ2 is seen in 70% of these patients (seen in 90% of patients with CD) with the remaining 30% having the HLA DQ8 (10%) and HLA DQ1 (20%). As some of these serological markers may not be 100% specific or sensitive, it is advisable that all these tests are done in all patients suspected of having GA. New markers are emerging such as tissue transglutaminase antibodies against TG6. TG6 may well be the

autoantigen in the neurological manifestations and ultimately prove to be the best marker for GA.

Up to 60% of patients with GA have evidence of cerebellar atrophy on magnetic resonance imaging (MRI). Some patients, in addition, will have evidence of white matter abnormalities which are often extensive and confluent. Even in those patients with GA who have no evidence of cerebellar atrophy on MRI, proton MR spectroscopy of the cerebellum reveals abnormalities, supporting the hypothesis that cerebellar neuronal physiology is abnormal.

Management

The benefits of a gluten-free diet in the treatment of patients with CD and dermatitis herpetiformis have long been established. There are very few studies, mainly case reports, of the effect of gluten-free diet on the neurological manifestations of GS. All but one of these reports primarily concern patients with established CD who then develop neurological symptoms. In the majority of these case reports, adherence to the gluten-free diet is assumed or assessed by improvement of gastrointestinal symptoms. Such an approach is inadequate if partial adherence to the diet is insufficient for neurological improvement to occur. The best marker of strict adherence to a gluten-free diet is serological evidence of elimination of circulating antigliadin antibodies. A small, uncontrolled study looked at the use of intravenous immunoglobulins in the treatment of four patients with GA without enteropathy. All four patients improved. All of these case reports and small studies suggest variable but overall favorable response to gluten-free diet.

Only one systematic study of the effect of gluten-free diet on a cohort of patients presenting with neurological dysfunction, with or without an enteropathy, has been published. Forty-three patients with GA were enrolled. There was significant improvement in performance in all the ataxia tests and in the subjective global clinical impression scale, in the treatment group when compared to the control group. The significant improvement in all the tests when comparing treatment and control groups was apparent even after excluding patients with an enteropathy. The study concluded that a gluten-free diet appeared to be an effective treatment for GA. It was suggested, however, that close monitoring should be undertaken using regular antigliadin antibody estimation and dietetic review to ensure strict adherence to the gluten-free diet.

Prognosis

As the end result of prolonged exposure to gluten in patients with GA is the loss of Purkinje cells, early diagnosis and treatment are imperative to prevent permanent disability. Strict gluten-free diet results in stabilization of the ataxia. It is important to monitor adherence to the diet by regular (e.g., every 6 months) serological testing for GS related antibodies.

See also: Ataxia.

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GM1 Type 3 Gangliosidosis

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Glossary

Athetosis – Involuntary slow continuous distal writhing movements.
Chemical chaperone therapy – Therapy based on chemicals that enhance enzyme activity by stabilizing the mutant protein.
Chorea – Irregular, unpredictable, brief involuntary movements that flow from one part of the body to another in nonstereotyped fashion.
Dystonia – Movement disorder characterized by involuntary twisting movement or abnormal postures resulting from simultaneous contraction of agonist and antagonist muscles.
Gangliosides – Components of the outer leaflet of plasma membranes. They are highly concentrated in neuronal plasma membranes but their function in neurons is unknown.
Gene therapy – Correction of an enzyme deficiency by insertion of a normal gene into the genome to replace an abnormal, disease-causing gene.
A carrier (vector) is used to deliver the therapeutic gene to the patient's target cells.
Hyperkinetic dysarthria – Speech disorder associated with hyperkinetic diseases, mainly characterized by aprosodia, imprecise articulation, abnormal orofacial movements, and vocal forcing.
Speech apraxia – Disorder of speech motor programming, mainly characterized by effortful groping for articulatory gestures, difficulties with the initiation of utterances, dysprosodia, and context-dependent variability of speech performance.
Substrate reduction therapy – Therapy aimed at relieving a deficient enzyme of an excessive substrate burden by pharmacological inhibition of substrate biosynthesis, thereby reducing substrate accumulation.

Definition and History

GM1 gangliosidosis (GM1-g) is an autosomal recessive metabolic disorder due to β-galactosidase deficiency. The gene that encodes this enzyme is located on chromosome arm 3p21.33. β-galactosidase catalyzes glycoconjugates with a terminal β-galactose, including ganglioside GM1, oligosaccharides and keratan sulfate (**Figure 1**). Deficient enzyme activity leads to the accumulation of these substrates, particularly in neurons. Following the first reports from Norman and Craig in 1959, GM1 gangliosidosis was proposed as a new inborn metabolic disorder in the early 1960s by Landing and O'Brien, and β-galactosidase deficiency was first demonstrated by Okada and O'Brien in 1968.

β-Galactosidase deficiency can manifest clinically as either Morquio B disease or GM1 gangliosidosis. Morquio B disease mainly involves generalized skeletal dysplasia without CNS involvement. GM1 gangliosidosis is classified into three clinical subtypes according to the degree of residual enzyme activity and substrate accumulation, which correlates with clinical severity. Type 1 is the most severe form, with rapidly progressive diffuse neurological deterioration, facial and skeletal abnormalities, and visceromegaly; death occurs during the first years of life. Patients with type 2 have less severe skeletal changes and slower neurological deterioration but usually die during childhood. Type 3 (GM1-3g) is characterized by later onset with only mild skeletal abnormalities, a protracted clinical course with survival into adulthood, predominant movement disorders, and selective accumulation of GM1 gangliosides in the striatum.

Genotype–Phenotype Correlation and Pathophysiology

The main substrates that accumulate in β-galactosidase deficiencies are keratan sulfate in Morquio B disease and ganglioside GM1 in GM1 ganglisosidosis, partly explaining the different clinical phenotypes. More than 100 mutations have now been identified in the *GLB1* gene in patients with Morquio B disease and GM1 ganglisosidosis. Neither the type nor the location of mutations has been clearly linked to the clinical phenotype. In GM1-3g, non-Japanese patients usually have heterozygous mutations located throughout the gene, whereas most Japanese patients are homozygous for the I51T mutation.

Altered intracellular signaling and neurotransmission, increased autophagia, and mitochondrial dysfunction have been reported in animal models of GM1 gangliosidosis. Postmortem analysis of the brains of GM1-3g GM1 patients shows abnormalities largely restricted to the striatum, including accumulation of ganglioside GM1 and its

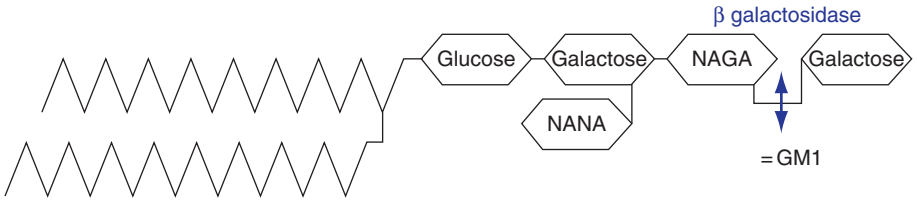

Figure 1 Biochemical defect in GM1 gangliosidosis. β-galactosidase deficiency prevents hydrolysis of the terminal β-galactosyl residues of GM1 gangliosides, leading to massive accumulation.

derivatives, neuronal loss, morphological abnormalities of neurites, and gliosis. Although the precise pathogenesis of the neurological disorders is unknown, it likely involves the metabolic and morphological effects of GM1 ganglioside accumulation. The residual enzyme activity present in GM1-3g patients may protect the brain from these effects, with the exception of the striatum, where GM1 ganglioside turnover may be higher.

Epidemiology

The incidence of GM1 gangliosidosis could be estimated at about 1 in 200 000 births. GM1 gangliosidosis seems to exist worldwide but a higher incidence has been reported in Malta, Cyprus, southern Brazil, and in Bulgarian gypsies. Type 3 accounts for about one-third of cases, and Japanese patients are overrepresented. It is not clear whether it reflects or not a higher incidence of this form in this country.

Clinical Features

Movement disorders are almost always present in the GM1-3g clinical subtype. These patients' initial psychomotor development is usually normal. Onset occurs at a median age of 6 years, and before age 20 years in 85% of cases. Most patients gradually develop generalized dystonia and related gait and speech disorders. Dystonia is an early manifestation and remains prominent throughout the disease course. Major facial involvement with facial grimacing, suggestive of symptomatic dystonia, is particularly significant, as associated swallowing disorders can be life-threatening. Speech disorders can progress to anarthria, leading to severe problems of communication. Patients typically have complex speech alterations consistent with combined hyperkinetic dysarthria and speech apraxia. Dystonia is often associated with akinetic-rigid parkinsonism that also gradually worsens with aging, giving the patients a 'stuck in glue' appearance. Choreoathetoid movements can also be present, mostly in the early stages of the disease. A pyramidal syndrome and mental retardation can be observed and are usually mild when present. Short stature, likely related to skeletal dysplasia, is frequent and can be a good, albeit nonspecific diagnostic clue. Scoliosis and musculo-tendinous retractions are frequent during the course of the disease, most likely secondary to chronic dystonia.

Diagnostic Work-up

Bone radiography can frequently detect minor bone dysplasia, which is a good diagnostic clue to GM1-3g. In particular, flattening or anterior beaking of the vertebral bodies, flattening of the femoral head and acetabular hypoplasia are suggestive of the diagnosis in patients with generalized dystonia. Brain MRI can show hyperintensities of the posterior putamina on T2-weighted images. To confirm the diagnosis, β-galactosidase deficiency has to be established by measuring its activity in leukocytes or skin fibroblasts; values range from 2% to 10% of normal. Molecular analysis of the *GLB1* gene can be performed later, as a basis for reliable genetic counseling and prenatal diagnosis.

Treatment and Prenatal Diagnosis

There is currently no way of preventing or even slowing the progression of the neurological disorders associated with GM1-g. The development of several animal models has made it possible to test new therapeutic approaches, some of which warrant evaluation in clinical trials. In mice, substrate reduction therapy by pharmacological inhibition of gangliosides biosynthesis, and restoration of enzyme activity by gene therapy or chemical chaperone therapy can reduce brain ganglioside accumulation and/or improve the neurological phenotype. Chemical chaperone therapy may be particularly interesting for GM1-3g patients, who usually have some residual β-galactosidase expression. Symptomatic drug therapy of generalized secondary dystonia is usually disappointing but GM1-3g patients can derive some benefit from anticholinergic drugs or benzodiazepines. Deep brain stimulation is also a therapeutic option in this setting, although the improvement is less marked and less predictable than in patients with primary dystonia. Finally, physiotherapy, speech rehabilitation, and swallowing rehabilitation are crucial in improving these patients' quality of life and prognosis. As each subsequent sibling has a 25% risk of being affected and there is no effective

therapy, prenatal diagnosis should be discussed with affected families. It can be based on β-galactosidase assay in fetal amniotic cells, or on the detection of previously identified mutations in trophoblast biopsy specimens.

Prognosis

Clinical severity and the rate of progression both vary widely from one patient to the next, ranging from severe disability in adolescence to mild symptoms and normal social interaction with slow deterioration and survival into old age. The survival of severely disabled patients depends on their swallowing function (risk of respiratory infections and acute respiratory failure), and on their overall management, especially the prevention of decubitus complications.

See also: Akinetic-Rigid Syndrome; Anticholinergics and Movement Disorders; Athetosis; Benzodiazepines and Movement Disorders; Chorea; Choreiform Disorders; Dysarthria; Dystonia; Dystonia, Secondary; GM2 Gangliosidosis.

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GM2 Gangliosidosis

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Glossary

Ataxic dysarthria – Speech disorder associated with a cerebellar syndrome and mainly characterized by dysprosodia, imprecise articulation, and poor coordination of respiration with speech.
Athetosis – Involuntary slow continuous distal writhing movements.
Chorea – Irregular, unpredictable and brief involuntary movements that flow from one part of the body to another in non stereotyped fashion.
Dystonia – Movement disorder characterized by involuntary twisting movement or abnormal postures resulting from simultaneous contraction of agonist and antagonist muscles.
Gangliosides – Components of the outer leaflet of plasma membranes. They are highly concentrated in neuronal plasma membranes but their function in neurons is unknown.
Gene therapy – Correction of an enzyme deficiency by insertion of a normal gene into the genome to replace an abnormal, disease-causing gene. A carrier (vector) is used to deliver the therapeutic gene to the patient's target cells.
Hyperkinetic dysarthria – Speech disorders associated with hyperkinetic diseases mainly characterized by aprosodia, imprecise articulation, and abnormal orofacial movements.
Pharmacological chaperone therapy – Therapy based on pharmacological compounds that enhance enzyme activity by stabilizing a mutant protein.

Substrate reduction therapy – Therapy aimed at relieving a deficient enzyme of an excessive substrate burden by pharmacological inhibition of substrate biosynthesis, thereby reducing substrate accumulation.

Definition and History

GM2 gangliosidosis (GM2-g) is an autosomal recessive metabolic disorder due to β-hexosaminidase deficiency (**Figure 1**). The enzyme is composed of a dimer of two subunits α and β encoded by genes *HEXA* and *HEXB* and two isoforms do exist: hexosaminidase A formed by the hetero dimer αβ and hexosaminidase B formed by the homo dimer ββ. GM2 gangliosidosis can be caused by defects in the genes *HEXA* (Tays–Sachs disease, where only the isoform A is deficient), *HEXB* (Sandhoff disease, where both isoforms are involved) or *GM2A*, an activator required for both isoforms activity. These three genes are located on chromosome 15q23–q24, 5q13, and 5q31.3–33.1, respectively. The normal products of these three genes are required to hydrolyze GM2 ganglioside; deficient activity results in GM2 ganglioside accumulation, particularly in neurons. Tay first identified the cherry-red macular spot observed in the infantile form in 1881, and Sachs, in 1887, identified characteristic neuropathological abnormalities (neurons with distended cytoplasm and ballooning dendrites). They initially called the disease amaurotic idiocy. In 1962, Svennerholm found that ganglioside GM2 is the main neuronal storage compound in GM2-g, and hexosaminidase A deficiency was first demonstrated by Okada and O'Brien in 1969. At the same time, Sandhoff reported that some patients were missing both hexosaminidase A and B.

GM2 gangliosidosis is divided into three clinical subtypes according to the age at onset. In general, the later the disease occurs, the more slowly it progresses. Type 1 (infantile type) begins in the first year of life with rapidly progressive diffuse neurological deterioration and death before 4 years of age. Type 2 (juvenile type with onset between 2 and 10 years) and type 3 (adult type with onset after age 10 years) are more slowly progressive neurological disorders in which the clinical manifestations depend on which parts of the central nervous system are affected. Although rarely prominent, movement disorders can occur in these later-onset forms.

Genotype–Phenotype Correlation and Pathophysiology

The degree of residual enzyme activity partly determines the clinical severity. Mutations that lead to the production of no mRNA, or highly instable mRNA, result in a complete lack of enzyme activity and cause the most severe infantile forms of GM2-g. Late-onset forms are due to less severe point mutations within the coding region, resulting in stable mRNA and residual enzyme activity. In heterozygous patients, disease severity is determined by the less severe of the mutated alleles. For example, at least one G269S or W474C mutation in the *HEXA* gene may be associated with a milder phenotype.

The pathogenesis of the neurological disorders in GM2-g patients, although poorly understood, is primarily due to GM2 and GA2 ganglioside accumulation in neurons. This progressive storage leads to neuronal dysfunction that has been attributed to the disruption of intracellular structures, impaired axonal transport and neurite outgrowth, altered intracellular signaling and neurotransmission, and an abnormal inflammatory response. The residual enzyme activity present in late-onset forms may protect neurons that have a low rate of ganglioside biosynthesis.

Epidemiology

The incidence of GM2 gangliosidosis has been estimated at about 1 in 150 000 births. GM2 gangliosidosis seems to occur worldwide but a higher incidence has been reported in Switzerland, Japan and eastern Quebec, in Louisiana Cajuns, Ashkenazi Jews (Tay–Sachs disease); Lebanese and Lebanese-Canadians, Creoles from northern Argentina, Metis Indians from Saskatchewan, and Maronites from Cyprus (Sandhoff disease). The incidence of Tay–Sachs disease among Ashkenazi Jews was as high as 1 in 3000 births before a screening and genetic counseling program led to a 90% reduction.

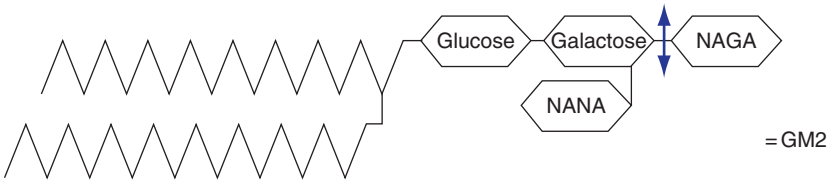

Figure 1 The biochemical deficiency in GM2 gangliosidosis. β-Hexosaminidase deficiency results in an inability to remove the terminal *N*-acetyl-galactosamine residue from GM2 ganglioside, leading to massive GM2 ganglioside accumulation.

Clinical Features

Movement disorders can occur in both the juvenile and adult forms of late-onset GM2 gangliosidosis. Type 2 patients usually have progressive tetraparesis, epilepsy, and dementia. Visual disturbances including optic atrophy and macular cherry-red spot can be present. In addition, rare patients with a less severe juvenile mono-symptomatic forms characterized by pure generalized dystonia have been reported. These pure dystonic forms with a more protracted course are probably underdiagnosed. In type 3 patients, movement disorders are frequent usually in association with more complex neurological disorders. The combination of movement disorders with more common features resulting from cerebellar and motor neuron dysfunction is suggestive of late-onset GM2-g. Psychotic symptoms, mild pyramidal signs, painful sensory polyneuropathy, dysautonomia, vertical supranuclear palsy can also be observed. Movement disorders are occasionally the predominant clinical abnormality. They are observed in 30–50% of patients and include tremor, generalized or focal dystonia, chorea, and parkinsonism. Most patients gradually develop severe gait disorders and become wheelchair-bound within about 20 years after disease onset. Dementia and visual disturbances are very unusual in this form. Progressive speech disorders, mainly consisting of ataxic and/or hyperkinetic dysarthria, are almost always present and gradually result in severe communication difficulties. Swallowing disorders can become life-threatening later in the disease.

Diagnostic Work-up

In late-onset GM1-g, brain MRI can show cerebellar atrophy, either in isolation or associated with mild overall brain atrophy. Neurophysiological examination can reveal abnormalities consistent with anterior horn cell disease or axonal sensory polyneuropathy. Ophthalmological examination is usually normal but some cases of optic atrophy or macular cherry-red spots similar to those seen in the infantile form have been reported in the type 2 form. Rectal biopsy can show membranous cytoplasmic bodies in ganglionic cells from the mesenteric plexus, similar to those observed in the brain. To confirm the diagnosis, β-hexosaminidase deficiency has to be established by measuring its activity in leukocytes or skin fibroblasts. Molecular analysis of the *HEXA*, *HEXB*, or *GM2A* genes can be performed later, as a basis for reliable genetic counseling and prenatal diagnosis.

Treatment and Prenatal Diagnosis

There is currently no way of preventing or even slowing the progression of the neurological disorders associated with GM1-g. The development of several animal models has made it possible to test new therapeutic approaches, some of which warrant evaluation in clinical trials. In mice, substrate reduction therapy based on pharmacological inhibition of ganglioside biosynthesis with miglustat and restoration of enzyme activity by gene therapy have both been found to reduce brain accumulation of gangliosides and/or to improve the phenotype. However, in human, miglustat failed to stop the neurological deterioration in clinical trials. Pharmacological chaperone therapy can increase enzymatic activity in vitro and may be particularly interesting for patients with late-onset disease, who usually have residual β-hexosaminidase expression. Drug therapy of movement disorders associated with GM2-g is usually disappointing. Patients with dystonia and/or choreoathetosis may benefit from treatment with anticholinergic drugs, benzodiazepines or low-dose tetrabenazine. The associated parkinsonism is occasionally dopa-responsive. Psychiatric disorders associated with GM2-g are difficult to treat, and the drugs used (particularly phenothiazines) can lead to neurological deterioration. Physiotherapy, speech rehabilitation, and swallowing rehabilitation are crucial for these patients' quality of life and prognosis. Prenatal diagnosis should be proposed to affected families, as each subsequent sibling has about a 25% risk of being affected. It can be based on β-hexosaminidase assay in fetal amniotic cells, or on the detection of previously identified mutations in trophoblast biopsy specimens.

Prognosis

In type 2 and type 3 GM2-g, severity and the rate of progression both vary widely, ranging from severe disability in adolescence to mild symptoms and normal social interaction with slow deterioration and survival into old age. The survival of severely disabled patients depends mostly on swallowing function (risk of respiratory infections and acute respiratory failure) and on overall management, especially the prevention of decubiti complications.

See also: Athetosis; Chorea; Choreiform Disorders; Dystonia; Dystonia, Secondary.

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Relevant Websites

http://www.ommbid.com/ – Online Metabolic and Molecular Basis of Inherited Disease.

H

Hallervorden–Spatz Syndrome (PKAN)

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Glossary

Autosomal recessive – A mode of inheritance of a disease where two copies of an abnormal gene must be present in order for the disease to develop.
Dystonia – Movement disorder producing muscle contractions with characteristic postures.
Pigmentary retinopathy – A disorder of the retina characterized by deposits of pigment and increasing loss of vision, present in many neurodegenerative diseases.

Definition and History

Hallervorden–Spatz syndrome is an autosomal recessive neurodegenerative disorder. Mutations in the gene encoding pantothenate kinase 2 cause the disorder, which includes abnormal movements, vision defects, and psychiatric problems. The disorder is now referred to as pantothenate kinase-associated neurodegeneration or PKAN.

First described in 1922 by Julius Hallervorden and Hugo Spatz, the eponym for this disorder is no longer favored. These two German neuropathologists participated in objectionable Nazi-era programs. To discredit Hallervorden and Spatz, the medical community sought to abandon the eponym in favor of a rational moniker. Following the discovery of its genetic basis, Hallervorden–Spatz syndrome became known as pantothenate kinase-associated neurodegeneration (PKAN).

Historically, the term Hallervorden–Spatz syndrome encompassed any neurodegenerative disorder associated with high brain iron. Now, the overarching term for this heterogeneous group of disorders is neurodegeneration with brain iron accumulation, or NBIA, of which PKAN is one form.

Pathogenesis/Pathophysiology

PKAN is caused by mutations in *PANK2*, which encodes the mitochondrial form of pantothenate kinase. This key regulatory enzyme phosphorylates vitamin B5, or pantothenate, and commits it to the biosynthesis of coenzyme A. While the precise cascade of metabolic perturbations arising from defective *PANK2* is uncertain, PKAN is an inborn error of coenzyme A metabolism.

PANK2 is one of four homologous genes to encode a pantothenate kinase. Such redundancy at the level of the genome suggests a specific role for each member of this enzyme family. PANK2 is associated with mitochondria, and its unique biochemical features suggest a possible localization to the intermembranous space. There, PANK2 is proposed to function as an indirect sensor of matrix coenzyme A levels, signaling to the cytoplasmic pantothenate kinases 1 and 3.

Defects in PANK2 are predicted to lead to aberrant levels of mitochondrial coenzyme A. However, the limited tissue vulnerability (brain, retina, testis) in PKAN suggests that most cells can overcome this defect. Possible reasons include a relative predominance of PANK2 versus PANK1 and PANK3, high energy demands, or high oxidative stressors. Regardless, the cascade of changes lead to tissue damage, and in the brain, iron accumulation. Clearly, the primary defect precedes accumulation of high amounts of iron. However, abundant iron almost certainly contributes to disease pathogenesis, and it remains the best recognized feature of this rare disorder.

Epidemiology/Risk Factors

PKAN is a rare autosomal recessive disorder. Incidence is estimated to be in the range of 1 in 250–500 000 worldwide. There is no ethnic predilection for mutations in *PANK2*, although specific mutations may be more commonly associated with certain ethnicities. For rare recessive disorders in general, consanguinity increases risk.

Clinical Features and Diagnostic Criteria

PKAN can be generally divided into two phenotypic groups: classic and atypical. Classic disease is clinically homogeneous and is characterized by onset in the first 5 years, with a rapid progression to loss of ambulation by age 15 years. The most common presenting feature is gait abnormality due to limb dystonia, with frequent falls from poor balance. The dystonia worsens with time and progresses to involve more body parts. Dysarthria is common as well. Pigmentary retinopathy occurs in most patients with classic disease, although clinical compromise is generally limited by the more significant neurologic impairment.

Atypical PKAN includes all patients with *PANK2* mutations who do not fit into the classic category. Atypical disease is later in onset, ranging from late childhood to early adulthood. Also, progression is slower, with a loss of ambulation often not until well into adulthood. Furthermore, although patients with atypical disease eventually develop disabling dystonia, the presenting features are more commonly neuropsychiatric disturbances. These may include impulsivity, obsessive-compulsive disorder, depression, and tics. Some patients will carry a diagnosis of Tourette syndrome prior to being diagnosed with PKAN. As a general rule for atypical PKAN, later onset is associated with a slower progression.

For the majority of PKAN patients, characteristic MRI findings lead to the correct diagnosis. The eye-of-the-tiger sign refers to the characteristic MRI pattern found PKAN. Specifically, the sign describes hypointense signal in the globus pallidus in conjunction with a region of central or anteromedial hyperintensity on T_2-weighted imaging. PKAN can be confirmed by direct DNA testing for mutations in *PANK2*.

Differential Diagnosis

The eye-of-the-tiger sign is considered to be virtually pathognomic for PKAN (**Figure 1**). Rare reports have offered evidence to refute this notion; however, none of these has provided sufficient data to challenge this robust association. Therefore, especially in the context of supporting clinical data, the eye-of-the-tiger sign indicates PKAN.

NBIA encompasses a heterogeneous group of disorders that includes PKAN, as well as neuroferritinopathy, aceruloplasminemia, infantile and atypical neuroaxonal dystrophy and idiopathic NBIA. The specific MRI patterns associated with these disorders differ from that of PKAN, though all include high regional iron in the basal ganglia.

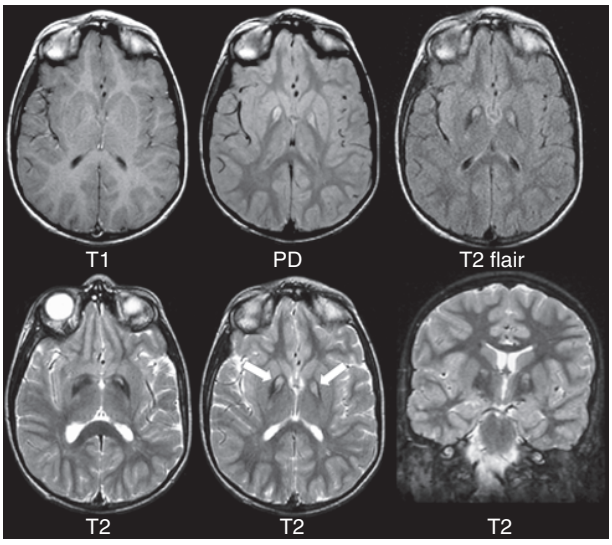

Figure 1 ''Eye of the tiger'' abnormality, T2-weighted imaging shows hypointense signal in the globus pallidus with a region of central or anteromedial hyperintensity (white arrows).

Diagnostic Workup/Tests

When the MRI shows the eye-of-the-tiger sign, diagnostic studies for PKAN are indicated. Blood may be sent for DNA sequencing of *PANK2* in order to confirm the diagnosis. Laboratories currently offering clinical testing can be found at GeneTests. The sensitivity of current screening tests is >98%.

Management

Efforts are underway to develop rational therapies for PKAN. Currently, treatment remains palliative. The two drugs most commonly beneficial in both classic and atypical PKAN are baclofen and trihexyphenidyl. L-DOPA is not beneficial in PKAN, although it may be useful in non-PKAN forms of NBIA. Transient benefit has been reported in some PKAN patients from deep brain stimulation with bilateral electrodes placed in the globus pallidus interna. Newer formulations of CNS-acting chelators may also have a role in limiting the secondary iron accumulation in PKAN. Risks of systemic iron deficiency, especially in children, remain of concern.

Prognosis

PKAN is a relentlessly progressive neurodegenerative disorder. Currently available interventions do not alter the course of disease. In classic disease, the rate of progression typically leads to a loss of ambulation by age 15 years and commonly as early as 5–10 years of age.

Progression is characterized by periods of rapid decline interspersed with plateaus. The factors leading to these episodes of exacerbation remain unknown but seem not to be simple catabolic stress. Once lost, skills are not usually regained.

In contrast to classic disease, atypical PKAN varies with onset from adolescence to adulthood. For these less severe forms, the rate of progression typically is slower.

See also: Dystonia; Eye-of-the-Tiger Sign; Neuroferritinopathy.

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Hallucinations and Movement Disorders

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Glossary

Delusion – False beliefs based on incorrect inference about external reality that is firmly sustained despite what almost everyone else believes and despite what constitutes incontrovertible and obvious proof of evidence to the contrary.

Hallucination – Sensory perception that has the compelling sense of reality of a true perception but that occurs without external stimulation of the relevant sensory organ. Hallucinations may be visual, auditory, olfactory, gustatory, somatic, or tactile.

Illusion – Misperception or misinterpretation of a real external stimulus.

Presence (sense of presence, hallucination of presence) – Vivid sensation that somebody is present nearby, when no one is there and no one is seen.

Psychosis – Applied to PD or other neurodegenerative diseases, this term usually refers to a mental state characterized by hallucinations and/or delusions.

Simple/complex visual hallucinations (VH) – Simple VH consist of elementary visual phenomena such as geometrical patterns, shadows, or flashes. Complex, or formed, VH consist of people, animals, or objects.

History

Movement disorders and hallucinations coexist in a number of conditions, especially in Parkinson's disease (PD) and dementia with Lewy bodies (DLB). An early detailed description of hallucinations in the course of PD was provided by Victor Parant, a French psychiatrist, in 1883. Since the end of the nineteenth century, views on hallucinations and PD have evolved in three stages: in the first stage, they were considered coincidental or end-stage nonspecific phenomena; they were later viewed as a side effect of an antiparkinsonian treatment mainly using dopaminergic agents; more recently, they are viewed as the product of complex interactions of treatment and disease-related factors. Hallucinations and delusion emerged as common and typical features of DLB in the early 1990s.

Clinical Features

The typical hallucinatory syndrome of PD and DLB appears in patients with a clear sensorium and recurs in short sequences (seconds or minutes). Hallucinations may occur at any moment, but are more frequent in the evening and during the night. Complex visual hallucinations (VH) are the most common type, and mostly consist of persons, who may or may not be familiar, and less often animals or objects. The hallucinated figures are usually single or few, and may be relatively stereotyped in a given patient. Hallucinations appear and vanish suddenly, sometimes when the patient tries to check their reality by approaching or touching them. Hallucinatory images are seen superimposed on the normal background scene. Simple VH are uncommon. Auditory hallucinations may be elementary (ringing, knocks, etc.), or more often, complex. When auditory verbal hallucinations are present, they are neutral and clearly different from the pejorative or threatening auditory hallucinations characteristic of schizophrenia. Tactile hallucinations, in most cases, involve contact with small animals or the feeling of being touched by someone. Olfactory, and less often, gustatory hallucinations have been reported in series and case reports. Related 'minor' phenomena include visual illusions (typically seeing an inanimate object as a living being) and a sense of presence. Hallucinatory phenomena may also accompany: for instance, the patient may hear the conversation of unreal persons, or see the small animal he feels creeping on his legs. In a minority of cases, especially in patients with cognitive impairment, delusions may accompany hallucinations.

Patients who are free of cognitive impairment realize the hallucinatory nature of their hallucinations. Demented patients commonly lose this insight. Some patients with cognitive impairment may have partial and (or) fluctuating insight.

Epidemiology

Frequency

In PD, as shown by most cross-sectional prospective studies, VH are present in one quarter to one third of PD patients. Auditory hallucinations are rarer. Hallucinations in other modalities were not systematically sought in most studies, so their prevalence may be underestimated. If illusions and minor forms of hallucinations (e.g., a sense of presence) are taken into account, the prevalence is higher, reaching 40–75% of chronically treated PD patients. Lifetime prevalence of hallucinations is higher than in point prevalence studies, reaching at least 50%. Finally, the prevalence of hallucinations is higher in PD patients with dementia, with figures (50–70%) similar to those observed in the course of DLB.

Studies of hallucinations in other parkinsonian disorders (multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration) are infrequent, so it is difficult to estimate their occurrence in these conditions. However, the available data suggest that hallucinations are rarely present in patients with parkinsonism associated with non-Lewy body parkinsonism.

Risk Factors

In PD, the role of dopaminergic treatment has been considered critical. However, disease-related factors also play an important part. In clinical studies, the main disease-related factor is severe cognitive impairment and/or dementia. Other significant concomitants of hallucinations or psychosis are older age, a longer PD duration, a greater severity of PD, altered dream phenomena (vivid dreams, nightmares, rapid eye movement (REM) associated behavioral disorder), daytime somnolence, and abnormalities of visual input due either to coincident ocular disease or to specific retinal dysfunction affecting contrast sensitivity and color discrimination. A facilitating role for depression is suggested by some, but not all, studies.

Pathophysiology

Imaging or biological studies provide information on the pathophysiology of VH, but no single integrated mechanism has been identified. Neuroimaging studies of PD yielded heterogeneous results, but suggested a decreased visual input ('bottom-up' processes) and a disinhibition of 'top-down' cortical processing. In PD and DLB, pathological studies have shown an association between VH and higher densities of Lewy bodies in the temporal lobe and in the amygdala as well as in other cortical areas. The involvement of dopaminergic, serotoninergic, and/or cholinergic widespread projection pathways in the genesis of hallucinations has been postulated mainly on the basis of indirect pharmacological evidence or more theoretical considerations. The core dopaminergic hypothesis postulates that hallucinations result from the overstimulation of the mesocorticolimbic dopaminergic receptors. Variants of this model focus on several neurotransmitter systems through a cascade of activations and inhibitions. Among these, researchers have advocated both a serotoninergic–dopaminergic imbalance and a monoaminergic–cholinergic imbalance.

Finally, hallucinations may constitute a common end pathway of different, and possibly combined, underlying mechanisms. No simple model can account for the full diversity and heterogeneity of the factors associated with hallucinations in PD. Diederich et al. proposed an integrated model based on Hobson's work on factors

regulating consciousness. A more general model of complex VH involves cognitive and psychology-based models of scene perception.

Diagnostic Work-Up

As hallucinations are not witnessed by physicians, they cannot be directly studied or quantified with ease. The examiner is dependent on what the patient or his/her caregiver reports. When the patient is cognitively impaired, one may assume that only striking hallucinations or those associated with behavioral disorders will be recorded by the caregiver. Prospective studies devoted to the prevalence and/or phenomenology of hallucinations in PD or DLB have used structured or semistructured questionnaires. Other studies and therapeutic trials used various specific or nonspecific scales, the latter being derived from the fields of dementia or psychiatry. The impact of hallucinations must be carefully evaluated. Most hallucinations are nonthreatening, but they may induce anxiety and/or behavioral disorders in some patients. The consequences should also be evaluated in the caregiver, as hallucinations are often poorly understood and accepted.

Management

Nonpharmacological approaches are recommended in all cases. They include providing information on hallucinations to the patient and his/her caregiver; promoting coping strategies; identifying depression or other comorbid psychiatric conditions; checking visual acuity; and evaluating cognition by brief bedside tests. Reducing doses of antiparkinsonian drugs, psychopharmaceuticals, analgesics, and/or anticholinergics given for indications other than those of PD should be considered. If cognitive impairment is present, cholinesterase inhibitors may be added to the regimen. However, evidence that these drugs reduce hallucinations or other psychotic symptoms relies on open-labeled studies. Finally, if hallucinations are responsible for severe anxiety and/or behavioral distress, an antipsychotic drug can be used. According to a 2007 meta-analysis, clozapine is the only atypical antipsychotic fully recommended in this setting. This drug has demonstrated safety and efficacy in controlled trials, but requires blood cell count monitoring for potential agranulocytosis.

Prognosis

Once they occur, hallucinations become a recurrent and chronic problem in most patients with PD. Patients with mild hallucinations and retained insight tend to have more severe hallucinations and lose insight as the disease progresses. Hallucinations are associated with the development and progression of dementia in both cross-sectional and longitudinal studies. Even though prognosis has improved with the use of atypical antipsychotics, hallucinations are associated with an increased risk of nursing home placement and mortality.

See also: Dementia with Lewy Bodies; Dementia, Movement Disorders; Parkinson's Disease: Definition, Diagnosis, and Management; Psychosis in Parkinsonism.

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Hand-reach Task

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Glossary

6-OHDA – 6-Hydroxydopamine (6-OHDA) is a neurotoxin that targets catecholamine neurons and is commonly used to model of Parkinson's disease in animals.
Basal ganglia – A group of subcortical nuclei that is anatomically located between the cerebral cortex and the thalamus. The nuclei consist of the striatum (caudate and putamen), globus pallidus, the subthalamic nucleus, and the substantia nigra.
Bradykinesia – One of the cardinal symptoms of Parkinson's disease and prevalent in a range of movement disorders, bradykinesia refers to the slowness of movements. Difficulty in initiating movement, completing repetitive tasks, and performing simultaneous movements are other noted manifestations.
Dystonia – A group of movement disorders that present involuntary movements and sustained muscle contractions generating twisting movements and abnormal postures. Dystonias can be functional or result from brain injury or other neurodegeneration.
Essential tremor – This progressive, adult-onset disease exhibits characteristic tremors that are rhythmic and exacerbated by voluntary actions. It is the most ordinary tremor and frequently misdiagnosed as Parkinson's disease. Emerging views propose that essential tremor might be a family of diseases unified by the presence of kinetic tremor.
Huntington's disease – An inherited progressive neurodegenerative disorder associated to the genetic mutation of the IT15 gene. The disease presents motor and cognitive dysfunction associated to striatal and cortical neurodegeneration.
Hypokinesia – The reduction of desired movements associated with a decrease in muscle activity. This includes the speed and size of movements.
MPTP – 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is a human neurotoxin that inhibits the mitochondrial complex I. It affects dopaminergic nigral neurons and induces parkinsonian syndrome. MPTP is used to model Parkinson's disease in mice and monkeys.
Parkinson's disease – A progressive neurodegenerative disease of unknown origin that affects 1% of the population over the age of 55. Typical symptoms include tremor, rigidity, bradykinesia, and postural instability. The morphological hallmarks of the disease are dopaminergic nigral cell death and intracytoplasmic aggregations called Lewy bodies.
Tourette's syndrome – A childhood-onset movement disorder that presents involuntary, sudden, and repetitive tics in motor activity or vocalizations. This disease of unclear etiology is often considered a comorbid syndrome since there is high prevalence of Tourette's patients experiencing psychiatric disorders, such as obsessive-compulsive disorder, depression and attention deficit/hyperactivity disorder.

Defining 'Hand Reach Task'

A hand reach task (HRT) is usually defined as a test to assess the gross and fine motor skills of a subject. Gross motor skills are defined as larger movements of the body as sitting up. Fine motor skills refer to the use of small muscle groups to manipulate petite objects, such as to hold a pen between the thumb and a finger. The HRT implies ability to plan, initiate, coordinate hand–eye movement, and execute dexterity.

Anatomy of a Successful HRT

Successful completion of a HRT requires voluntary movements that incorporate neural commands to different muscle groups and input from sensory systems in order to create accurate and well-executed motor actions (**Figure 1**). The pyramidal system or the corticospinal tract directly controls the distal muscles that are responsible for voluntary action. Axons from the motor areas of the cerebral cortex project through the internal capsule to the midbrain and continue down the brainstem into the medullary pyramids where the descending fibers cross to the opposite side, known as the pyramidal decussation. At this point, the pathway is referred to as the lateral corticospinal tract. The fibers synapse in the spinal cord to a lower motor neuron that will travel to a motor neuron pool that activates the limb and hand muscles.

The HRT relies on the sensory system to provide information on the location and trajectory of the object,

the force and sensitivity required to pick up the object, and orientation and balance of other body parts. This information is part of the feedback and a feedforward system that is mediated by the thalamus to produce a successful HRT. The thalamus translates sensory input into a form readable by the cerebral cortex. Furthermore, the thalamus supports the accuracy and planning of the HRT by delivering information from the cerebellum and the basal ganglia to the motor areas of the cortex. The cerebellum, in turn, helps to regulate the execution of the movements by processing information from the sensorimotor areas of the cortex via the pons and sending it back to the system by output connections to the thalamus and from there to the motor areas of the cortex. The basal ganglia have a key role in higher-order planning, and seem to be responsible for the initiation and control of movement. These nuclei regulate motor cortex function through their thalamocortical projections. They receive massive inputs from the cortex and their output pathways connect back to specific motor areas (directly or indirectly via the thalamus) along with the prefrontal cortex. The basal ganglia also relay information to the cerebellum and have direct access to motor areas in the brain stem reticular formation.

Who Can Present Difficulties Performing a HRT?

As the HRT requires a system that includes grasp tool (hand), output information (corticospinal nerves), input information (sensory system), and central control (prefrontal cortex, basal ganglia, cerebellum, thalamus), a 'malfunction' on any part of this system will affect the successful completion of this task. Due to the highly coordinated action required to initiate and perform HRTs, these tasks are widely used to evaluate diseases that affect

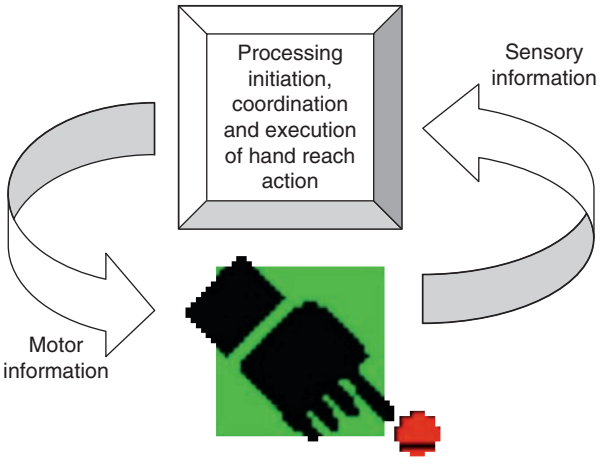

Figure 1 Elements needed for successful completion of a hand reach task.

'central control,' such as movement disorders. Typically, movement disorders are defined as affecting the ability to generate and control movements, by disturbing basal ganglia function. Decreased inhibitory output from the basal ganglia to frontocortical areas has been associated to hyperkinetic activity and increased inhibitory output with hypokinesia. Some common movement disorders are Parkinson's and Huntington's disease, essential tremor, Tourette's syndrome, and dystonia. As Parkinson's disease is the second most common neurodegenerative disease, many HRTs have originally been developed and used to assess this disease.

Using HRTs as Preclinical and Clinical Evaluation Tools

Evaluation of hand reach ability can be used as a diagnostic tool, to evaluate disease progression and to assess therapies (**Table 1**). As such, HRTs have been developed and adapted to assess patients and animal models of disease. HRTs can provide key information on manual dexterity on their own or as part of a battery of tests, including electrophysiological and imaging analysis to understand in vivo the functional components of the system. Equivalent tests could be transferred from the lab to the clinic and back in order to understand the disease and the limitations of a treatment.

HRTs for Laboratory Animals

Animal testing for HRT usually requires training and commitment of time and resources. These issues have been a limiting factor for their application, yet there is increased awareness of their importance to provide unbiased, more sensitive quantification of motor skills. **Table 2** lists key tests used to evaluate HRT in different species. HRTs for rodents are not widely used. The typical test is the 'staircase test' that evaluates the animals' ability to grasp and retrieve food from wells in two staircases with steps positioned downward and bidirectional from the animal. Variations of this test include placing two staircases side by side, or two staircases arranged in an upside-down V where the highest steps are placed side by side.

In comparison to rodents, monkey studies have frequently used HRTs to evaluate primate's complex motor planning and execution skills. There is a range of tests that evaluate the grasping action (reach and grasp and conveyor

Table 1 Clinical and basic research applications of hand reach tasks

Diagnostic tool
Evaluation of disease progression
Assessment of disease modifying strategies
Monitoring of potential side effects

Table 2 Tests used to evaluate hand reach task in different species

Species	*Test*	*Reference*
Rat	Staircase task	Fricker et al.
Monkey	Reach with alternating hands	Bankiewicz et al.
	Reach and grasp	Van Kan and McCurdy
	Conveyor belt	Annett et al.
	Lateralized reward retrieval task	Schneider et al.
	Reaching into tubes	Annett et al.
	Recessed wells	Emborg et al.
	Staircase task	Montaya et al.
	Movement assessment panel	Zhang et al.
	Extinction with double simultaneous Stimulation	Schneider et al.
	Response to a moving target	Schneider et al.
	Object retrieval detour task	Taylor et al.
	Operant task	Schneider et al.
	Level pulling	Ellis et al.
	Free-reach device	Van Kan and McCurdy
	Drinking action	Bennett et al.
	Look and point	Desmurget et al.
Human	Pinch grip task	Vrancken et al.
	Reach and Grasp	Castiello and Bennett
	3D virtual reality	Messier et al.

Within each species category, tests are organized from the most simple to more complex, requiring more extensive training.

belt), handedness (reach with alternating hands), planning (object retrieval detour task), or spatial hemineglect (lateralized reward retrieval task). Tests can be manually operated (reach in to tubes, recessed wells) or take advantage of automated computerized systems (movement assessment panel). Different variations of the tests can be used to increase the difficulty level (movement assessment panel). Complex tests usually require extensive training for acclimation of a restraining device, as well as comprehension of the proposed challenge (extinction with double simultaneous stimulation, response to a moving target, operant task, level pulling, and free-reach device). When selecting a test, it is important to match it to the scientific question and to the experimental conditions (e.g., combination of a HRT with electrophysiological measures requires animal restraining).

HRTs for Humans

HRTs are a simple, noninvasive method to evaluate movement disorders in humans that have the potential of being combined with functional imaging or electrophysiology. HRTs include evaluation of overall activity, initiation, reaction time (drinking action, look and point, and reach and grasp) and speed and strength (pinch grip task). New computerized systems create a virtually distorted environment to assess patient's learning speed of a new task (3D virtual reality).

Conclusions

As our understanding of movement disorders increases, the use of a battery of tests to evaluate different components of these disorders becomes more important. Biomarkers of disease progression are intensely searched for. In that regard, the movement disorder field will benefit from the systematic application of HRTs to compare novel therapies aiming to improve function, induce neuroprotection (e.g., trophic factors), or circuit repair (e.g., transplants for cell replacement). Unbiased quantifications of HRTs deficits and improvements have the potential to shed light on disease progression or disease modifying strategies. In that context, the use of HRTs in the lab that has a clinical equivalent will be key to predict future successful therapies.

See also: Bradykinesia; GDNF (including Nurturin); Huntington's Disease; Multiple System Atrophy: Animal Models; Parkinson's Disease: Definition, Diagnosis, and Management; Parkinson's Disease: Animal Models; Stepping (Forelimb Akinesia) Test.

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Harmaline Tremor Model

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Glossary

β-Carboline – A structure in which the ethylamine side chain of two-ring tryptamine has been reconnected to the indole ring with a carbon atom. β-Carbolines vary according to side chains and the saturation of the third ring.
Conductance – The flow of ions through an open ion channel so as to produce a membrane voltage change.
Deep cerebellar nuclei – These include the fastigial, interpositus, and dentate nuclei and are the sole output neurons of the cerebellum.
Gap junctions – Where the surfaces of specific neurons fuse and form pores composed of connexin proteins, so that electrical and cytosolic coupling occurs.
Inferior olive – A collection of neurons in the ventral medulla that receives signals from the spinal cord and cerebral cortex and projects climbing fibers to Purkinje neurons.
Preclinical model – An animal model of a human disease that has predicted whether therapies tested on it will show efficacy in patients.
Purkinje cells – Very large neurons that integrate multiple inputs to the cerebellum and are the sole output neurons of the cerebellar cortex, projecting to the deep cerebellar nuclei.
Synchrony – Refers to the state in which a population of neurons share membrane voltage changes or fire action potentials at precisely the same time.

Harmaline-Induced Tremor in Animals

Among β-carbolines, the 7-methoxy compounds harmaline and harmine are tremorogenic (see **Figure 1**). Within minutes of administration, each produces a whole-body postural and kinetic tremor in mammals with a peak frequency ranging from 8–10 Hz in monkeys to 10–16 Hz in mice (see **Figure 2**), that lasts as long as several hours. Experimentally, such tremor is assessed with rating scales, electromyography, or motion detection systems.

Harmaline/harmine doses of 10–20 mg/kg are often used in rats, with mice requiring twice as much. Repeated dosing causes a loss of the tremor response (tolerance), suggested to result from physiological changes such as the failure of the expected harmaline-induced rhythmic inferior olivary (IO) and Purkinje neuron firing to occur.

Neuronal damage occurs after harmaline, but rats and mice show differences. Strips of cerebellar cortex display Purkinje cell loss and microgliosis in rats, whereas mice show no such changes but instead exhibit microgliosis in accessory IO subnuclei without cell loss.

The Anatomy of Harmaline Tremor

IO neurons project climbing fibers to Purkinje cell dendrites, releasing glutamate, aspartate, and peptides to produce complex spikes. On systemic harmaline administration, IO neurons of the medial accessory (MAO) and dorsal accessory (DAO) nuclei fire rhythmically and synchronously, generating rhythmic Purkinje cell complex spikes in the vermis and paravermis; these cortical regions project to the fastigial and interpositus deep cerebellar nuclei (DCN), which also

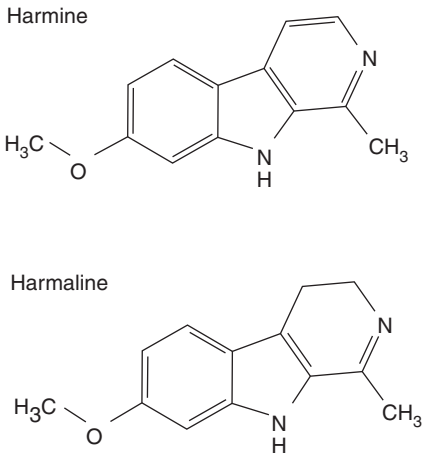

Figure 1 Chemical structures of harmine and harmaline.

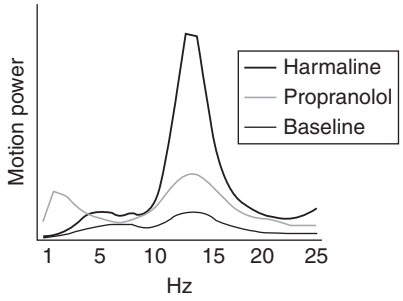

Figure 2 Motion power frequency spectrographs of a sample mouse. During baseline, motion power is mainly represented at low frequencies. After subcutaneous harmaline, 20 mg kg^{-1}, a 10–16 Hz motion power peak emerges, corresponding to visible whole-body tremor. The magnitude of the tremor peak is reduced by intraperitoneal propranolol, 20 mg kg^{-1}.

receive collaterals from MAO and DAO. The DCN send projections to brainstem nuclei and thalamus, as well as a reciprocating inhibitory projection back to the IO subnuclei. The end result is a rhythmic activation of bulbar reticular nuclei and spinal motoneurons, expressed behaviorally as tremor.

Selective IO destruction by systemic 3-acetylpyridine eliminates harmaline tremor. Cutting the climbing fibers does not affect harmaline-induced IO bursting, but eliminates Purkinje cell and fastigial nucleus bursting. Moreover, harmaline-induced bulbar reticular nuclei bursting, but not IO bursting, is eliminated by the removal of the cerebellum including the DCN. Llinás and Volkind observed that cooling of the cerebellar cortex does not abolish harmaline-induced motoneuron firing, and suggested that the olivo-nuclear loop is sufficient to sustain tremor. Supporting this notion, mice with complete Purkinje cell degeneration, but intact olivo-nuclear climbing fibers, can manifest harmaline tremor. Neither cooling the motor cerebral cortex, lesions of the ventrolateral thalamus or globus pallidus, or intercollicular transections abolish tremor in cats or monkeys. Harmaline thus activates IO, with enlistment of the DCN, brainstem, and spinal cord as minimum requirements for tremor expression.

Physiology of Harmaline Tremor

IO rhythmic subthreshold oscillations involve a high-threshold calcium conductance that is terminated by a calcium-dependent potassium conductance, creating an after-hyperpolarization that deinactivates a low-threshold calcium current. That causes a rebound spike that triggers the high-threshold calcium spike and may or may not be enough to trigger a sodium spike. The subthreshold oscillation frequency is approximately 10 Hz, whereas individual IO cells usually fire at 1 Hz. These oscillations are tightly synchronized among ensembles of IO neurons via electrical coupling that is mediated by connexin-36 gap junctions. Purkinje cell complex spike firing is synchronized within small vertical cortical bands, due to their control by the projection of an electrically coupled IO ensemble.

Through an unexplained mechanism, harmaline hyperpolarizes IO neurons, thereby increasing the rebound low-threshold calcium spike. Each rebound discharge is then associated with bursts of sodium action potentials. Thus the IO neurons are made more excitable by harmaline and convert to rhythmic 8–16 Hz burst-firing that upon network propagation is expressed as tremor.

Connexin 36-null mice lack IO or Purkinje cell synchrony, yet unexpectedly mount a relatively normal harmaline tremor response. On the other hand, the broad-spectrum gap junction blocker carbenoxolone suppresses harmaline tremor. Conceivably, harmaline tremor requires synchrony that can be mediated at another level, for example in DCN, by other gap junctions.

Effect of Drugs on Harmaline Tremor

Serotonin

Lesions of serotonin fibers to the IO or drugs that reduce serotonin receptor activation (methysergide, *para*-chlorophenylalanine, low-dose trazodone) attenuate harmine- or harmaline-induced tremor, whereas drugs with the opposite effect (5-hydroxytryptophan, citalopram, imipramine) exacerbate tremor.

Norepinephrine (NE) and Dopamine (DA)

Systemic or intraventricular injection of the NE precursor L-threo-3,4-dihydroxyphenylserine suppresses harmaline tremor in rats, whereas blockade of NE synthesis with α-methyl-*p*-tyrosine exacerbates tremor. Electrical

stimulation of locus ceruleus also suppresses harmaline tremor; lesions have the opposite effect. Harmaline tremor is suppressed by β1- and β2-adrenergic antagonists, but the latter appear more effective. Evidence indicates that propranolol acts both peripherally and by directly counteracting harmaline's physiological effects on IO neurons. Levodopa and DA receptor agonists (apomorphine, piribedil) reduce harmine tremor in rodents.

Glutamate

Dizocilpine, an antagonist of the *N*-methyl-D-aspartate (NMDA) receptor channel, and competitive NMDA receptor antagonists (CPPene, 2-amino-5-phosphonovalerate) each suppress harmaline tremor in rodents, indicating a role for this receptor in tremor expression.

Alcohol

Suppression of harmaline tremor by ethanol has been well replicated, but the mechanism is unclear. Contrary to expectation, a moderate dose of ethanol induces increased rhythmicity and synchrony of vermal Purkinje cell complex spikes, and by inference, IO ensemble activity. Moreover, ethanol fails to affect harmaline-induced rhythmic complex spike activity. These observations suggest that alcohol acts elsewhere other than IO to mask tremor expression.

Antiepileptic Drugs (AEDs)

Recent studies have shown harmaline tremor suppression by zonisamide and lacosamide, the latter with efficacy comparing favorably with propranolol and primidone. De Ryck and colleagues surveyed AEDs and found that levetiracetam had little effect on tremor, whereas the derivative brivaracetam was effective without producing sedation. Primidone and clonazepam were effective but sedating. Carbamazepine and gabapentin also reduced tremor. In brainstem slices, brivaracetam counteracts harmaline's effects on IO physiology, suggesting a direct action on IO.

Harmaline Tremor as a Preclinical Model of Essential Tremor (ET)

ET and the harmaline animal model differ in a number of respects, and the evaluation of its predictive success awaits further testing of compounds in both animals and humans. **Table 1** summarizes a comparison of harmaline and ET tremor.

Harmaline tremor is drug-induced, acute, and self-limited, whereas ET is a nonremitting progressive condition. Harmaline acts on the IO to produce tremor; in ET, IO's role is less certain. Eye-blink conditioning, which depends on the olivo-cerebellar pathway, is impaired in ET patients. Cerebellar cortical hypermetabolism is present in both ET and the harmaline model; in the latter, it is known to depend on climbing fiber activation. Interestingly, alcohol increases IO blood flow in ET but not control subjects, suggesting that IO physiology differs in ET.

On comparing the tremor response to drugs in **Table 1**, it should be noted that ET is likely biochemically heterogeneous, which may limit the predictive validity of the harmaline model. Another problem is uncertainty about

Table 1 Comparison of harmaline rodent tremor model and essential tremor

Feature	*Harmaline tremor*	*Essential tremor*
Clinical		
Action tremor	Yes	Yes
Time course	Acute	Chronic
Inducing agent	Pharmacologic	Probably neurodegenerative
Role of inferior olive	Definite	Uncertain
Cerebellar hypermetabolism	Yes	Yes
Role of thalamus	Not essential	Essential
Response to drugs		
Primidone	Suppresses	Suppresses in some
Clonazepam, diazepam	Suppresses	Suppresses in some
Gabapentin	Suppresses	Suppresses in some
Carbamazepine	Suppresses	Does not suppress
Levetiracetam	Does not suppress	Does not suppress
Propranolol	Suppresses	Suppresses in some
L-dopa, DA agonists	Suppresses	Do not suppress
Anticholinergics	Do not suppress	Do not suppress
Ethanol	Suppresses	Suppresses in some
γ-Hydroxybutyrate	Suppresses	Suppresses in some
Caffeine	Worsens	Worsens in some
Citalopram, imipramine	Worsens	Worsens in some
1-Octanol	Suppresses	Suppresses in some

the extent to which reported harmaline tremor suppression represents nonspecific motor activity reductions. Potential remedies are to employ tremor measures that are insensitive to locomotor activity levels and to select doses shown in independent tests not to cause sedation or impair motor performance.

Of 13 agents listed in **Table 1**, correspondence prevails in 11/13. Carbamazepine and dopaminergic drugs suppress harmaline tremor, representing false positives as these are not effective for ET. To date, the model has been employed to predict clinical efficacy for just one compound that has been in published clinical trials: 1-octanol. Encouragingly, pilot trials indicate that 1-octanol has clinical efficacy.

See also: Carbon Monoxide Poisoning; Postural Tremor; Tremor; Tremor: Drug-induced; Tremor, Essential (Syndromes); Tremor, Essential: Genetics.

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Hemiatrophy Hemiparkinsonism

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Glossary

Dystonia – An uncommon disorder characterized by involuntary muscle contractions that cause uncontrollable, often painful, twisting of the affected body parts, which interferes with the performance of many day-to-day tasks.

Parkin (also known as *PRKN*, or *PARK2*) – A gene implicated in autosomal recessive juvenile parkinsonism. Mutations in the *parkin* gene might be involved in the accumulation of defective proteins in the cells, leading to nigral neuronal degeneration.

Perinatal – Pertaining to or occurring in the period shortly before and after birth, variously defined as beginning with completion of the 20–28 week of gestation and ending 7–28 days after birth.

Striatum – Part of the basal ganglia of the brain that is involved in the planning and modulation of movement pathways but also in cognitive processes that require executive function. It includes the caudate nucleus and the putamen.

Definition and History

Hemiatrophy hemiparkinsonism (HAHP) is a rare neurological condition initially proposed as a distinct syndrome in 1981 by Klawans. He described four cases characterized by the occurrence of body hemiatrophy and ipsilateral

hemiparkinsonism. This syndrome differs from a unilateral presentation of idiopathic Parkinson's disease (IPD) by early age of onset, clinical evidence of hemiatrophy, unilateral parkinsonism on the same side of hemiatrophy, action-provoked dystonia that occurs prior to the introduction of levodopa therapy, and slow progression.

Although a minimal asymmetry of body size is considered normal, marked asymmetry (2–3 cm in limb length or asymmetry of the face and chest) is rare. In order of frequency, the body parts affected in hemiatrophy are hands, feet, and face. No right- or left-sided predominance has been reported in HAHP. The asymmetry is often recognized early in life (e.g., shoe and glove size discrepancies), suggesting that the atrophy is a result of a developmental failure rather than a process occurring later in life, as seen in conditions such as the Parry–Romberg syndrome. Parkinsonism presents with rest tremor, bradykinesia, and rigidity predominating on the same side of hemiatrophy, although very minor signs can sometimes be detected on the other side of the body. Some individuals eventually develop progressive, contralateral parkinsonism, but the main signs remain predominantly on the hemiatrophic side of the body. Pyramidal tract dysfunction, such as exaggerated tendon reflexes and Babinski sign, is commonly seen in HAHP patients. Dystonia is an often-reported early sign in HAHP. It normally begins several years before the introduction of levodopa therapy, and before other parkinsonian signs develop. It is usually confined to the foot, although the arm, face, and neck can also be involved. Frequently, dystonic movements occur only with the movement of the involved body part (action-induced dystonia) and there is no dystonia at rest.

Pathogenesis

The average age of onset of parkinsonian symptoms in HAHP is ~40 years, and no gender prevalence has been reported. The presence of corticospinal signs suggests that motor areas can also be involved, and cases of hemiatrophy related to brain injuries involving the postcentral frontal lobe have been reported. HAHP has been frequently associated with abnormal pre- and perinatal injuries, including prolonged or traumatic labor or delivery, premature delivery, breech presentation, or neonatal hypoxia. Perinatal stress may underlie brain injuries and subsequent development of HAHP, as supported by studies in which experimental animals were exposed in utero to toxins such as lipopolysaccharide, eventually leading to reduced dopaminergic neurons at birth. Perinatal injuries can also explain the early onset of symptoms and might support the reason for slow school learning in some of the described individuals. In addition, although early life insults often cause asymmetric neurological findings, they may be associated with whole brain injury, potentially explaining why parkinsonian signs sometimes evolve over years to include the contralateral side. However, perinatal complications have not been found in all HAHP patients, leading some authors to dispute whether to include this association as a criterion to differentially diagnose HAHP from IPD. Similarly, dystonia has been frequently reported as a presenting symptom of IPD, especially of early onset PD (EOPD) and in monogenic forms of PD (*PARK2*); however, other features of parkinsonism usually develop within few months in these latter cases. A diagnosis of IPD should always be considered in cases of adult-onset foot or leg dystonia.

Diagnostic Evaluation

Conventional neuroradiological examinations are inconstantly informative. Some studies show no cerebral, cortical, or ventricular asymmetry at CT or MRI scans, while others show hemicalvarial thickening, paranasal sinus enlargement, or frank hemiatrophy of the brain with cortical, subcortical, ventricular, and basal ganglia atrophy. Functional studies have provided more information; both fluorodopa (FDP)- and fluorodeoxyglucose (FDG)-PET scans show a decrease in striatal FDP uptake and striatal glucose metabolism on the side of the brain opposite the hemiatrophic part of the body. The dopamine transporter activity seems accordingly reduced when beta-CIT SPECT is employed. Notably, fluoroethylspiperone (FESP)-PET, which assesses dopamine D2 receptor binding capacity, does not show any binding reduction, suggesting a nonreceptor mechanism for the striatal dysfunction in HAHP. Unlike FDP-PET, which highlights the dysfunction along the nigrostriatal pathway, but is not capable of separating HAHP from IPD, FDG-PET shows a metabolism reduction exclusively in the striatum, supporting the theory of isolated dysfunction of striatal neurons. EEG anomalies, such as paroxysmal polyspike activity in the frontal area, and CSF abnormalities, that is, a homovanillic acid concentration of less than one third of the normal level, have been described only once. Similarly, genetic mutations have been reported only by a study that performed an extensive analysis of the *parkin* gene on a HAHP patient and found a duplication of exon 7. The presence of *parkin* mutations could justify, in some HAHP individuals (in addition to global perinatal brain damage), the clinical involvement of the contralateral side, and explain why some researchers could not find any side-to-side differences with FDP-PET scanning. Heredity for HAHP has never been reported, even though the occurrence of HAHP has been described in one pair of twin brothers, and few cases confirmed familiality for IPD. No mention of genetic mutations was provided in this latter report.

Treatment

To date, only two main treatments for HAHP have been reported: pharmacological and surgical. Levodopa treatment has given inconsistent results. The original report by Klawans showed no response to either dopaminergic or cholinergic drugs. Other studies, however, reported a sustained response to levodopa. These observations suggest that different types of lesions may cause HAHP. Parkinsonism is normally seen as a condition characterized by dopamine depletion due to nigral degeneration. However, a primary dysfunction of the striatum could also lead to parkinsonism. In cases of HAHP with striatal dysfunction as a consequence of postcentral brain injuries, a low or absent response to dopaminergic drugs might be anticipated. To date, there have been no postmortem examinations of HAHP brains to test this hypothesis. In addition, in all published studies, inclusion criteria for HAHP patients have been highly variable in terms of drug response to levodopa and other dopaminergic drugs, making treatment conclusions difficult to draw.

Only five patients have been reported after surgical treatment: three with thalamotomy and two with deep brain stimulation (DBS) directed to the ventral intermediate nucleus (VIM) of the thalamus and to the subthalamic nucleus (STN) respectively. Thalamotomy was not successful and only the patient who received STN DBS improved.

Prognosis

Despite the reduced response to conventional treatments, HAHP has a slow progression and a better prognosis compared with IPD.

See also: Bradykinesia; Deep Brain stimulation; Dystonia; Dystonia, Task-specific; Electroencephalography (EEG); Levodopa; PARK2, parkin; PET Imaging in Movement Disorders; Rest Tremor; Rigidity; SPECT Imaging in Movement Disorders; Surgery for Movement Disorders, Overview, Including History; Thalamotomy.

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Hemiballismus

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Glossary

Ballism – Large amplitude involuntary movements with jerking, irregular, flailing, flinging, and exhausting qualities.
Hemiballismus, hemiballism – Ballism affecting one side of the body.

History and Clinical Presentation

Ballism is derived from the Greek verb meaning *to throw.* This movement disorder involves large-amplitude involuntary jerking, irregular flailing, flinging, and exhausting movements. They are among the more distressing of the hyperkinetic disorders for patients to endure and for their families and clinical practitioners to observe. The term

ballism or ballismus is variably credited, in its initial use, to Plouequet, Pfefferkorn, Kussmaul, and von Economo and probably dates back to the early 1800s. Ballismus is similar to chorea because of the unpredictable and random character of movements, but in ballism, the movements are more severe and proximal, whereas in chorea, the movements are distal. When ballism occurs on only one side of the body, the cause is usually a cerebrovascular accident and the condition is termed hemiballismus.

Pathophysiology

Although hemiballismus has been associated with damage to the contralateral subthalamic nucleus (STN), especially by hemorrhage, it has long been recognized that lesions in other locations may contribute to the appearance of these movements. In fact, an STN lesion is only rarely found in isolation.

In a report of 22 cases of patients with hemiballismus who had either CT or MRI, the STN was abnormal in only 6, and only 1 had the STN as the sole site of identified pathology. Other sites combined with the STN included the pons, midbrain, thalamus, and caudate. Notably, some cases have structural abnormalities identified only in the parietal, parietotemporal, or temporal lobes, and 7 of the 22 had no abnormalities detected at all on imaging. It is possible that conventional imaging is insufficiently sensitive to detect all the sites of pathology in hemiballismus.

Models of the basal ganglia network, involving cortical motor areas, the caudate and putamen, the globus pallidus, substantia nigra, STN, and thalamus, are under continuous refinement to explain the motor phenomena associated with diseases. It is known that the STN is functionally important to these basal gangliar circuits. The concept of hemiballism and its pathophysiology has shifted from a focus on this nucleus to the appreciation that lesions within a larger and more complex circuitry are likely responsible for the movement disorder.

Differential Diagnosis

The single most common cause of hemiballismus is a vascular lesion created either by stenosis or hemorrhage. Recently, several cases in association with hyperglycemia and opportunistic central nervous system infections in HIV patients have been reported. Other etiologies for hemiballismus include trauma, systemic lupus erythematosis, metastatic neoplasm, multiple sclerosis, tuberous sclerosis, tuberculoma, hypocalcemia with hypoparathyroidism, hypoglycemia, and vascular malformations (**Table 1**).

Table 1 Causes of hemiballismus

Brain hemorrhage or ischemic infarction
Hyperglycemia
Toxoplasmosis or other opportunistic infection in immunocompromised patient
Metastatic neoplasm
Multiple sclerosis
Tuberous sclerosis
Head trauma
Tuberculoma
Vascular malformation
Hypocalcemia with hypoparathyroidism
Hypoglycemia

Many of these causes provoke hemiballismus through vascular complications associated with the underlying diagnosis. In one case of hemiballismus associated with hyperglycemia, MRI T1-weighted images demonstrating hyperintense signals in the putamen were associated with petechial hemorrhages detected on postmortem examination. The majority of cases of hemiballismus associated with hyperglycemia have been among Asian patients, although no explanation for this has yet been identified. Rarely, hemiballismus can be seen in multiple sclerosis, and in one reported case, a plaque was identified in the STN.

Examination

Hemiballismus is so striking that the examiner must take care to focus on the remainder of the neurological examination to detect more subtle signs that may yield clues to the underlying cause. Generally, both the arm and leg are affected by large-amplitude movements that are jerking or flailing in appearance. They may cause patients to slide out of their chair or abrade and bruise their limbs. As is true with involuntary movements in general, hemiballismus increases with heightened emotional states. When the patient is relaxed and unstimulated, the movements may reduce in amplitude and resemble chorea. Similarly, the chorea of Huntington's disease or that induced by dopaminergic medication in Parkinson's disease may, in some circumstances, appear to become ballistic, but in these cases, the movements involve both sides of the body. However, patients with Parkinson's disease are typically asymmetric in both their parkinsonism and their dyskinesia. Therefore, both sides of the body must be observed carefully in all cases of seeming hemiballism.

The majority of cases of hemiballismus are due to a vascular event, hyperglycemia, or an opportunistic infection in an immune-compromised patient, and therefore, the history and examination should be directed to these etiologies. The primary process causing hemiballismus can cause additional problems in the central or peripheral nervous system, and hence a thorough examination is

essential, even though the dramatic hemiballism may compromise the detection of subtle findings. Considering that even in vascular cases of hemiballismus, a minority had lesions restricted to the STN, the patient must be assessed for evidence of infarction elsewhere.

Testing should include brain imaging on an urgent basis, since some of the known processes causing hemiballismus, such as hemorrhage, ischemic infarction, or mass lesions, require prompt attention. MRI is preferable for most conditions, but may require sedation or anesthesia in order to allow the patient to be scanned. For patients with recent onset of hemiballismus, urgent hospitalization is reasonable. A rapid assessment of the serum glucose level should be accomplished for all patients with hemiballismus. Other blood tests, particularly regarding an ischemic etiology, include a complete blood count, including platelets, PT, and PTT and an evaluation for hypercoagulability syndromes. A complete chemistry panel, including calcium levels, should also be obtained. Low calcium should be investigated by assessing the parathyroid hormone. The erythrocyte sedimentation rate at minimum should be checked as a screen for lupus, vasculitis, or other autoimmune disorders.

Prognosis and Treatment

Despite early descriptions of dire outcomes, more recent series of cases indicates a favorable prognosis with spontaneous resolution or substantive improvement of movements within weeks or months for the majority of cases. The provocative underlying disease and its severity are likely the principal determinants of outcome.

In the acute period, when the movements are most disruptive and potentially injurious, some cases will require treatment. Neuroleptic medications have long been established as being effective and remain the first choice among most clinicians, although no one specific medication has been identified to be superior to others. Clozapine has been reported to be helpful where other neuroleptics have failed. The presynaptic, dopamine-depleting medications reserpine and tetrabenazine have also been reported to be beneficial. Other medications reported to be helpful include valproic acid, gabapentin, topiramate, sertraline, and combinations of a neuroleptic with reserpine, tetrabenazine, or diazepam.

For patients in whom hemiballismus persists and medications have not been helpful, functional neurosurgery may be an option. Pallidotomy, thalamotomy, and deep brain stimulation of the thalamus have been reported to be effective. However, for the majority of patients, given the natural history of spontaneous resolution of hemiballismus within weeks, it is prudent to allow sufficient time to pass before considering surgical treatment.

See also: Basal Ganglia; Basal Ganglia, Functional Organization; Subthalamic Nucleus.

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Hemifacial Spasm

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Definition and History

Hemifacial spasm (HFS) is characterized by unilateral, involuntary, irregular clonic twitches or tonic (rarely) contractions of the muscles of the face innervated by cranial nerve VII. Patients complain of involuntary twitching of the facial muscles, with the initial symptoms usually involving the lower lid and the orbicular muscle of one eye. The spasms may progress in severity and may spread to the lower face on the same side. Some patients will have intermittent or mild symptoms with intervals during which they are asymptomatic.

These contractions involve the mimetic muscles; patients may have both tonic and clonic activity in these muscles. The symptoms may be exacerbated by specific movements of the face, changes in head posture, physical or emotional strain (anxieties, upset, stress), and fatigue. Remissions rarely occur.

Involuntary contractions may also be observed during sleep in ~80% of patients. A familial history is seldom obtained although some families have been described.

HFS occurring in conjunction with trigeminal neuralgia is termed tic convulsif.

HFS is not dystonia, although some of the treatments used may overlap with those used for blepharospasm.

Pathogenesis/Pathophysiology

For a long time, this disorder was considered a psychogenic disorder. Over the last 40 years, however, the organic basis of HFS has been firmly established.

There have been many proposed mechanisms for HFS, an issue that remains unresolved. Lesions and/or disinhibition of the nucleus of the facial nerve have been speculated. More recently, HFS has been attributed to compression of the facial nerve by blood vessels or ectopic structures in the region of the nerve. The vulnerability of the nerve to compressive injury is thought to relate to the fact that upon emergence into the cerebellar angle, the facial nerve is not myelinated and merely ensheathed by a thin arachnoidal membrane. In addition, the facial nerve may be at increased risk of compression at the point of exit from the brainstem and entrance into the internal auditory canal.

How the compression of the nerve by a blood vessel leads to contractions of the facial muscles has not been clearly established. Compression of the nerve and consequent demyelination may lead to ectopic excitation and axonoaxonal ephaptic transmission between the demyelinated fibers. In addition, the root exit zone may act as a trigger zone. The antidromic impulses can excite the facial nucleus and produce a kindling effect rendering the facial nucleus hyperexcitable, which, in turn generates impulses down the facial nerve eliciting the muscular contractions.

Compression of the nerve may occur in different regions. The vulnerability of the root exit zone alone has been proposed to be one of the primary mechanisms. This zone is a transition zone that is 2–3 mm in length between the central and peripheral axonal myelination and is located at the nerve's exit from the pons. However, studies have shown that only one-fourth of HFS patients have a demonstrable nerve compression at this particular site. Compressions in the attached segment (i.e., an area between root exit point and the root detachment point) are much more common and occur in nearly two-thirds of the patients. Hence, atypical HFS is more common than compression to the posterior or rostral side of the nerve with compression at the brainstem. The site of each region compressed presumably impacts on the clinically picture. Moreover, it is felt that the severity of compression correlates with the severity of HFS symptoms. There is still controversy as to whether HFS is more typically caused by more distally located compressions.

The AICA (anterior inferior cerebellar artery) is the primary blood vessel thought to cause facial nerve compression. The posterior inferior cerebellar artery and vertebral artery (tortuosity) are frequently involved as well. Multiple compressing vessels were found in about one-third of the cases. Rarely, aneurysms of these vessels may cause HFS. Bilateral compression resulting in bilateral HFS is an exception. Although compression of the facial nerve is considered to be one mechanism, ~25% of normal controls will show vascular loops that are compressing the facial nerve, suggesting that this phenomenon alone is not enough to produce HFS.

Space-occupying lesions such as meningioma, acoustic neuroma, schwannoma, bony abnormalities of the skull, parotid gland tumor, and pilocytic astrocytoma of the fourth ventricle are believed to be nonvascular origins of HFS. Lacunar pontine infarction may be another rare cause. Bilateral HFS has been reported in association with multiple sclerosis.

Epidemiology/Risk Factors

HFS is a very common disease with an overall prevalence of about 10/100 000 – and is even more prevalent in Asia. HFS usually begins in the fifth decade, and increases with advancing years. It is very seldom seen in childhood or adolescence. Some patients may be genetically predisposed to developing HFS, but most cases are sporadic. Risk factors include arterial hypertension (in up to two-thirds of the patients), vascular diseases, and smoking. Women are afflicted approximately twice as often as men.

Clinical Features and Diagnostic Criteria

HFS is marked by synchronous unilateral contractions of muscles innervated by the facial nerve. There is variable involvement of the muscles of the lower face. Symptoms will typically originate in the area of the orbicularis oculi muscle of the eye and may spread in a caudal or cranial direction. There is a lot of variability in the pattern and temporal course of the disorder. Some cases are characterized by onset in the orbicularis oris muscle of the mouth and the buccinator muscles. The frontalis and stapedius muscles are much less involved, although rhythmic clicking may sometimes be a symptom of the latter. These symptoms are enhanced by fatigue, emotional strain, and light. HFS is not associated with pain or other sensory changes in the face. Corneal reflexes should be normal. Although patients with HFS may have mild facial asymmetry, there is no paralysis of facial muscles in untreated HFS. If there are additional neurological deficits, then a consideration of other possible etiologies included space-occupying lesions should be excluded.

Bilateral HFS is very rare. When it occurs, the spasms are usually independent of each other and not synchronous on both sides of the face. It is postulated that in bilateral HFS there is bilateral compression of the facial nerve.

HFS may seriously impact the patients' quality of life. This arises from the sensations of the muscular contractions, involuntary eyelid closure that appears like winking, visual impairment, and sometimes speech involvement or lack of control of salivation. The continuous contractions may also interfere with sleep. In addition, the symptoms may be socially disabling. The winking of the eye and grimacing of the face may attract attention, making patients feel stigmatized and misunderstood. In some cases, muscle contractions can also become esthetically disfiguring. In severe cases, HFS may be functionally and socially disabling.

Differential Diagnosis

Differential diagnosis include local processes that may involve the region close to the exit of the facial nerve from the brainstem. Unilateral blepharospasm is the most important differential diagnosis at the onset of the disease (involving solely the orbicular muscle of the eye). In contrast to HFS, blepharospasm typically involves both eyes and does not have the synchronous, simultaneous rapid contractions of the muscles. However, there have been cases when both disorders may be present in a single patient.

Meige's syndrome, which is the combination of blepharospasm and oromandibular dystonia or lower facial dystonia involves muscles supplied by the facial nerve, but may also involve muscles innervated by other nerves, including cranial nerve V. Similar to blepharospasm, the muscle contractions may be more irregular, and bilateral in comparison to the synchronous muscle contractions of HFS (**Figure 1**). In contrast to HFS, oromandibular dystonia affects only the lower face and jaw and does not involve the upper face, as in HFS.

Synkinesias following facial paralysis (post-Bell's palsy synkinesis) may clinically resemble HFS. Synkinesias do not occur at rest but on activation of the muscles innervated by the facial nerve, such as eye blinks or smiling.

Eye and facial tics, occurring either a simple motor tic or as a part of Gille de la Tourette syndrome may sometimes be a part of the differential of HFS. However, motor tics involving the eyes are often bilateral, associated with eye rolling, and arise secondary to an 'urge' to move. In addition, motor tics are typically suppressible, whereas HFS is not. Other disorders that can be included in the differential diagnosis are myokymia (in brainstem lesions), tardive dyskinesia, epilepsia partialis continua, and psychogenic facial spasm.

Diagnostic Work-up/Tests

The diagnosis of HFS is based on history and clinical findings. Neuroimaging of the brain and brainstem with magnetic resonance imaging (MRI) will rule out structural lesions, including space-occupying lesions of the brain/cerebellar pontine angle. In many cases, MRI/magnetic resonance tomographic angiography can help us identify pathologic neurovascular contact at the root entry zone or more distally, especially when the anterior inferior cerebellar, posterior cerebellar, or vertebral artery is involved. Parotid tumors – a very rare cause of HFS – should also be considered in the appropriate patient.

In most patients, if imaging studies are normal, no further diagnostic work-up is necessary. However, in some patients in whom the movements are not typical, electromyography may be helpful. In HFS, the EMG of muscles innervated by the facial nerve shows typical high-frequency and short-duration bursts occurring synchronously in all muscles involved, aside from frequent signs of peripheral neurogenic lesion with abnormal spontaneous

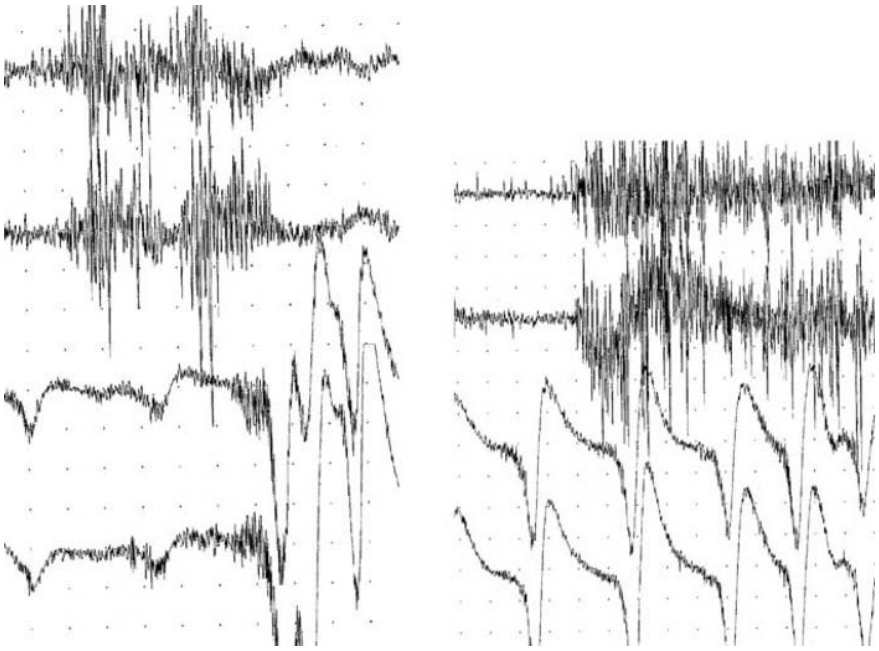

Figure 1 EMG in a patient with Meige's syndrome: Involuntary, asynchronous contractions of the orbicularis oris muscle (track 1 and 2) and the orbicularis oculi muscle (track 3 and 4).

activity, and motor unit potential change even. The blink reflex (e.g., R1/R2-junction, contralateral early R1-component) and magnetic evoked potentials (prolonged latencies) are may also be useful in particular patients.

Management

Many pharmacologic treatments and surgical procedures have been used for the treatment of HFS. Some of these are still in use today. Membrane-stabilizing agents – anticonvulsants in particular – are oral medication. Medications reported to improve HFS include carbamazepine, clonazepam, phenytoin, gababentine, and baclofen. The benefit from these drugs have been modest and often not sustained. The use of the oral medications may be somewhat limited by the occurrence of adverse effects. Injections of neurolytic agents, such as doxorubicin, have been considered as a treatment option but there are inadequate studies of these agents, and the potential adverse effects may outweigh the benefit.

Injections of botulinum neurotoxin (BoNT) to the tonically or clonically activated musculature is considered a safe and effective treatment for HFS. Many consider the treatment of choice. Injections of BoNT have been shown to be beneficial in controlling the HFS, and the adverse effects are usually mild and reversible.

The success rates of various studies range between 76% and 100%.

Dosage and injection sites may substantially vary and clearly depend on the clinical picture. The orbicularis oculi muscle of the eye and platysma muscle if involved are the most common muscles injected for HFS. Although there are no comparative studies assessing different techniques for injection, most investigators target the pretarsal segment of the orbicularis oculi muscle rather than the preseptal area. Injections of the lower face are avoided because of the weakness that may occur, causing sagging of the angle of the mouth, speech problems, difficulty with forming a seal for drinking, and drooling.

The doses of BoNT used for HFS are very small. Injections are given subdermally, and EMG guidance is not usually needed. The dose is frequently lower than what would be needed in blepharospasm. The injection sites are chosen according to the clinical picture. Possible injection sites are demonstrated in the illustration below. Undesired effects include incomplete paralysis of the injected muscles, or weakness of adjacent muscles. Ptosis and local hematomas may occur in up to 10%. The effect of injections begins ~2–3 days following injection and maximizes up to 2 weeks following injection. The effect of BoNT injections lasts from 2 to 6 months with most patients seeking retreatment after 3–4 months. A few patients have a sustained benefit and may only require injections on an annual basis.

Most patients will require continued treatment to maintain benefit.

The primary surgical procedure for HFS is a decompressive intervention (surgical vascular decompression of the facial nerve, Janetta's technique). This operation aims at eliminating the pathologic contact of nerve and vessel by interposition of muscles, surgical gauze, or use of fibrin

glue. Success rates are quoted between 80% and 97%, with relapse rates up to 25%. Microsurgical vascular decompression is proposed to act by separating the artery from the facial nerve and can provide sustained improvement. However, this procedure is associated with a potential for serious complications including facial paralysis, deafness/hearing loss, excessive bleeding, and even death. The recurrence rate is about 20%.

Prognosis

HFS is usually a chronic disorder. Spontaneous remissions have been described but are rare. Facial weakness can occur in some patients, involving the orbicularis oris muscle of the mouth and resulting in sagging of the labial angle with disordered speech and sialorrhea. This mild paralysis must be distinguished from the possible untoward effects of treatment.

See also: Blepharospasm; Botulinum Toxin.

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HIV Infection and Movement Disorders

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Glossary

Chorea – From Greek: circle dance. Irregular and usually fast involuntary movements affecting one or more body segments or generalized to the entire body. When generalized, these movements appear to flow randomly from one body part to the next.
Dystonia – Involuntary and persistent muscle contractions affecting one or more muscle groups that can lead to involuntary, repetitive movements and postures of body segments.
Hemiballismus – Large amplitude, irregular involuntary movements affecting the proximal extremities on one half of the body (movements may resemble kicking or throwing).
Movement disorders – General term that refers to abnormal execution of movements or presence of abnormal involuntary movements.
Parkinsonism – A term used to describe a constellation of symptoms typical of Parkinson's disease and similar disorders (Parkinson-like diseases) that include bradykinesia (slowing of movements), rigidity (increased muscle tone, usually with the typical 'cog-wheel' phenomena), and tremor.
Tremor – Rhythmic involuntary oscillatory movement of a body part. Tremors are classified on the basis of clinical setting (resting, postural, kinetic), frequency (high or low), and intensity.

Definition and History

Movement disorders are common among human immunodeficiency virus (HIV)-infected individuals, with both hypokinetic and hyperkinetic syndromes that may manifest themselves at all stages of the disease and occasionally appear as the first clinical manifestations of HIV infection. HIV-infected individuals are also exquisitely prone to developing movement disorders after exposure to dopamine-blocking drugs.

Since the early stages of the epidemic, a variety of movement disorders have been recognized in HIV-infected subjects. While most movement disorders observed before the introduction of highly active antiretroviral therapy (HAART) were due to opportunistic infections or neoplasms affecting the basal ganglia, with the widespread use of HAART, most of the movement abnormalities are now observed in subjects with HIV dementia (HAD) and are thought to be a clinical consequence of dopaminergic and basal ganglia dysfunction caused by chronic HIV infection. The basal ganglia are in fact one of the brain regions that preferentially hosts the virus and in more advanced stages of HIV infection neuronal loss and other neuropathological changes are observed in the substantia nigra and the striatum. Nigral dopaminergic cells seem particularly vulnerable to the viral envelope protein glycoprotein (gp) 120, which reduces dopamine uptake and can cause apoptosis. Another HIV protein, Tat, produces mitochondrial dysfunction and excitotoxicity and may contribute to

the cascade of events responsible for the dopaminergic neuronal loss.

A number of abnormalities in the structure of pre- and postsynaptic striatal dopaminergic synapses have also been described, providing further explanation to the vulnerability of HIV-infected individuals to developing motor dysfunction and movement disorders.

Clinical Syndromes

Parkinsonism in HIV-Associated Dementia

Since its first historical descriptions, motor slowing and other motor abnormalities were recognized as an integral part of HAD. With evolving knowledge of the underlying mechanism of the disease, and renewed clinical categorization, motor dysfunction, and particularly extrapyramidal signs became one of the essential diagnostic criteria of HIV 'minor cognitive motor disorder,' a possible early stage of HAD. Motor abnormalities remain an important component of the syndrome even in the HAART era. Most of the motor abnormalities in the early stages of the disease are limited to mild bradykinesia and psychomotor slowing that can manifest before other cognitive changes become apparent. Interestingly, most of the neuropsychological abnormalities that characterize HAD are also reminiscent of those observed in Parkinson's disease, with prominent attention problems and executive dysfunction, that at least in part correlate with abnormal dopaminergic tone. In later stages, HAD is often accompanied by frank hypomimia, dysarthria, hypophonia, bradykinesia, loss of manual dexterity, and gait and balance problems. As the disease progresses, some patients become clinically indistinguishable from individuals with advanced idiopathic Parkinson's disease and dementia.

Subclinical motor dysfunction attributable to abnormal basal ganglia function, including prolonged reaction time and subtle abnormalities in rapid alternating movements can be demonstrated in asymptomatic individuals, and may predict patients at risk for HAD.

A rare, predominantly parkinsonian syndrome associated with neurological problems and cognitive changes has also been described in HIV-infected children. It is unclear whether this syndrome is a pediatric equivalent of the motor-cognitive syndrome of HAD, or is a distinct clinical and pathological entity.

Other Forms of Parkinsonism in HIV

In addition to parkinsonism associated with HAD, a rapidly progressing pure parkinsonian syndrome can develop in the course of HIV infection. In rare cases, a Parkinson-like disorder may be the presenting manifestation of HIV infection, without concomitant systemic or neurologic abnormalities. As discussed in one of the following sections, many cases of Parkinsonism in HIV are drug-induced.

As the use of HAART has transformed HIV into a chronic infection, there is growing evidence suggesting an increased vulnerability to developing parkinsonism in older chronically infected subjects. The reason for this presumed vulnerability remains unclear, but it is possible that subjects already predisposed to Parkinson's disease may develop early and more severe signs of Parkinsonism due to the concomitant chronic dopaminergic dysfunction produced by HIV.

Tremor and Other Movement Disorders in HIV-Associated Dementia

A low-frequency, predominantly resting tremor is often observed in HAD as part of an accompanying parkinsonian syndrome. A predominantly postural and symmetrical tremor, occasionally with a kinetic component, is also a frequent finding in HAD.

Hyperkinetic movement disorders, including chorea, dystonia, and myoclonus, are also occasionally observed in HAD, often as a part of a mixed hypokinetic-hyperkinetic complex motor disorder.

Other Forms of Tremor

Postural tremor in HIV infection can also be present in isolation, without evidence of concomitant HAD. A coarse postural and kinetic tremor may also be consequent to opportunistic infections involving the midbrain.

More often, tremor in HIV is caused by drugs that interfere with the dopaminergic system, such as neuroleptics or antiemetics, or as a complication of antidepressants. Rarely, tremor is observed as a side effect of preventive treatment of pneumocystis carinii pneumonia with trimethoprim-sulfamethoxazole.

Hyperkinetic Movement Disorders

The majority of hyperkinetic movement disorders are related to discreet lesions affecting the basal ganglia and the related motor pathway projections. Virtually, all movement disorders have been described in HIV infection, including focal, segmental, and generalized dystonia, myoclonus, chorea, and choreo-atethosis, hemiballismus, and tremors.

Before the introduction of HAART, chorea, often in the form of hemichorea-hemiballismus was s a common complication of AIDS, usually consequent to toxoplasmic abscess or other opportunistic infections. With the introduction of HAART, chorea has become uncommon, although choreic movements may, in rare occasions, manifest themselves in patients with HAD without any other obvious lesion affecting the basal ganglia.

Dystonia is also an uncommon neurological complication of HIV infection, and although it may be due to an underlying opportunistic infection or other lesions affecting the basal ganglia, it is often caused by exposure

to drugs that interfere with dopaminergic transmission. In rare instances, dystonia may be a manifestation or a complication of HIV encephalopathy.

Myoclonus is another uncommon complication of HIV, usually observed as part of the clinical constellation of HAD.

Up to a third of patients with chronic HIV infection controlled with HARRT have also been reported to have symptoms consistent with restless legs syndrome.

Drug-Induced Movement Disorders

Many movement disorders in HIV are caused, unmasked, or worsened by drugs that interfere with the dopaminergic system. The neuronal loss in the substantia nigra, the pathological changes in the basal ganglia, and the consequent dopaminergic dysfunction, in HIV-infected individuals, are likely explanations for their vulnerability to extrapyramidal side effects. These side effects may develop even after limited exposure to low doses of neuroleptics or after treatment with drugs with a lower potency for inducing extrapyramidal complications, such as metoclopromide and prochlorperazine. It has been estimated that in HIV-infected individuals, exposure to neuroleptics in general and haloperidol in particular are respectively associated with a 2.4- and 3.4-fold greater risk of developing extrapyramidal side effects.

Although parkinsonism is the most common drug-induced movement disorder, dystonia, tremor, and chorea have all been reported as side effects of dopamine-blocking agents.

Among drug-induced movements, a rare Parkinsonian syndrome induced by ritonavir and other antiretroviral agents deserves special mentioning. These antiretroviral agents in patients with concomitant Parkinson's disease may increase the effect of L-dopa and cause uncontrollable dyskinesias.

Therapeutic Strategies

There are no specific treatments for HIV-associated movement disorders, and most symptomatic treatments used in the general population are also utilized in HIV-infected individuals. Since the introduction of HAART, most neurological complications, including movement disorders, have become less common and less severe, and it is not uncommon that in HAART naïve patients, neurological manifestations improve solely as a result of effective antiretroviral treatment.

Parkinsonism is empirically treated with dopamine agonists, monamine oxidase inhibitors (MAO-I), and L-dopa, with variable results. In general, however, the response to treatment is less robust than in idiopathic Parkinson's disease, and it is not uncommon that the treatment proves ineffective. Side effects from dopaminergic mediations are also more common and more severe in HIV-infected patients. Individuals who respond well to L-dopa treatment may also have a higher risk of developing early and severe L-dopa motor complications, especially dyskinesias.

Treatment of hyperkinetic movements also relies on symptomatic agents, with no clear evidence of a different response to treatment among HIV-infected subjects. When the involuntary movements are caused by an opportunistic infection or other lesions affecting the basal ganglia, resolution of the underlying problem leads to amelioration of the movement abnormality.

While there is no known preventive treatment, there are reasonable hopes that an ever more effective control of HIV infection with HAART may maintain neurological health and prevent the onset of neurological complications, including Parkinsonism and other movement disorders. There is however increasing concern that an aging population with an underlying dopaminergic dysfunction may be more prone to developing Parkisnons's disease and other neurodegenerative disorders of ageing.

See also: Basal Ganglia; Basal Ganglia, Functional Organization; Bradykinesia; Chorea; Dystonia; Myoclonus; Postural Tremor; Tremor.

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Hoehn and Yahr Staging Scale

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Glossary

Construct – Any conceptual or abstract attribute that is not directly observable (e.g., intelligence).
Convergent validity – Correlation with other measures used to evaluate the same or related constructs.
Dopaminergic – Relating to the neurotransmitter known as dopamine.
Known-groups validity – A scale's ability to detect differences among groups.
Ordinal – Level of measurement which classifies attributes by order of rank.

Parametric – Statistical tests for continuous variables with normal distribution.
Parkinsonism – Syndrome that includes hypokinesia, rigidity, and tremor.
Reliability – Extent to which a scale is free of random error.

History

The Hoehn and Yahr staging scale (HY) was published in 1967, exactly 150 years after James Parkinson's seminal description of Parkinson's disease. The paper, in which Margaret M. Hoehn and Melvin D. Yahr included the first description of the scale, sought to display information about the course of 'Parkinsonism,' so that the potential effect of new treatments could be determined. Prior to its publication, some evaluative instruments, such as those by Schwab (1960), Canter et al. (1961), and Petrinovich and Hardyck (1964), had been published. None of these, however, gained the wide recognition and importance accorded to the HY.

Immediately after its introduction, the HY became, and indeed continues to be, the most commonly applied tool for the classification of Parkinson's disease (PD) patients. Its simplicity and ease of use make this scale attractive and useful for clinical practice and research. As a consequence of the HY's relevance, a Movement Disorder Society Task Force reviewed this instrument and published its conclusions in an overall laudatory critique in 2004.

Description

The HY was described by its authors as 'an arbitrary scale based on the level of clinical disability.' It is a five-level measure consisting of: stage I – unilateral involvement only, usually with minimal or no functional impairment; stage II – bilateral or midline involvement, without impairment of balance; stage III – first sign of impaired righting reflexes; stage IV – fully developed, severely disabling disease; and stage V – confinement to bed or wheelchair unless aided. The most relevant modification of the HY was introduced in 1987 by the Unified Parkinson's Disease Rating Scale (UPDRS) Development Committee. This version includes stages 1.5 (unilateral plus axial involvement) and 2.5 (mild bilateral disease with recovery on pull test). In addition, stage 0 (no signs of disease) was added to the original scale. These later adaptations have not been clinimetrically tested. The HY furnishes a global assessment of PD severity based on a combination of clinical features and disability.

Applications

In consonance with the original intention of its authors, the HY has been applied to a diversity of studies on the natural history of PD and its course relative to the effects of the diverse treatments. HY staging provides an overall description of the patient's condition vis-à-vis PD, allowing for a generally accepted clinical translation to mild (stages I and II), moderate (stage III), and severe (stages IV and V) levels. As an indicator of PD progression, change in HY stage is an important feature in the course of the disease and influences its management.

Not only is the scale commonly used to select patients for clinical trials and other types of applied research, but it is also used to stratify samples for data analysis in epidemiological studies and outcomes research. It has been incorporated into other composite rating scales such as the MDS-UPDRS and the Core Assessment Programs for Surgical Interventional Therapies in PD (CAPIT and CAPSIT-PD). Correlation between disease stage and dopaminergic-activity markers in neuroimaging has been demonstrated in longitudinal and in cross-sectional studies. Lastly, the HY is a benchmark for testing and developing newer rater and patient-based PD measures.

The Hoehn and Yahr Scale as a Measure

HY is an ordinal scale, since it ranks disease severity according to an order that ranges from the mildest (stages I or II) to the most severe disease stages (stage V). Hence, steps in this scale cannot be presumed to be equal, and parametric statistical methods should not be applied for the purpose of HY data-analysis. The HY conceptual and measurement model is beset by some problems, namely: (1) the combination of impairment and disability, which often renders stage assignment difficult in cases where there are discrepancies between these two aspects of disease assessment; (2) the lack of consistency between disease onset and lowest scale rank for a proportion of patients who apparently begin PD in stage II; (3) the absence of strict relationship between increment in stage and increasing disability, something that mainly affects stages I–III; (4) the possibility of wide variability in severity within each stage, due to the small number of categories; (5) the emphasis on balance and bilateral involvement does not specifically focus attention on upper limb function, motor complications, and nonmotor symptoms of PD all of which may play important overall roles in the final severity of PD.

As an outcome measure, HY is valuable for charting clinical disease progression. At present, however, without a restorative therapy for PD, improvement in HY should be interpreted, not as a regression to earlier phases of the disease, but rather as a symptomatic effect on

manifestations that influence stage assignment. Furthermore, due to the great gap between stages (scant precision), the scale is poorly responsive to current interventions. The application of the HY is not standardized and therefore, the scale is prone to spurious variability in the assignment of scores. Furthermore, modifications (see earlier text) have been introduced without clinimetric validation.

Psychometric Attributes

Due to the scale's structure, only some properties can be tested. With regard to reliability, several studies performed on the original version of the HY have reported a moderate-to-substantial level of interrater agreement (κ values, 0.44–0.71). Test–retest has not been examined. Convergent validity with other PD rating scales has been extensively tested against other measures, including the Schwab and England, UPDRS subscales, Intermediate Scale for Assessment of PD, Rating Scale for Gait Evaluation, Freezing of Gait Questionnaire, and the Short Parkinson's Evaluation Scale/Scales for Outcomes in Parkinson's Disease-Motor (SPES/SCOPA-Motor). These evaluations have yielded the following correlation coefficients: 0.26–0.84 with functional scales; 0.62–0.87 with motor examination scales; 0.44–0.67 with motor complications. Additional correlation has been determined with: SCOPA-autonomic, 0.35–0.60; SCOPA-Cognition, −0.39 to 0.66; and nonmotor symptoms questionnaire, and scale, 0.31 and 0.33, respectively. Low/moderate or nonsignificant correlations (always <0.40) have been found between HY and the following PD-specific scales: Parkinson's Disease Sleep, SCOPA-Sleep, and Parkinson Psychosis Rating Scales.

Both generic and specific health-related quality of life (HRQoL) measures have been used in PD, and the HY has been frequently used as the global severity benchmark. These studies showed a variable, largely moderate association between HY and summary indices of generic HRQoL measures, and a moderate-to-high correlation between specific HRQoL instruments (PDQ-39, PDQL, and PDQUALIF) and HY. While dimensions relating to physical aspects, such as mobility and functional status, generally displayed a close association with HY staging, other domains (such as emotional role, mental health, pain, social support) showed a less robust correlation. Disease severity has a global effect on most determinants of and factors associated with HRQoL. For most of the clinical scales and HRQoL instruments, known-groups (discriminative) validity has been demonstrated on the basis of sample stratification by HY stage or severity level.

Conclusions

Over 40 years after its introduction, the HY continues to be a reference for classification of patients in relation to the evolutionary phases and global severity of PD. The ad hoc Movement Disorder Society Task Force recommends that the original version be used until such time as clinimetric testing of the modified version, that includes 0.5, 1.5, and 2.5 designations, has been completed. Despite ambiguities and lack of standardization, HY staging is the most widely used instrument for assessment of PD patients and the primary benchmark for other types of measures.

See also: CAPIT, CAPSIT; Parkinson's Disease Questionnaire-39 (PDQ-39); Parkinson's Disease: Definition, Diagnosis, and Management; Rating Scales in Movement Disorders; Schwab and England Activities of Daily Living Scale; Unified Parkinson's Disease Rating Scale (UPDRS) and The Movement-Disorder Society Sponsored-unified Parkinson's Disease Rating Scale (MDS-UPDRS).

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Hot-Cross Bun Sign

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The Hot-Cross Bun Sign

The hot-cross bun sign (**Figure 1**) is the neuroradiological finding of cross-shaped abnormal hyperintensity in the pons, resembling a hot-cross bun (a pastry bearing a white cross traditionally eaten in the UK at Easter). The hot-cross bun sign was first described in patients with multiple system atrophy, as a differentiating feature in comparison with findings of normal pontine structures in patients with Parkinson's disease. The underlying pathological feature is thought to be the degeneration and gliosis of the transverse pontocerebellar fibers and raphe pontis, which stand out against a background of intact tegmentum and pyramidal tracts. On T2-weighted images and proton density weighted sequences, the vertical and horizontal fibers give the appearance of a white cross. The sensitivity of the signs is 40–50% in patients fulfilling the criteria for probable multiple system atrophy (higher in MSA with predominant cerebellar ataxia and lower in MSA with predominant parkinsonism), and it is typically associated with pontine atrophy and hyperintensities in the middle cerebellar peduncles on T2-weighted images. The hot-cross bun sign is absent in patients with Parkinson's disease and progressive supranuclear palsy, making this a specific finding in the context of differentiating these syndromes. However, the hot-cross bun sign has been reported in patients with other disorders associated with olivopontocerebellar atrophy, including SCA 2- and SCA 3-associated disorders and vasculitis. The hot-cross bun sign has been incorporated in the diagnostic criteria for multiple system atrophy.

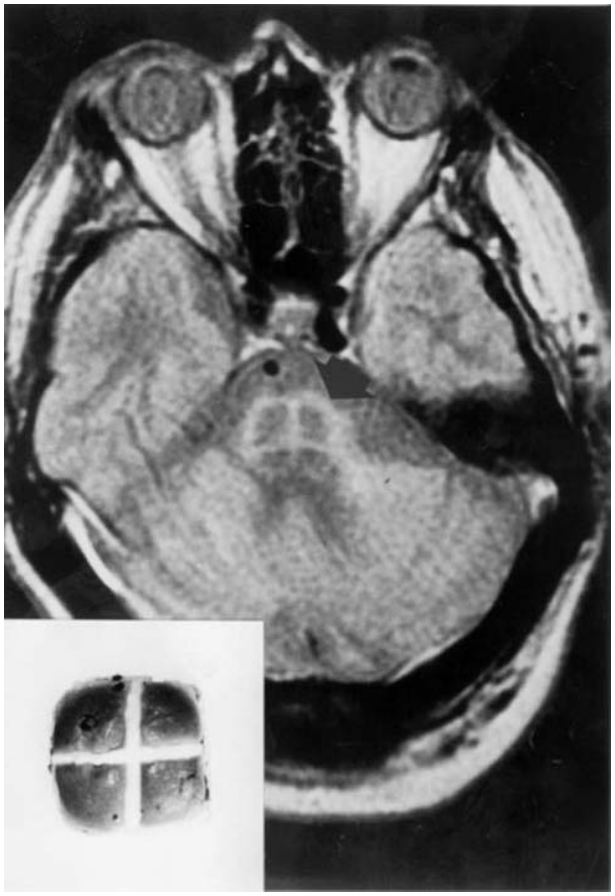

Figure 1 Hot-cross bun sign. Reproduced from Schrag et al. (1998) Clinical usefulness of magnetic resonance imaging in multiple system atrophy. *Journal of Neurology, Neurosurgery and Psychiatry* 65: 65–71, with permission from Journal of Neurology, Neurosurgery and Psychiatry.

See also: Multiple System Atrophy; Olivopontocerebellar Atrophy; SCA2; Striatonigral Degeneration.

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H-reflex

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Glossary

H/M ratio – This ratio represents the percentage of the motoneuron pool that is active at any particular time. This ratio is between the amplitude of the maximum M-wave and the amplitude of the tested H-reflex.

M-wave – This is the electrically stimulated direct motor response. The M-wave elicited by supramaximal stimulation is used for motor nerve conduction studies. The maximum M-wave represents 100% of the activity of the specified muscle's motoneuron pool.

Parkinson's disease – A neurodegenerative disorder that causes motor symptoms such as tremor, rigidity, and bradykinesia.

Introduction

The H-reflex can be used to assess changes in motoneuron pool reflex excitability. This reflex, also known as the Hoffmann reflex, is an electrically stimulated reflex that excites the muscle spindles Ia afferents. When electrical stimulation is applied over a nerve, this causes action potentials to be transmitted to the spinal cord where monosynaptic or polysynaptic connections cause motoneurons to reach threshold, thereby, causing the extrafusal muscle to contract. The overall level of reflex excitability may be influenced by excitation of Ib afferents from Golgi tendon organs, group II afferents from muscle spindles, and larger cutaneous afferents. While the H-reflex was originally suggested to be analogous to the tendon jerk, the central timing of the H-reflex is shorter than the tendon response, allowing for the possibility that more spinal processing occurs with the tendon response. Therefore, it is possible that both responses use slightly different pathways, and hence, it may not be appropriate to directly compare these responses.

The H-reflex can be evaluated either through the latency of the response or the reflex size (peak to peak amplitude). While there are established values for the latency of this response (time from stimulus application until initial deflection from baseline), this is not the case for the amplitude. The validity and reliability of the H-reflex amplitude have been evaluated by Crayton and King and Hugon et al. Because of the variability of the amplitude of the H-reflex, one test measurement should consist of the average of at least 5–7 (and up to 20) H-reflex measurements. The amplitude of the H-reflex also exhibits a wide intersubject variability in reflex recording; however, there is small test/retest variability within each subject. Because of this variability, changes in the amplitude of the H-reflex should only be analyzed relative to each subject's baseline H-reflex value.

Several methods, which evaluate H-reflex amplitude changes, have been used to assess spinal reflex excitability. One method assesses the percentage change of the test H-reflex amplitude in comparison to a control (baseline) H-reflex amplitude. However, this method of analysis requires an understanding of how changes in stimulus intensity can influence the amplitude of the H-reflex. At low stimulation intensities, Ia afferents are activated first which causes activation of the muscle's motoneurons eliciting a small amplitude H-reflex. As stimulation intensity further increases, the amplitude of the H-reflex increases which activates alpha motoneurons, and the direct muscle response (M-wave) is now observed. As the stimulation intensity further increases, the amplitude of the H-reflex becomes progressively larger up to a critical point, after which the amplitude of the H-reflex becomes progressively smaller until the H-reflex is no longer present. Therefore, test H-reflex alterations elicited by a given conditioning stimulus depend not only on the conditioning volley, but also on the amplitude of the control H-reflex. This aspect of H-reflex recruitment makes it difficult to determine the 'true' amount of reflex facilitation or inhibition. For instance, a small control H-reflex could result in a large amount of facilitation, while a larger control H-reflex would result in a smaller amount of facilitation. Therefore, using percentage change may make it difficult to estimate the real amount of either facilitation or inhibition of the motoneuron pool.

The H/M ratio, which is the ratio of the size of the H-reflex to the size of the M-wave, is an alternate method of analyzing changes in motoneuron reflex excitability. The H/M ratio represents the percentage of the motoneuron pool that may be considered to be active at any particular time. The maximum M-wave represents 100% of the activity of the specified muscle's motoneuron pool. The H/M ratio allows a quantification of the percentage of the active motoneuron pool. This interpretation enhances the ability to compare changes in the H-reflex between subjects. Crone and colleagues established that regardless of differences in the maximum H-reflex, the

change in sensitivity to facilitation followed the same pattern as long as the control reflex sizes are explored.

The H-reflex recovery curve, which is a variation of the H-reflex, can also be used to assess motoneuron pool reflex excitability. The recovery curve is elicited by stimulating a nerve with paired stimuli at intervals from 1 ms to 10 s. The magnitude of the recovery curve at a given interstimulus interval refers to the percentage ratio of the test H-reflex amplitude to the unconditioned H-reflex amplitude, with these amplitudes being plotted as a function of the intervals between the reflexes. The recovery curve in healthy subjects consists of several phases. The first phase occurs with interstimulus intervals from 3 to 10 ms with the test reflex varying in size with simulation intensity. Next, there is an inhibition phase which is then followed by a facilitatory phase which occurs at stimulus intervals between 50 and 400 ms (peaks at 200–300 ms). Finally there is another inhibition phase which can last from 5 to 10 s.

In addition to changes in motoneuron reflex excitability, changes in the H-reflex have also been used to evaluate reciprocal Ia inhibition, Ib inhibition/facilitation, and presynaptic inhibition. Reciprocal Ia inhibition is evaluated by using a test H-reflex and a conditioning response (paired stimulus paradigm). The H-reflex is elicited with a low intensity stimulus (designed to stimulate primarily the muscle spindle Ia afferents) supplying the antagonist muscle. If the antagonist stimulation is given at the appropriate time, the test H-reflex in the agonist can be inhibited. Ib inhibition/facilitation is also assessed using a paired stimulus paradigm. However, unlike Ia inhibition, Ib inhibition/facilitation can be measured in the antagonist or synergists muscles acting at different joints within a limb. Finally, several techniques have been established whereby the H-reflex can be used to assess presynaptic inhibition. One method assesses H-reflex amplitude changes after vibration has been applied to either the tested muscle or a different muscle. In this method, the amount of inhibition is assessed by analyzing the amplitude change between the amplitude of the H-reflex prior to, and then after vibration. Presynaptic inhibition can also be assessed while testing for reciprocal inhibition between extensors and flexors in the forearm. Finally, Hultborn and colleagues showed a more difficult, but more specific method of analyzing presynaptic inhibition. In this method, the amount of H-reflex facilitation in one muscle is assessed while a monosynaptic heteronymous Ia volley is being applied to another muscle.

H-reflex changes have been evaluated in individuals with neurological disorders. It is known that slowing down of the H-reflex latency can be detected long before nerve degeneration in hereditary and acquired demyelinating neuropathies are observed. However, the scientific and clinical implication related to changes in the H-reflex amplitude is not as clear. For instance, Angel and Hoffmann observed that the H_{max}/M_{max} ratio was higher in individuals with spasticity. In contrast, other studies have concluded that changes in the H_{max}/M_{max} ratio were not a good measurement tool to quantify changes in spasticity. The literature is also mixed regarding the H-reflex changes when assessing rigidity. While no difference was shown in the H-reflex recovery curve when Parkinson's disease (PD) subjects with rigidity were compared to healthy subjects, other studies showed that rigid PD subjects exhibited an abnormal H-reflex recovery curve. Along this line, changes in the H-reflex behavior correlated with the level of rigidity in PD subjects. Studies are also mixed regarding changes in presynaptic inhibition in individuals with neurological disorders. While studies have shown a decrease in presynaptic inhibition in subjects with upper motoneuron lesions, others researchers have shown no change in presynaptic inhibition in the same type of subjects. While changes in the amplitude of the H-reflex can be used to measure several different parameters related to changes in spinal reflex excitability, it is clear that more research is needed in order to determine the clinical relevance of H-reflex changes in individuals with neurological disorders.

See also: Electromyography (EMG); Motor Evoked Potential; Motor Unit.

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Huntington, George

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Glossary

George Huntington (1850–1916) – American general practitioner, who gave the classic description of hereditary chorea (Huntington's disease) in 1872.
Huntington's disease – Neurodegenerative disease transmitted as an autosomal dominant trait and characterized by adult onset, chorea, dementia, psychiatric disturbances, and a tendency to suicide, as characterized by George Huntington in his classic description in 1872.

Although genealogical studies suggest that Huntington's disease has existed since at least the seventeenth century, it had not been differentiated from other forms of chorea until the nineteenth century. The rarity of the disease, confusion with other more common neurologic conditions, inadequate appreciation of the role of heredity in the etiology of disease, and publication of some early clinical reports in inaccessible places without identification of cases all contributed to the delay in recognition. Although clinical descriptions of hereditary chorea were given by several authors from 1841 to 1868, there had been no general recognition of the disorder until the description by George Huntington (1850–1916) in 1872.

George Huntington (**Figure 1**) grew up in the 'drowsy, secluded village' of East Hampton on the eastern end of Long Island, where both his grandfather and his father practiced medicine. Huntington in later years stated that his grandfather, Dr. Abel Huntington, came to Long Island from Connecticut in 1797 and found hereditary chorea well established there. From years of contact with patients afflicted with hereditary chorea, Huntington's grandfather, and later his father, began to recognize the clinical features of the disorder.

George Huntington first encountered victims of 'that disorder' at the age of 8 while riding with his father on his professional rounds. As Huntington recalled in 1910, 'Driving with my father through a wooded road leading from East Hampton to Amagansett, we suddenly came upon two women, mother and daughter, both bowing, twisting, grimacing. I stared in wonderment, almost in fear. What could it mean? My father paused to speak with them, and we passed on . . . . From this point, my interest in the disease has never wholly ceased.'

Around 18, Huntington began preliminary medical studies under his father's guidance, prior to matriculation at the College of Physicians and Surgeons of Columbia University, New York. After graduation in 1871, Huntington returned to East Hampton and for several months assisted his father in practice. He was particularly interested in the cases of hereditary chorea still living in the area, and studied the clinical notes of cases treated previously by his father and grandfather. Huntington incorporated this material in an essay entitled 'On chorea,' which was carefully edited by his father.

Late in 1871, Huntington took the advice of a relative and moved to Pomeroy, Ohio to set up a general medical practice. Huntington brought his unpublished paper with him and at the age of 21 presented it before the Meigs and Mason Academy of Medicine at Middleport, Ohio on February 15, 1872. In his presentation, Huntington noted that. . .

> The hereditary chorea . . . is spoken of by those in whose veins the seeds of the disease are known to exist, with a kind of horror, and not at all alluded to except through dire

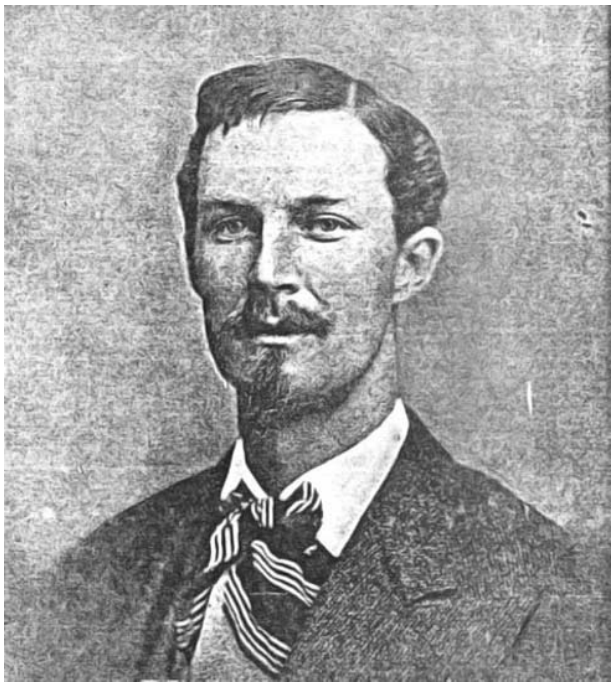

Figure 1 George Huntington in 1872 around the time of publication of his classic paper, 'On chorea.' Photograph from 'the Huntington number' of Neurographs.

> necessity, when it is mentioned as 'that disorder.' It is attended generally by all the symptoms of common chorea, only in an aggravated degree, hardly ever manifesting itself until adult or middle life, and then coming on gradually but surely, increasing by degrees, and often occupying years in its development, until the hapless sufferer is but a quivering wreck of his former self... There are three marked peculiarities in this disease: 1. Its hereditary nature. 2. A tendency to insanity and suicide. 3. Its manifesting itself as a grave disease only in adult life... When either or both the parents have shown manifestations of the disease, and more especially when these manifestations have been of a serious nature, one or more of the offspring almost invariably suffer from the disease, if they live to adult age. But if by any chance these children go through life without it, the thread is broken and the grandchildren and great-grandchildren of the original shakers may rest assured that they are free from the disease... It begins as an ordinary chorea might begin, by the irregular and spasmodic action of certain muscles, as of the face, arms, etc. These movements gradually increase, when muscles hitherto unaffected take on the spasmodic action, until every muscle in the body becomes affected (excepting the involuntary ones), and the poor patient presents a spectacle which is anything but pleasing to witness. I have never known a recovery or even an amelioration of symptoms in this form of chorea; when once it begins it clings to the bitter end. No treatment seems to be of any avail, and indeed nowadays its end is so well known to the sufferer and his friends, that medical advice is seldom sought. It seems at least to be one of the incurables.

As his presentation was well received, Huntington submitted his manuscript to the editors of the Medical and Surgical Reporter of Philadelphia, where it was published on April 13, 1872. Although Huntington's article had been published almost three decades before Mendel's laws were simultaneously rediscovered and made known by DeVries, Correns, and Tschermak von Seysenegg in 1900, there was already growing interest in hereditary neurodegenerative diseases, especially in light of Friedreich's work on hereditary ataxia. Huntington's description of hereditary chorea was considered particularly important by his contemporaries, because of his clear and concise description, and because it demonstrated that hereditary conditions could have their clinical onset in adulthood. Huntington's paper was abstracted for international yearbooks, widely discussed, and published verbatim in scholarly texts. Because of this attention, by the late 1880s authors began referring to hereditary chorea as 'Huntington's chorea,' as did Huntington himself after about 1895.

In 1903, in a presentation in Columbia, South Carolina, to the Tri-State Medical Society (i.e., Virginia and the Carolinas), Huntington expanded upon his original description of the clinical features:

> Of very gradual onset, the symptoms are progressive, and seldom commence suddenly... [Whole] groups of muscles are put into action as if by voluntary effort, as if the patient were posturing or making grimaces. He has a dancing or swaying movement of legs and body, and the mouth and other facial muscles are drawn and twisted into the most ludicrous shapes; the tongue is protruded and then suddenly withdrawn, the head nodding and neck twisting at the same time. The contortions are never localized to one muscle or set of muscles, but the whole muscular system seems to be involved. The facial muscles seem to be usually the ones first involved, then the arms, trunk and legs, and occasionally all simultaneously. The voice is changed to a thick nasal tone and sentences are spoken in a jerky way. It is not a stammer, but jerky, as one would expect from the irregular contraction of the vocal muscles, the lips, tongue, etc... Voluntary muscular efforts are often interrupted and impeded on account of imperfect co-ordination, so that if the patient desired to shake hands with another, he would go through quite a rigamarole of movements before accomplishing his object... Some patients are very irritable and easily provoked, occasionally wildly maniacal. Some become gradually helpless and demented, while others show but little mental impairment to the end.
>
> The diagnosis is made upon the family history largely; upon the period of life at which the disease manifests itself, seldom, if ever, occurring before adult life, and most

> frequently between 25 and 40; the character of the spasmodic movements being slower and of larger range than those of ordinary chorea... [The] general progress of both mental and physical symptoms, ever tending onward and downward to the end, point decidedly to this form of the disease... The patients are born with nerve cells not having the capacity of living but for a limited time, and when the cells begin to degenerate, the symptoms of chorea commence to show themselves... No treatment that is of any effect has yet been found.

In 1908, Dr. William Browning of Brooklyn, New York edited a special edition of 'Neurographs,' in honor of Huntington in which Huntington's work was applauded by many, including Osler. While accepting that Huntington was not the first to describe hereditary chorea, Osler noted in regard to Huntington's description that 'In the history of medicine there are few instances in which a disease has been more accurately, more graphically, or more briefly described.'

Huntington spoke on hereditary chorea at the New York Neurological Society on December 7, 1909, with Drs. William Browning (1856–1941), Smith Ely Jelliffe (1866–1945), and Charles Loomis Dana (1852–1935) among those in attendance. A modest man, Huntington readily credited the contributions of his grandfather and father:

> It must also be remembered that, without the facts and observations handed down to me by my grandfather, Dr. Abel Huntington, and my father, Dr. George Lee Huntington, the medical lives of whom both were spent in East Hampton, Long Island, and whose memory is still cherished there by the few remaining who once knew them – I never could have formulated a picture of the salient characteristics of the disease so true and so complete as to make of it a so-called classic. As in old Greece the pupil sat at the feet of his teacher, so your essayist sat at the feet of these two, and whatever of honour, whatever of praise, whatever of scientific worth there is, is due much more to them, than to him to whom has come this unsought, unlooked for honour.

The characteristics of Huntington's disease recognized by George Huntington in 1872 and by his father and grandfather before him – the distinct clinical profile, midlife onset, and inheritance pattern – made the disease ideal for investigation by genetic linkage analysis a century after Huntington's description.

See also: Huntington's Disease: Genetics; Huntington's Disease.

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Huntington's Disease: Genetics

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Glossary

Genetic anticipation – Worsening and/or earlier onset of disease over generations, usually due to increasing size trinucleotide repeat expansion mutation over the generations.

Huntingtin – The protein product of IT15 contains polyglutamine repeat expansion mutation in HD.

Huntington's disease (HD) – Progressive neurodegenerative disease associated with chorea, psychiatric disturbance, and dementia.

***IT15* – Huntington's disease gene** – The gene mutated with CAG repeat expansion in Huntington's disease.

Trinucleotide repeat expansion mutation – Increase in length of a normally occurring DNA sequence containing repeat units of three nucleotides.

History of Huntington's Disease Genetics

Huntington's disease (HD) is a progressive movement disorder characterized by major features of chorea, psychiatric disease, and dementia. In the 1840s, HD was first described in the medical literature as 'chronic hereditary chorea' when several physicians described accounts of people with involuntary movements and mental disturbances that were inherited from a similarly affected parent. In 1872, George Huntington wrote what is considered as the classic description of HD in his landmark paper '*On Chorea*,' in which he also clearly described the genetic nature of the condition, stating, 'When either or both the parents have shown manifestations of the disease, one or more of the offspring invariably suffer from the condition. It never skips a generation to again manifest itself in another. Once having yielded its claims, it never regains them.'

In 1955, Americo Negrette described communities in Lake Maracaibo, Venezuela with an unusually large fraction of the population affected by HD. Nancy Wexler began work in that community in 1981, which eventually led, in 1983, to the identification of a genetic marker linked to HD at the end of the short arm of chromosome 4. Predictive linkage testing was implemented as a way of assessing the likelihood that individuals at risk for HD had inherited the disease. After much work attempting to identify the disease-defining linked gene, the causative mutation in HD was identified in 1993 as a trinucleotide (CAG) repeat expansion mutation in the *IT15* gene at chromosomal location 4p16.3.

The HD Mutation and Inheritance

The gene responsible for HD, *IT15* (also called *HTT*), encodes a ubiquitously expressed 350 KDa protein termed huntingtin. The causative mutation, an expansion of a tract of uninterrupted CAG repeats, is located within the coding sequence of the gene, 17 codons downstream of the ATG translation initiation codon in exon 1. The expanded CAG repeat in the mutation codes for an expanded polyglutamine tract in huntingtin. This mutational mechanism occurs in nine other diseases, known to be caused by abnormal expanded polyglutamine tracts, including many of the dominantly inherited spinocerebellar ataxias.

Identification of the disease-associated mutation led rapidly to a large number of studies characterizing the population distributions of normal and disease allele sizes and genotype–phenotype interactions. Based on these studies, current consensus is that normal alleles have 9–26 CAG repeats, with 17–20 repeats found most commonly and representing the majority of the alleles in the population. Intermediate or 'premutation' alleles of 27–35 repeats are not associated with clinical symptoms but can be meiotically unstable and expand to disease-causing mutations of 36 repeats or more when passed on to offspring. Alleles that have 36–40 repeats exhibit incomplete penetrance in that they are associated with disease in some individuals but not in all, although the penetrance disease at each of these mutation sizes is not well-defined. Alleles with 41 or more repeats are thought to always cause HD if the individual lives long enough.

There is earlier onset and more severe disease with increasing length of the CAG repeat sequence. There is, however, a wide variation in the age of onset observed with any given repeat number and thus CAG repeat number has poor specific predictive value for the age of onset for a given individual. The number of CAG repeats, in fact, accounts for about 60–70% of the variation in the age of onset, with the remainder of variation contributed by modifying genes and environmental factors. Survival models have been developed to predict the probability of neurological (motor) disease onset of HD at different ages based on CAG repeat length. Several reports have identified genes that modify the age of onset of HD in one or several cohorts, including polymorphisms in Huntingtin-associated protein-1 (HAP1), transcription factor p53 (TP53), human caspase activated DNase (hCAD), ubiquitin C-terminal hydrolase L1 (UCHL1), GluR6 kainate glutamate receptor (GRIK2), glutamate receptor subunits NR2a, and NR2B (GRIN2A and GRIN2B), but some of these have failed to be replicated or have not yet been studied in sufficient independent cohorts.

Inheritance of HD is autosomal dominant with anticipation, a phenomenon in which the age of onset becomes earlier and disease severity increases in successive generations. In HD, the molecular basis for this phenomenon is explained by the meiotic instability in the number of CAG repeats passed on from parent to child. The repeat mutation may increase or decrease in size when passed from parent to offspring, although expansion is more common (73% of transmissions) than contraction (23% of transmissions). There is a gender bias for the expansion of the HD CAG repeat mutation, such that paternally inherited alleles carry a much higher risk of significant further expansion when passed on to a child, due to large size increases that occur in spermatogenesis relative to

oogenesis. Thus, large expansions of the CAG repeat mutation during replication happen almost exclusively in males, and likewise, severe, early-onset juvenile HD, which typically results from alleles of >50 repeats, is almost always inherited from the father. Thus, the characteristics of the mutational instability in the CAG repeat mutation explain the prior clinical observation of genetic anticipation in HD when the mutation was inherited paternally. Similarly, new onset cases of HD, for which there is no family history, are now known to arise because of expansion of an intermediate allele in the 'premutation' range (27–35 repeats) into the disease-causing range, generally when inherited through the paternal line. No cases of expansion of alleles in this size range to disease-causing alleles on maternal transmission have yet been reported.

Somatic instability of the HD mutation can be seen such that there may be some mosaicism for slightly different mutation sizes in different tissues of the body. Although this finding may contribute to selective vulnerability in the CNS, it does not typically confuse genetic testing results.

Genetic Testing for Diagnosis of HD

Genetic diagnosis of HD can now be accomplished through a simple PCR assay, which determines the size of the CAG repeat sequence and can be performed by most molecular diagnostics laboratories. DNA testing to confirm diagnosis in symptomatic cases is the current standard of care.

While genetic testing for asymptomatic cases is also now easy to accomplish, care must be taken to make sure that the individual being tested wants the test done, understands the implications of the result, and is not depressed or suicidal, particularly when receiving positive test results. Despite the ease of obtaining the test, current data suggest that only about 5% of individuals at risk choose to pursue testing. Those who do have testing generally utilize the result to help to make career and family choices. Currently, protocols are typically used to exclude suicidal individuals from testing, inform the person seeking testing about the implications of the test results for themselves and others in the family, identify potential sources of support for the person receiving the result, and to ensure protection of confidentiality. Individuals who undergo recommended pretest assessment and counseling protocols generally feel that their overall experience with the testing process is positive. Although anxiety and stress increase immediately after receiving a positive result, this returns to baseline and within 2 years, stress levels are lower than pretest, irrespective of the outcome. Persons with a negative result can experience stress from the so-called 'survivor guilt,' which can be handled with counseling.

Prenatal testing is only infrequently done, due predominantly to the resistance to abortion for a relatively late-onset disease. Preimplantation testing, although expensive, is becoming increasingly utilized to avoid pregnancies with HD-affected fetuses. Elderly individuals who are asymptomatic may undergo exclusionary testing to allay fears that children or grandchildren may be at risk for HD. Experience with issues arising in association with genetic testing for HD has provided a model for approaches to testing in other late-onset disorders.

Epidemiology of HD

The prevalence of genetically diagnosed HD in Caucasian populations is about 5–7 affected individuals per 100 000. Higher frequencies exist in genetically isolated populations with a few founders, such as the population at Lake Maracaibo. Prevalence in Asian and African populations is less than 10% that of Caucasian populations (<0.5 affecteds/100 000). This is largely due to the higher frequency of borderline alleles of 27–35 repeats in Caucasian populations, although reasons for the increased prevalence have not been discovered.

Animal Models of HD

Transgenic animal models of HD have been created in mice, *Drosophila*, and *Caenorhabditis elegans*. The fly and mouse models show neuronal polyglutamate inclusions, progressive late-onset motor dysfunction, and neuronal dysfunction followed by neuronal death, with pathology dependent on polyglutamine length. Of note, when the transgene is switched off in clinically symptomatic mice, the clinical symptoms and inclusions resolved, suggesting that treatment to limit toxicity could be helpful even later in the course of the disease. The animal models have continued and will continue to provide an extremely valuable resource for understanding the pathogenesis of the disease and for testing new potential treatments targeted to the underlying mechanism of disease.

Cellular and Molecular Pathogenesis of HD

Huntingtin is expressed in all human cells, with highest concentrations in the brain and testis. The function of the normal protein is still incompletely understood as are the specifics of the underlying mechanisms active in HD.

One possible mechanism of disease that could occur in an autosomal dominant disease like HD is haploinsufficiency, in which the genetic defect leads to the reduction of a vital protein to half the normal levels resulting in disease

due to inadequate amounts of the protein for normal function. This mechanism is unlikely in HD for a number of reasons: (1) the CAG repeat expansion is the only mutation in *IT15* that causes HD – if haploinsufficiency caused HD, there would likely be other disease-associated mutations; (2) carriers of a balanced translocation that transects the *IT15* gene on one chromosome and render it inactive do not develop HD; (3) individuals with a terminal deletion of 4p and who are missing one copy of *IT15* do not develop HD; (4) the absence of one copy of the HD gene does not cause a disease phenotype in mice; and (5) although homozygous deletion of the gene in mice is associated with embryonic lethality, individuals homozygous for an HD-associated CAG expansion develop normally. Taken together, this data suggest that the CAG repeat mutation does not work through a loss-of-function mechanism and that haploinsufficiency of *IT15* is probably not associated with specific clinical manifestations.

Rather, the CAG repeat mutation appears to be inherited dominantly because it operates through a gain-of-function mechanism, generating a new toxic function not intrinsic to the normal huntingtin protein, and likely resulting from cellular toxicity of the polyglutamine expansion. In support of this concept, homozygous cases of HD show similar age of onset (although perhaps more rapid progression) to heterozygous cases with an allele size similar to the larger allele in the homozygous case. The best lines of evidence supporting the gain-of-function mechanism for HD include the demonstration that expression of expanded polyglutamine peptides alone in Drosophila causes neurodegeneration. Further, a mouse model with the CAG repeat sequence inserted into the *Hprt* gene developed a late-onset neurological disease that progressed eventually to death. Transgenic overexpression of polyglutamine expansions, introduced either into the full-length huntingtin protein or just in exon 1, also results in neurodegeneration in mice and *Drosophila*.

As in other diseases (such as dominant spinocerebellar ataxias), the HD-associated expanded CAG repeat is transcribed into mRNA and translated into a polyglutamine stretch the Huntingtin protein. Since such expanded polyglutamine sequences result in selective neurodegeneration in nine other conditions, all the nine diseases show neuronal inclusions containing aggregates of polyglutamines, and all the nine diseases show correlation of the age of onset and the length of the polyglutamine repeat, it seems highly likely that the polyglutamine expansion confers a toxic effect.

Another line of evidence in support of a gain-of-function mechanism in HD is the tendency for polyglutamine strands to aggregate after 37 consecutive glutamine residues. This process has a time lag before initiation and proceeds faster with longer glutamine repeat sequences, findings that could help to account for the delayed onset of the disease in HD, the strong correlation of onset with repeat length, and the size of repeat (36–40 repeats) at which humans begin to show the disease phenotype.

Wild-type huntingtin is found mostly in the cytoplasm, with a small portion intranuclear. The protein is known to be associated with the plasma membrane, endocytic and autophagic vesicles, the ER, the Golgi apparatus, mitochondria, and microtubules. The huntingtin protein contains 28–36 HEAT repeat sequences distributed along the entire length of the huntingtin protein. HEAT repeats are degenerate 50 amino acid sequences comprising two antiparallel α-helices forming a hairpin. These motifs are usually involved in protein–protein interactions and are found in proteins that play roles in intracellular transport, microtubule dynamics, and chromosome segregation.

Huntingtin contains an NES (nuclear export signal) near the C-terminal and it is also thought that the N-terminal 17 amino acid sequence may serve as an NES due to its binding with the nuclear exporter protein, Tpr (translocated promoter region). The polyglutamine expansion mutation appears to interfere with the huntingtin–Tpr interaction, resulting in an accumulation of mutant huntingtin in the nucleus. The N-terminal 17 amino acids also, in conjunction with the first three HEAT repeats and the region surrounding them, appear to play a role in targeting huntingtin to multiple membrane-bound organelles in the cell. The 17 amino acid N terminal sequence also contains several lysine residues that compete for SUMOylation and ubiquitination, and thus are potentially involved in the regulation of half-life, localization, and nuclear export of wild-type huntingtin and may modify the toxicity of the expanded polyglutamine mutant huntingtin. Huntingtin also undergoes palmitoylation for the regulation of trafficking and function and this process is disturbed in mutant huntingtin. Both wild-type and mutant huntingtin undergo cleavage by various intracellular proteases, including caspases, calpain, and an aspartic protease. It is not known what role proteolytic cleavage plays in normal function and metabolism of huntingtin but it is known that cleavage of mutant huntingtin plays an important role in disease pathogenesis as the intact mutant huntingtin shows significantly less cellular toxicity than the cleaved N-terminal fragments.

There has been an enormous research effort put forth to understand the normal functions of huntingtin over the past 15 years. However, these functions have been difficult to pinpoint due to lack of similarity to other proteins, localization everywhere in the cell, and interactions with so many other cellular proteins (over 200) that a specific area of impact is impossible to define. Evidence is beginning to accumulate that huntingtin is a scaffold protein that may act as a master regulator of converging pathways for intracellular trafficking and signaling. Presumably through such a mechanism, there is support for roles of huntingtin in iron homeostasis, regulation of apoptosis (through caspase interactions), nucleocytoplasmic

shuttling of transcriptional regulators and mRNA, binding and sequestration of transcription factors (particularly restrictive element transcription factor (REST), which regulates transcription of brain-derived neurotrophic factor (BDNF), vesicle trafficking, long- and short-range transport along microtubules (including transport of vesicles containing BDNF), and negative regulation of glutamate receptor *N*-methyl-*D*-aspartic acid (NMDA) and mGluR1) activity at the synapse (through interactions with PSD-95 and optineurin). Support for these diverse roles of huntingtin is predominantly based on defects that occur in huntingtin knockdown models.

It has become fairly clear that the mechanism of disease induction by mutant huntingtin involves proteolytic cleavage, resulting in an N-terminal fragment containing the polyglutamine expansion. In animal models, N-terminal huntingtin fragments are sufficient to produce clinical disease and intranuclear inclusions, and recent data suggest that inhibition of caspase 6 cleavage of mutant huntingtin rescues both behavioral symptoms and neuropathological abnormalities in mice expressing a full-length mutant huntingtin transgene. Thus, proteolytic cleavage likely converts a relatively nontoxic full-length mutant huntingtin into toxic N-terminal fragments.

Intranuclear and intracytoplasmic inclusions of mutant huntingtin are pathological hallmarks of the CNS disease in HD, and these kinds of aggregates are also seen in all known polyglutamine diseases. It is unclear whether the inclusions are toxic, protective, or just represent an epiphenomenon. The density of inclusions in human brain correlates with CAG repeat length but not with areas of the brain most affected. In cell culture, there is a correlation between aggregate formation and cell death. Overexpression of heat shock proteins that reduce aggregation also reduces cell death in cellular and mouse models of HD. However, reduction in aggregates may be due to reduction of oligomeric precursors, which could be the actual toxic species. Inclusion formation has not seemed related to disease in a number of studies. Overexpression of certain proteins like the transcription factor CA150, or crossing the HD mouse with a tissue transglutaminase deficient mouse, has resulted in partial rescue of clinical features and neuronal toxicity, while increasing inclusions. One study demonstrated that HD cells with large inclusions were less compromised than those with diffuse mutant huningtin.

Mutant huntingtin does appear to interfere with numerous cellular processes, even if this is not primarily mediated by aggregate formation. Mutant huntingtin interacts with cAMP response element binding (CREB)-binding protein and Sp1 transcriptional regulators, altering the levels of downstream products of genes regulated by these transcription factors. An example of this effect includes the alteration of BDNF regulation by mutant huntingtin, which shows abolished binding and regulation of REST/NRSF (neuron-restrictive silencer factor), a transcription factor normally regulated by the wild-type protein. The lack of binding by mutant huntingtin leads to an accumulation of REST/NRSF in the nucleus, with resultant excessive transcriptional repression of regulated genes, including BDNF. Other examples of results of proposed aberrant transcriptional regulation by mutant huntingtin include decreased D2 receptor expression, and decreased premordial germ cell (PGC)-1α leading to decreased mitochondrial biogenesis and energy deficit.

There have been numerous reports linking various forms of mitochondrial dysfunction and deficits in energy production to HD. A decrease in ATP production with increasing CAG repeat number has been demonstrated, both in the normal and disease-causing range and this was linked to enhanced calcium influx through NMDA receptors. Mutant huntingtin appears to impair the motility of mitochondria, with aggregates potentially impairing the physical passage of mitochondria along neural processes, and causing them to accumulate adjacent to aggregates.

It has been proposed that mutant huntingtin impairs the ubiquitin–proteasome system (UPS) in HD and this alters protein turnover and processing, thus contributing to the disease mechanism. There are, however, conflicting data derived from various HD-affected tissues, and cell culture and transgenic models. Although the majority of data seem to support impairment of the UPS at some level, including the recent data showing an increased amount of polyubiquitin chains in HD transgenic mice, HD knock-in mice, and human HD brain, all possible explanations for this finding have not been evaluated, explanations for conflicting findings in prior studies have not been identified, and thus definitive evidence of impairment of the UPS in HD remains elusive.

In any case, it seems clear that mutant huntingtin interactions may compromise a diffuse array of cellular processes, including transcriptional regulation, apoptosis pathways, mitochondrial function, neurotransmitter release, and axonal transport. This has led to many potential pathways to investigate for targeted treatment of HD. Yeast two-hybrid screens, aggregate retardation assays, genome-wide RNAi screens, and cell-based assays have been utilized to identify potential HD interacting proteins that might serve as treatment targets and might act as genetic modifiers of disease expression. Numerous candidates have emerged and are in the process of being evaluated.

Huntington-Like Disease Genetics

Huntington-like (HDL) conditions have a clinical picture indistinguishable from HD, chorea is prominent, and onset ranges from young adult to middle age. Inheritance is autosomal dominant for HDL1, 2, 4, and autosomal

recessive for HDL3. The mechanism for HDL1, 2, and 4 is gain of function and there is polyglutamine toxicity with intranuclear inclusions in HDL2 and HDL4, although the genetic mechanism is unknown for HDL3. HDL1 results from a mutation consisting of extra octapeptide repeats in the *PrP* gene. HDL2 is caused by a CTGCAG repeat expansion in the *junctophilin-3* gene. It is the most common of the HD phenocopies and is particularly prevalent in populations of African origin. Of affected patients, 10% have acanthocytes. Normal *junctophilin-3* alleles have 6–28 repeat units, while HDL2 alleles have 44–57 repeats. The age of onset correlates with the repeat length, but unlike HD, the gender bias for expansion is maternal. The mechanism of disease is thought to be mRNA toxicity with inclusions. HDL3 has been described in one family and neither the genetics nor mechanism of disease is known. HDL4 is also SCA17, with mutations in a TATA box binding protein and most individuals with a mutation in this gene have ataxia but the condition can present as an HD phenocopy. This condition results from an expansion of a CAACAG repeat with normal alleles having 25–42 repeats, intermediate alleles 43–48 repeats, and disease-causing alleles more than 48 repeats.

Other autosomal dominant disorders that can mimic HD are dentato-rubro-pallidal-luysian atrophy (DRPLA) and neuroferritinopathy, which results from FTL gene mutations and resultant mutant ferritin light protein. Affected patients have low blood ferritin, iron deposition on MRI, and mitochondrial respiratory chain dysfunction. Other autosomal recessive disorders that can resemble HD include Wilson's disease, chorea-acanthocytosis (VPS13A gene), pantothenate kinase-associated neurodegeneration (PKAN, Hallarvorden–Spatz disease), although PKAN usually presents with more dystonia and there is iron deposition in the basal ganglia. Mutations in PANK2 and PLA2G6 cause diseases similar to PKAN that may mimic HD. X-linked McLeod syndrome has a phenotype similar to chorea-acanthocytosis, although it has absent Kx antigens on erythrocytes. Diagnostic evaluation of a patient with HD-like symptoms, but negative for an HD-associated *IT15* CAG repeat expansion mutation, would include acanthocytes, copper level, ceruloplasmin, ferritin levels, an MRI for iron deposition, and then if these are normal, DRPLA DNA and if African American, HDL2. If these are negative, then an SCA17 DNA test could be done, followed by other gene sequencing based on clinical data. As not all causes of HD phenocopies are yet known, a specific genetic etiology will not be identified for some patients.

See also: Chorea; Choreiform Disorders; Dentatorubropallidoluysian Atrophy; Huntington, George; Huntington's Disease-like 2; Huntington's Disease; Senile Chorea.

Further Reading

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Relevant Websites

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www.huntington-study-group.org – Huntington's Study Group website.
www.genetests.org – Genetests site for Genetics reviews and testing labs.

Huntington's Disease-like 2

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Glossary

Acanthocyte – Abnormally spiculated red blood cell.
Endoplasmic reticulum – A cellular organelle with multiple functions, including protein processing and calcium storage.
Open reading frame – A section of DNA that has the potential of being encoded into protein, based on the presence and spacing of start and stop signals.
Transcript – The RNA molecule transcribed from the DNA of a gene.

The Differential Diagnosis of Huntington's Disease

Individuals with a progressive, adult onset, autosomal dominant disorder characterized by chorea with concomitant abnormalities of voluntary movement, cognition, and psychiatric status most likely have Huntington's disease (HD). Indeed, in carefully examined individuals with an HD-like syndrome or pathology in Europe and North America, as low as 1% do not have the *HD* mutation. Diagnosis is less certain in cases in which either the family history is unknown or the presentation is atypical. Once HD is considered in the differential diagnosis, HD genetic testing can quickly establish the disease as HD, or exclude HD from the list of differential diagnoses.

If HD is excluded, the differential diagnosis of an HD-like presentation becomes more challenging and largely depends on family history. With no known family history, almost any process that can affect the basal ganglia must be considered: infections (e.g., HIV, neurosyphilis), autoimmune (e.g., systemic lupus erythematosis), metabolic syndromes, tumors, strokes, trauma, and drugs. Probably, the single most common disorder considered along with HD is tardive dyskinesia, the movement disorder associated with long-term antipsychotic medicines. These individuals typically have chronic psychiatric diseases and may have movement abnormalities intrinsic to their psychiatric disorder, complicating diagnosis.

For individuals with the HD phenotype, but not the HD mutation, a family history of a nondominant disorder raises the possibility of Wilson's disease (a recessive disorder of copper metabolism): important to consider because of the availability of specific treatments. Other possible recessive disorders include pantothenate kinase-associated neurodegeneration (characterized by childhood onset and iron accumulation), chorea-acanthocytosis (characterized by abnormal morphology of red blood cells), some forms of ceroid neuronal lipofuscinosis, and unusual presentations of Friedreich's ataxia. X-linked familial inheritance pattern may be indicative of McLeod neuroacanthocytosis, while maternal transmission suggests a mitochondrial disease.

HDL2 Clinical Presentation

Huntington's disease-like 2 (HDL2) is an autosomal dominant disorder first detected in a family followed at Johns Hopkins in which affected individuals had an HD presentation but did not have the HD mutation. Affected members of the HDL2 family first identified at Johns Hopkins, as well as affected members of at least one other well-documented family, develop prominent weight loss, poor coordination, rigidity, dysarthria, hyperreflexia, bradykinesia, dystonia, and tremor, with minimal chorea or eye movement abnormalities and no cerebellar signs, by the age of 40. Depression, irritability, and apathy are common. The disease progresses to profound dementia and rigidity over 10–15 years. A second and apparently more common presentation of HDL2 resembles classic HD, with a somewhat older age of onset, more prominent chorea and dysmetric saccades, and less dystonia and other parkinsonian features. Familial factors, potentially including longer repeat expansion, appear to influence the type of presentation. Overall, HDL2 and HD cannot be clinically distinguished.

HDL2 Neuropathology

The neuropathology of HDL2, based on the published findings in eight brains, closely resembles HD. On gross examination, this pattern of degeneration was evident, with diffuse cortical atrophy, no evidence of white matter demyelination, severe atrophy of the caudate and the putamen, mild atrophy of the globus pallidum, and little evidence of abnormality in other structures. Microscopically, a dorsal-to-ventral gradient loss of small neurons was apparent in the striatum. Other than one case, there were no neurofibrillary tangles or unusual number of β-amyloid deposits. Lewy bodies have not been detected. On electron microscopy, numerous neurons showed features of autophagy, including autophagic vacuoles, as well as intranuclear fibrillar aggregations resembling those seen in HD. As in HD, HDL2 brains have prominent intranuclear inclusions, stained by antiubiquitin antibodies and antibodies thought to be specific to long polyglutamine repeats. The inclusions also stain for torsinA and TATA-binding protein (TBP), but not for huntingtin. Unlike in HD, inclusions have not been detected in neuropil. Recently, small RNA inclusions have also been detected in HDL2 brain (see the following section).

HDL2 Mutation, Genetics, and Laboratory Findings

The causative mutation of HDL2 was determined to be a CTG/CAG repeat expansion on chromosome 16q24.3, in the gene *junctophilin-3*. The presence of the mutation is established using a simple polymerase chain reaction (PCR) assay similar to that used for other repeat expansion diseases. This has facilitated the detection of >40 HDL2 pedigrees around the world. The highest frequency is in South Africa, where individuals of African descent with an HD presentation are almost as likely to have HDL2 as HD. Most other individuals with HDL2 are of African ancestry. Other laboratory findings, including MRI scans showing striatal and cortical atrophy, are

nonspecific. Interestingly, acanthocytes have been detected in some individuals; the implications of this finding are unclear.

The range of the *JPH3* repeat length in the normal population is 6–28 triplets, while in HDL2 the range is 40–58 triplets, with potential decreased penetrance of alleles of 40–45 triplets. This is remarkably similar to the huntingtin repeat, which has a normal range of 4–35 triplets, a range of incomplete penetrance of 36–39 triplets, and is fully penetrant with > 39 triplets. Like HD, longer repeats are correlated with a younger age of disease onset. Repeat length is modestly unstable during vertical transmission, with insufficient data yet available to establish a propensity for expansion.

HDL2 Pathogenesis

The pathogenic mechanism of HDL2 is intriguing and may shed light on HD pathogenesis. The original hypothesis, based on the clinical, genetic, and neuropathological similarity to HD, was that neurotoxicity was a result of polyglutamine toxicity, as is the case in HD and other CAG repeat expansion diseases. An open reading frame exists at the HDL2 locus in which the repeat is in-frame to encode polyglutamine, but thus far there has been no evidence that a protein containing an expanded glutamine repeat is generated from this site in HDL2. The only gene at the HD locus, *JPH3*, is on the reverse strand. The repeat, in the CTG orientation, falls within a variably spliced exon. Preliminary evidence suggests that in HDL2 *JPH3* transcripts containing the expanded repeat forms small aggregates (RNA foci, noted above) and that neurotoxicity may in part arise from toxic properties of the RNA transcript, similar to those observed in myotonic dystrophy type 1 and 2. In addition, there is a loss of expression of the *JPH3* protein product in HDL2, perhaps because the *JPH3* transcript with an expanded repeat is sequestered and unavailable for translation. Since *JPH3* protein appears to form part of the structural connection between plasma membrane and endoplasmic reticulum, loss of expression may contribute to neurotoxicity via dysregulation of calcium-mediated signaling pathways.

HDL2 Prognosis and Management

Like HD, there is currently no treatment to stop the progression of HDL2 to total debilitation and death. However, symptomatic care of the type provided to HD patients can be of great value to patients and their family. This effort should include education, occupational and physical therapy, support and respite for families, assistance with financial and legal planning, and vigorous treatment of psychiatric disorders. Treatment options that emerge from current clinical trials in HD may prove applicable to HDL2.

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See also: Chorea; Chorea–acanthocytosis; Choreiform Disorders; Dentatorubropallidoluysian Atrophy; Huntington, George; Huntington's Disease: Genetics; Huntington's Disease; SCA8; SCA17.

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Huntington's Disease

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Glossary

Apraxia – Inability to perform purposeful movements or to imitate gestures when motor strength and sensation are intact.
Dystonia – Abnormal contractions of muscle leading to sustained, twisting postures.
Genotype – The genetic makeup of an individual.
Neurodegenerative disease – A neurological disorder characterized by the loss of neurons and other brain cells causing decline in function and ability.
PHAROS (Prospective Huntington At Risk Observational Study) – A large, prospective trial to study the natural history of adults at risk for Huntington's disease who do not know their gene status.
Phenoconversion – The change from an asymptomatic state to manifesting the underlying genetic abnormality phenotype. In HD, the emergence of unequivocal motor signs in those at risk for the disease.
Phenotype – The physical or biochemical expressions of the genetic makeup of the individual as influenced by the environment.
PREDICT (Neurobiological Predictors of Huntington's Disease) – A large, prospective trial.
Presymptomatic HD (preHD) – Gene carriers of the HD gene mutation who do not show overt clinical signs or symptoms of the disease.
Striatum – Part of the basal ganglia nuclei consisting of the caudate and the putamen, the region of selective nerve cell loss in HD.
Total functional capacity (TFC) – A rating scale of function in HD used to assess the capabilities in several areas and determine the stage of disease.
Trinucleotide – A series of three of the building blocks (nucleotides) of DNA required to code a specific amino acid.
UHDRS (Unified Huntington's Disease Rating Scale) – A rating scale for the uniform assessment of clinical features of HD with components including: motor, behavioral, cognitive, and functional assessments, independence scale and total functional capacity.

Definition and History

Huntington's disease (HD) is a dominantly inherited, neurologically degenerative disease with typical onset in the mid- to late-1930s. It is caused by an unstable trinucleotide expansion in the huntingtin (Htt) protein gene coding region on chromosome 4 (4p16.3). The repeated trinucleotide sequence, cytosine–adenine–guanine (CAG), codes for glutamine and the mutation produces a polyglutamine expansion within the Htt protein. Disease manifestations include a characteristic choreiform movement disorder, progressive disturbance of gait and balance, worsening cognition and, in many, marked psychiatric symptoms. The disease process is relentless resulting in death 20–25 years after onset.

History

The term chorea (Greek: to dance) used to describe writhing, dance-like movements dates back to the 1500s. Although mostly seen in epidemics probably related to infectious diseases, clinicians noted that some forms of chorea occurred within families. HD was first recognized in Norway by Lund, in 1860, as a familial chorea associated with dementia. The disease was probably brought to the United States by people of northern European origin during migration in the early 1600s. It was best described by George Huntington in 1872, his first year after medical school, as a medical curiosity likely of little importance to his colleagues. The vivid, succinct description included a longitudinal perspective gathered by George Huntington based on his family of physicians' lengthy observation of the affected families on Long Island, New York. He described a tendency to insanity, a high risk of suicide, a choreic movement disorder of adult onset, and its hereditary nature. These are salient features of the disease to this day. His contribution led to the eponymous designation but the newer term 'Huntington's disease' is preferred over 'Huntington's chorea,' as chorea is not the only manifestation.

In the early 1970s, attention focused on a region near Lake Maracaibo in Venezuela where there was a very high prevalence of HD. Scientists studying this population discovered a genetic marker linked to HD on the short arm of chromosome 4. Predictive genetic linkage testing allowed better definition of risk for disease in HD families and paved the way for the definitive gene discovery on chromosome 4 in 1993.

Pathogenesis/Pathophysiology

Gross Pathology/Macrostructure

The pathology of HD was first correlated with chorea by Jelgersma and Alzheimer at the turn of the twentieth century. There is generalized atrophy of the entire brain at autopsy with corresponding decrease in brain weight. Gross gyral atrophy is most prominent over the frontal lobes and marked focal atrophy of the striatum occurs along with enlargement of the lateral ventricles. A neuropathological staging system of disease, grades 0 (none) through 4 (severe striatal pathology), is based on the pattern of atrophy and loss of neurons by gross and microscopic examination. Those with later stage disease show more shrinkage of the brain. Cortical ribbon thinning may be seen by on visual inspection and with magnetic resonance imaging (MRI).

Morphological assessments using MRI in patients with manifested HD and presymptomatic HD (preHD) demonstrate relative sparing of cortical gray matter with great reductions in cerebral white matter and striatal volumes. This differential effect on the gray and white matter occurs despite the microscopic evidence of neuronal loss in the cerebral gray matter. Some investigators have postulated a neurodevelopmental role of mutant Htt (mHtt), possibly causing increases of the gray matter, during embryogenesis. Quantitative MRI of the whole brain in preHD patients support this theory revealing larger cortical gray matter volumes compared with controls. These differences lessen as the preHD patients come closer to disease onset although still remain above the volume of controls.

Microscopic Pathology

The pathological hallmark of HD is the degeneration of the caudate and putamen, starting in the caudal regions. Postmortem microscopic examination of the HD brain reveals up to 95% loss of striatal neurons. The selective loss of medium-sized, spiny, cholinergic neurons of the caudate and putamen is associated with an increase in reactive astrocytes. There are also activated microglia found postmortem. Early pathological grades, grade 1 or 2 HD, have little involvement outside the striatum. By grade 3–4, there is a spread of pathological changes to include the paleostriatum, neocortex, thalamus, substantia nigra pars reticulata, subthalamic nucleus, and the cerebellum. No reactive gliosis is found in these nonstriatal parts of the brain. In the globus pallidus (GP), the projecting spiny enkephalin neurons of the GP externa are more vulnerable to cell death than the substance P containing medium, spiny neurons projecting to the GP interna. There is also loss of the cerebral cortex neurons in the third and fourth layers. Although the white matter is atrophic, it is not microscopically abnormal indicating probable loss of fiber passage and neuropil. PreHD and HD patients have pathologic evidence for increased density of oligodendrocytes that seems independent from the degenerative process.

Although the abnormal gene and gene product are present in all cell types, degeneration is confined to the central nervous system. Higher neuropathological grade at autopsy is positively correlated to an increase in neuronal loss and worse clinical motor impairment. There is greater nerve cell death seen with longer CAG repeat lengths and with younger age at onset. CAG repeat length dictates the rate of development of neuropathology, probably linearly from birth.

Intracellular Pathology

The development of transgenic models has provided a powerful tool to understand the pathogenesis of HD. Transgenic mice R6/1 and R6/2 lines have a stable CAG expansion in exon 1 of the HD gene. These mice develop a motor and cognitive disorder with underlying striatal and cortical degeneration. The discovery of intranuclear inclusions in the HD mouse model led to similar findings in autopsied HD patients. The inclusions or aggregates contain not only mutant huntingtin proteins but also a number of other proteins, including transcription regulating proteins, chaperones, proteasome subunits, and ubiquitin. Inclusions are identified by labeled antibodies against mHtt or ubiquitin and are found in vulnerable nerve cell populations long before the onset of disease. It is currently unknown why striatal neurons die as most cells and neurons with the same mutation are unaffected.

Huntingtin Protein

Wild type huntingtin (Htt) is expressed in all mammalian cells with highest amounts produced in brain and testes. It is highly conserved through evolution. Htt has 67 exons with the human gene mutation present in the first exon. The protein has a molecular mass of 349 kDa and the normal (wild type) protein has 3140 amino acids. It bears no homologies to other proteins but has a region that is similar to a protein motif involved in cytoplasmic transport. In the brain, Htt is found in neurons rather than glial cells and is seen throughout neurogenesis. Interestingly, knockout mice embryos that are genetically engineered without *Htt* genes die at gestational age 8–10 weeks. In those with the HD mutation, mutant gene product is also expressed throughout brain development. Although the function of wild type *Htt* is not completely known, it is believed to have a role in brain development. *Htt* is known to increase the production of brain-derived neurotrophic

Table 1 Number of CAG repeats and expression of Huntington disease

Less than 27 repeats	*27–34 CAG repeats*	*35–39 CAG repeats 'intermediate'*	*≥40 CAG repeats*
No HD	Very rarely express HD (based on recent clinical and pathological data)	May or may not express HD 'reduced penetrance'	Always express HD 'full penetrance' in time
No transmission to children	Increased risk for further CAG repeat expansion into intermediate or disease causing length in children	May transmit an expanded 'disease causing' mutation to children	50% chance of transmitting expanded mutation to children

factor through upregulation. As well, findings suggest *Htt* functions in cell vesicle trafficking, fast axonal transport, and mature cell gene expression.

HD patients express 'normal' wild type huntingtin protein as well as mutated Htt. Intracellular cleavage of the mutated Htt protein results in N-terminal fragments containing the enlarged polyglutamine tract. Abnormal processing of the protein forms dimers, oligomers, and eventually intracellular protein aggregation. It is not known whether the aggregation is protective or toxic to the nerve cell. The expanded polyglutamine tract leads to conformational changes that alter the cellular interactions of the protein. Neuronal dysfunction may be due to these abnormal protein–protein interactions that occur, possibly before aggregation, with cytoplasmic, proteasomal, and nuclear transcription proteins.

Most features of the disease result from a 'gain in function' within the cell nucleus due to the mutated gene product as it takes on new actions with known and unknown proteins. It is unlikely that disease is due to loss of function of *Htt* because disruption of the gene does not cause HD. However, new research also shows an effect from the loss of wild type *Htt* function, particularly, its effect on brain-derived neurotrophic factor (BDNF) production and cortical-striatal protein trafficking.

Ubiquitinated, intranuclear, neuronal inclusions are common to the inherited polyglutamine diseases but their role in causing disease is debated.

Epidemiology and Risk Factors

HD is present worldwide with the highest prevalence in western European nations. Global average estimates are 5–10 cases per 100 000 persons. Its prevalence is lowest among African and Asian populations. The average age at disease onset is 35–44 years old, although ranges of onset as early as 2 years old and as late as 80 years old have been described. HD can be found in members of any socioeconomic class and demonstrates an autosomal dominant transmission pattern within families. Autosomal dominance means each child of a gene carrier has a 50% chance of inheriting the abnormal gene.

The most reliable risk factor for disease is the presence of the gene mutation containing greater than 40 CAG repeats (**Table 1**). HD is then fully penetrant depending on life span. The age at onset is predicated on the CAG repeat length. Higher repeat length is associated with an earlier onset and more rapid progression of disease. Those with 35–39 CAG repeats may or may not express the disease but can pass an expanded mutation (into the definite disease-causing range) to their children. Those with 28–34 CAG repeats more rarely express the disease and are less likely to pass a disease-causing expansion than those with the longer repeats. People who have less than 27 repeats never have the disease.

There are several candidate genes that may modify age at onset including, transcription factor 53, human caspase activated DNAse, glutamate receptor 6 subunit (GluR6) of kainate receptor, MSX1 polymorphism, and NMDA receptor subunit 2B. Earlier age at onset is seen in the best described of these genes, GluR6, and also in those with a YY polymorphism in the UCHL1 gene regulating proteolysis.

In R6/1 and R6/2 mouse models of HD, environmental enrichment has been found to delay the onset of motor symptoms in affected mice but it is unknown how this impacts human onset of disease.

Clinical Features and Diagnostic Criteria in HD

The clinical features of HD are motor, psychiatric, and cognitive in origin. Typically, there is the gradual onset of a motor disorder starting with early eye movement abnormalities, fine dexterity loss, and then the evolution of twitchy choreiform movements. Some patients will have cognitive or psychiatric symptoms prior to the motor disorder.

Motor

Eye movement abnormalities start with slowing of visual saccades. There is progressive difficulty in initiating saccades and further slowing of voluntary saccades. These findings are easily demonstrated by asking the patient to follow an object that is moved in horizontal and vertical fields for testing extraocular movements and also by

asking the patient to quickly shift gaze between two objects when one object is moved. Later-stage patients have obviously abnormal, slow, jerky eye movements, and large head thrusting movements to initiate the saccades. Patients are poorly able to suppress eye movements toward a stimulus in the environment despite being so instructed.

An early finding in HD is impairment of fine motor movements of the hands as examination of finger taps and alternating movements reveals. There are initial small-amplitude distal choreic movements of the hands and feet that can be seen with the patient upon a table with legs dangling and arms in outstretched posture. Chorea increases to involve facial, neck, and trunk muscles, and more proximal limb movements emerge. Patients may demonstrate eyebrow raises, lip pursing, as well as involuntary inhalations. The chorea can cause trunkal extensions making the person appear to sit up taller or rock backwards. Larger amplitude chorea interferes with the performance of voluntary, accurate movements. There are greater deviations in performance because of effects upon the accuracy and speed of the movements. Chorea is variable through the disease and may significantly lessen in later stages replaced by a more rigid and bradykinetic motor disorder.

Independent of chorea is another classic motor feature of the disease, motor impersistence. The patient is unable to maintain a constant level of voluntary motor contraction that leads to a breakdown in sustained movements. Motor impersistence can be demonstrated by asking the HD patient to forcefully close their eyes. There will be breaks in the tightness of eye closure as witnessed by smoothing of the muscle folds. This can also be shown by asking the patient to lightly hold your hands and feeling the intermittently squeezing pressure. Motor impersistence worsens progressively with disease severity.

There is loss of balance, increased trunkal sway, and abnormal gait mechanics in HD. Gait testing using a long corridor walk will show increased stance time, tendency to lean back on the heels, decreased velocity, and variability of stridelength. Gait disturbance is independent of chorea and is not improved with the use of neuroleptics. Verbal cues and increased attention while walking may help to improve velocity but not variability of the gait pattern. Postural balance is maintained primarily by proprioception rather than visually. Falling occurs more frequently during progression. Patients with more advanced disease have worse balance and declining gait mechanics, ultimately resulting in a nonambulatory state.

Weight loss is seen despite adequate calories and increased appetite. This may be due to a higher energy expenditure described in HD, not just attributable to involuntary movements. Metabolic studies indicate a more catabolic state in people with HD. Compared with controls, there is more muscle wastage, particularly in larger proximal muscles, and hence patients with HD have less muscle strength.

Psychiatric

The spectrum of psychiatric disturbances in HD includes mood disorders, anxiety, apathy, obsessive–compulsive disorders, irritability, aggression, impulsiveness, and, sometimes, psychosis. There is no evidence for an early psychiatric personality that readily identifies which person in a family is more likely to develop the disease. In fact, personality disorders are sometimes found in unaffected members of the family, likely from environmental factors. Depression is the most common psychiatric manifestation of HD in any stage of illness. It presents in some cases prior to motor signs. The prevalence of depression is ~40–50% and is not correlated with cognitive impairment, CAG length, or motor symptoms. Depression can lead to a rapid decline in the patient's function. Suicide rates are four to five times higher than the general population.

Obsessive–compulsive disorder is also more prevalent in the HD population than in the general population. The tendency to obsessive–compulsive disorder can present in preHD patients as excessive worrying and checking behaviors. Other psychiatric manifestations similarly present at any stage do not typically parallel the progression of disease. For some, substance abuse and other pathological behaviors have origins in poor impulse control. The patient with HD can be very challenging to manage for psychiatric reasons.

Cognitive

People with the HD gene mutation are found to have normal intelligence prior to disease onset. There are no differences in levels of academic achievement in those with adult onset disease. Beginning early in disease, there are impairments of executive functioning with a decrease in working memory, planning, and attentional control. Patients have trouble in multitasking and shifting from one task to another. They tend to continue to follow old rules for task even when given entirely new tasks, showing limited flexibility in thinking.

Several expressions of deranged perception can be found. HD patients have impaired recognition of whole body angry postures and facial expressions of surprise, disgust, anger, or fear. Lack of understanding these nonverbal cues causes interpersonal conflicts through miscommunication. Patients may have decreased kinesthetic awareness and ideomotor limb apraxia when trying to mimic postures, gestures, and pantomime tool use. As well, patients have a poor awareness of self that can lead to minimizing or denying disease features that may be blatant to others.

Sleep disturbance is common in HD patients with reports of sleep fragmentation, decrease in slow wave sleep, and alterations in the circadian rhythm.

Diagnosis

The diagnosis is made based on a clinical examination showing typical choreiform movements in the setting of a known family history of HD. At the time of diagnosis, there are usually eye movement abnormalities, motor impersistence, and possible cognitive or behavioral changes. Recent intensive study on gene-positive presymptomatic persons has shown that many subtle abnormalities may precede the onset of the movement disorder. These include neuropsychological abnormalities on testing and very early changes in eye movements noted years prior to onset of chorea.

For systematic study of affected and at-risk persons, a rating scale was developed and validated by the Huntington Study Group. The Unified Huntington's Disease Rating Scale is a standardized rating scale that assesses motor, cognitive, behavioral, and functional capacity changes in HD. The motor subscale measures eye movements, motor control and fluency, muscle tone, slowness in movement, dystonia, chorea, balance, and gait. The cognitive portion includes verbal fluency testing, Stroop Interference testing, and the Symbol Digit Modalities test. The behavioral section queries 11 different psychiatric symptoms.

Also used to assess the patient is the total functional capacity scale (TFC). This scale consists of five items including occupational level, ability to handle financial affairs, ability to handle domestic (housekeeping/management) tasks, ability to perform activities of daily living, and the type of residence appropriate for the patient (home or nursing care). Scores range from 0 to 13; lower scores indicate lessened abilities and more advanced disease. These scores consistently decline over time. Clinical stages of disease have been defined based on the TFC score (see **Table 2**).

No specific biochemical abnormalities have been found in the blood or urine of HD patients. In longstanding HD, some studies report greater likelihood of glucose intolerance and abnormal response to challenge testing of insulin secretion. There may be reduced levels of testosterone found in males with HD.

In children at risk for HD, most common presenting features are decline in school performance, gait disorder, rigidity, bradykinesia, oral motor dysfunction, and/or seizures. Chorea is not common in children. The juvenile form of HD was described by Westphal, in 1905, as a progressive Parkinsonian syndrome. It occurs in ~8–10% of all cases of HD and is defined by manifestation of disease symptoms prior to age 20. Furthermore, 1–2% of juveniles have onset of symptoms prior to age 10. These individuals usually have very elongated CAG repeats expansions, from 70–250 repeats. Juvenile HD is much more likely to have been inherited through paternal transmission. There is an inherent instability of the expanded CAG mutation during germline mitotic divisions tending toward further expansion. The resulting longer CAG repeats in the child versus parent causes earlier onset of disease in the offspring known as 'genetic anticipation.' This most often happens in the paternal line during spermatogenesis as the 'mean increased change in length' is proportional to the 'increased number of CAG repeats.' Not all paternal sperm will have these marked expansions. Juvenile patients have more extensive symptoms and more rapid progression than adults. Disease manifestations include bradykinesia, rigidity, dystonia, seizures, ataxia, and intellectual deterioration.

Some younger adults, in their 20s, can present with clinical motor features more closely akin to juvenile onset showing profound bradykinesia, bradyphrenia, and dystonia rather than chorea. These patients do not necessarily inherit through the paternal line and other siblings commonly present in the same manner.

Presymptomatic Markers

Currently, we rely on nonspecific motor features, family, or patient reports of behavioral or other changes to herald

Table 2 Total functional capacity and stages of HD

Total functional capacity	*Engagement in occupation*	*Capacity to handle financial affairs*	*Capacity to manage domestic responsibilities*	*Capacity to perform activities of daily living*	*Care can be provided at*
Stage I	Usual level	Full	Full	Full	Home
Stage II	Lower level	Requires slight assistance	Full	Full	Home
Stage III	Marginal	Requires major assistance	Impaired	Mildly impaired	Home
Stage IV	Unable	Unable	Unable	Moderately impaired	Home or extended care facility
Stage V	Unable	Unable	Unable	Severely impaired	Total care facility only

Source: Shoulson I and Fahn S (1979) Huntington's disease: Clinical care and evaluation. *Neurology* 29: 1–3.

the onset of disease. A complicated formula, based on thousands of HD cases, has been created to predict the number of years to disease onset. This allows the study of asymptomatic people, who are closer or further from disease onset, for any differences using a battery of tools, including neurological examination, cognitive testing, psychiatric assessments, and brain imaging.

Most studies show evidence of oculomotor and cognitive deficits prior to definite onset of clinical disease. Investigations in psychiatric functioning in preHD patients have been more equivocal. Some show higher rates of hostility, irritability, psychological distress, and others have found no differences in the prevalence of psychiatric disorders in those with and without the gene mutation for HD. Psychiatric symptoms seem to be more common in those predicted to be near to disease onset but may be reported by patient and caregiver even far from onset. PreHD patients have a decreased ability to identify a 'disgusted' facial and verbal expressions. Similarly, those with HD express less disgust to unpleasant smell or food combinations.

The most promising biological markers for onset of disease are imaging tools. Positron emission tomography (PET) and functional MRI (fMRI) have shown changes in those with preHD before symptoms begin. PET imaging reveals in vivo activation of microglia in HD and preHD. On the basis of fMRI and MR spectroscopy studies, it is found that the changes in brain may precede the disease onset by decades. MR spectroscopy shows marked glutamate activity in juveniles, preHD-, and HD-manifested adults. MRI morphological volumetric assessments of the cortex, putamen, and the caudate also define changes years before estimated clinical onset. There is mounting support that the ongoing neuronal modulation, nerve cell dysfunction, or death begin more than a decade before diagnosis.

There is upregulation of immune system markers in HD. Interestingly, monocytes, peripheral white blood cells that aid in the immunological response of the human body, share a common precursor with brain microglia. The monocytes, like microglia, express mHtt protein and should show similar cellular reactions perhaps offering a biomarker of central nervous system pathology through studying easily obtained peripheral cells.

Differential Diagnosis

The differential diagnosis of HD includes several other inherited diseases, such as dentatorubral pallidoluysian atrophy, HD like-2 illness, SCAs 1, 3, and 17, neuroferritinopathy, and neuroacanthocytosis. Infectious, toxic-metabolic causes of chorea have a different time course and other associated features. These cases will lack family history and should not have eye movement abnormalities, motor impersistence, or progressive cognitive decline. If the presentation is primarily dystonic in nature, consider Wilson's disease.

Diagnostic Workup

The diagnosis is made on neurological examination, based on the presence of a typical movement disorder and other features in a person at risk for the disease. Confirmatory gene testing can be undertaken if there is clinical suspicion of disease with or without a family history. It is more cost-effective to check the gene status in a person with a family history of HD or typical clinical features of HD than to embark on a full workup of causes of chorea. A positive test is confirmatory for the diagnosis in the symptomatic person.

There are no other laboratory evaluations required for diagnostic workup. Brain imaging is not necessary as it is usually normal in early disease. In those with more advanced disease, there is enlargement of the lateral ventricles and bilateral atrophy of the caudate nucleus on imaging. As imaging modalities improve, they may provide a diagnostically important biological marker for onset of disease. Currently, the genetic mutation for HD determines that the person will have the disease but not precisely when its onset.

An electroencephalogram may be useful in childhood onset HD if seizure activity is suspected. Routine EMG/NCV is unhelpful.

Protocols have been developed for testing those at risk for HD, who are not yet symptomatic with illness. Presymptomatic testing includes psychological evaluation, counseling, and an assessment of readiness for testing. It identifies support people and networks to help with the testing process and in dealing with the results. Patients undergo a neurological examination to look for signs of the disease prior to testing. If there are obvious features and the patient is ready, most physicians will discuss the findings with the patient who may then decide to have confirmatory testing. The overwhelming majority of those at risk do not undertake presymptomatic testing. Many reasons underlie this decision including fear of knowing, fear of financial repercussions, and the possibility of genetic discrimination. All patients need support and confidentiality. Those who do test usually do so around marriage, childbearing, and during other life decisions.

Testing is not recommended for those with active, unstable psychiatric disease or suicidal ideation. Testing is not done in children at risk for HD unless there are definite and compelling symptoms such as bradykinesia, dystonia, cognitive decline, or seizures. It is not recommended to test an individual if it means the nonintended disclosure of another's gene status, such as a child testing before their parent or in the case of identical twins. Many

times, an older family member at risk but not symptomatic will choose to test to define the risk for their offspring.

Prenatal testing is available though rarely do patients choose this option.

Clinical Course

The progression of HD is divided into five stages based on the level of functional capabilities as assessed using the TFC (**Table 2**). The scale regards the working and domestic abilities, financial management, activities of daily living, and need for long-term care. Full capability in all realms equals 13 points. Most patients lose, on average, one point per year on their assessment. Other known markers of disease progression include total striatal volume on MRI (calculated), CAG repeat length, and Digit Symbol Modalities. More sensitive scales for following early and preHD patients are being developed.

Herein, because of overlap in this progressive disease, the disease course will be divided into early, middle, and late stage disease.

Early Course

Through observing the phenoconversion of gene-positive individuals to overt expression of HD, it is recognized that many patients have the onset of mild behavioral abnormalities or cognitive disruption before the motor disorder. Personality changes may be seen with a tendency to become easily irritated or aggressive. Outbursts and impulsive actions can occur. Depression is worse in the earlier stages of disease, peaking in stage 2 (see **Table 2**), then decreasing. Suicide is also more common in early disease, especially in those with a family history of suicide. The range of mood disorders may occur in this and any stage of HD. It is only apathy that directly correlates with disease progression, growing worse with the duration of disease.

Cognitive decline usually begins with a loss of organizational skills. Patients have difficulty following through with planning and attention to task. They have more concrete thinking and difficulty in learning new skills. This may lead to problems at work, especially if required to learn new skills on the job or if the job requires mental flexibility and changing tasks. Patients can become difficult to redirect and do not express themselves as well due to a decrease in verbal fluency.

The onset of chorea is insidious with initial finger flicking or piano playing movements. Chorea can increase to a movement disorder of variable amplitude and severity usually in the early to middle stages of disease. Restless movements of the limbs are seen with some attempt by the patient to blend the movements into normal actions. Early eye movement abnormalities are found with a delayed initiation of voluntary saccades and inability to suppress involuntary eye movements to a new stimulus. Motor features include slowed rapid alternating movements, motor impersistence, and decline in visual motor performance that all gradually worsen with progression of disease. A decrease in crispness of speech articulation begins and worsens significantly over time.

Midcourse

In the middle stages of disease, there is a more classical expression of chorea, seen in most HD patients, along with the development of balance disturbance. Movements are present throughout the waking day and the patient may be described as restless in bed at night. Choreiform movements are worsened by excitement, stress, and anxiety and lessened with relaxation. Ballistic movements of the limbs afflict those with severe chorea. The flinging motions can be misinterpreted as intentional hitting by others and can interfere with care. Patients have progressive worsening of clumsiness that they describe as difficulty holding onto objects or they knock things over by involuntary limb motions. Speed and dexterity of fine movements decline as does handwriting ability. More significant slowing of eye movement saccades makes the patient blink or turn their head to initiate and complete the saccade giving a peculiar lagging eye movement. On examination, abnormal opticokinetic response is seen and there is impairment in fixation of gaze.

All affected aspects of cognitive failing are worsened during this stage. Patients with HD tend to have preservation of language skills even in later disease. Worsening dysarthria compromises communication. Poor self-awareness consequently affects self-care and can lead to lack of acknowledgment of the disease manifestations. Situational apathy causes the HD patient to be less interested in their environment, less interactive, and show less motivation. Little suicide occurs in this stage. Psychiatric manifestations are likely but variable in presentation and patients can be very challenging to treat because of their loss of insight and impulsive nature. Many loss issues occur during this stage as patients face possible job loss and termination of driving privileges. Psychomotor abilities are most affected by the changes in cognition.

Advanced Course

The patient loses the ability to safely ambulate in this stage of disease due to severe imbalance and very frequent falling. Muscle mass is markedly decreased and strength lessens given the level of debilitation. Cognition steadily declines and the patients are demented. There is little reasoning ability and the patient is less able to respond to behavioral intervention. Changes in the environment or caretakers are not as well tolerated. Patients may rock,

grunt, and make other noises especially while eating. Appetite usually remains very good until late stages. There is severe dysphagia and dysarthria. Speech content decreases in complexity and prolonged pauses occur in responding. Studies have shown that the ability to understand, semantic knowledge, is largely intact. Psychiatric and behavioral problems are present. More severe eye movement slowness and dysfunction are seen. Ballistic or choreiform movements can be present but patients are more likely to be rigid and dystonic with time. The terminal rigid state resembles Parkinsonism.

Many will be placed in a nursing care facility due to their families' inability to manage advanced disease issues, such as incontinence of bowel and bladder. End of life discussions are held with the family. Death is due to complications and secondary illness from dysphagia, poor mobility, bedbound state, or injury from falling.

Weight loss of unknown cause occurs in HD patients, prior to overt symptoms in some, despite adequate nutrition. This unintended weight loss is seen in HD patients and in the murine animal model of HD. Loss worsens with advanced disease even without the presence of chorea. Although weight loss does not correlate to motor features it does correlate to CAG length, thus, those with longer CAG expansions show increased weight loss. There is speculation that a change in cell-based energy homeostasis or another metabolic process is guided by the length of CAG causing weight loss.

Variations in Age at Manifestation and Course

It is estimated that CAG length alone is responsible for ~70% of the variability in age at onset. The rest of the variability also seems to be genetically based rather than environmental. Generally, those with longer CAG repeat lengths have an earlier onset of disease. A longer CAG repeat is also directly associated with a faster rate of progression in motor, cognitive, and functional domains. Still, there is wide variability in rates of progression in HD. Those with shorter expansions have the most favorable prognosis. Heterogeneity in clinical presentation is not related to age at onset or to CAG length.

CAG Affect on Course

Longer CAG repeat length expansion is associated with greater rate of weight loss, younger age at onset, more severe CNS pathology, and faster progression of disease.

Juvenile HD Course

Juvenile onset HD has more extensive symptoms and more rapid progression of disease. Bradykinesia, rigidity, and ataxia occur much earlier than seen in adults. Almost half will develop epilepsy. The duration of disease is about 10 years to death.

Management

The ultimate goal in management of the disease is the prevention of onset and modulation of course progression. Such an intervention, aimed at the pathogenesis of disease, should be safe for long-term administration and would be best started as early as possible. Large, observational trials (PHAROS, PREDICT) are underway to delineate the subclinical state and signs definite enough to warrant diagnosis and biomarker studies. These trials will aid in design of neuroprotective trials based on the type of early symptoms and time to phenoconversion in gene carriers. There is no cure for HD, currently.

Numerous exciting therapies are being explored for prevention of disease onset and aim to enhance neurotrophic factors, nerve cell replacement, mutant gene silencing, and binding expression or splicing of mHtt to mitigate aggregation formation.

Many compounds used in the therapeutic trials of HD, thus far, have not shown slowing of functional decline, including idebenone, creatine, vitamin E, cysteamine, ethyl-EPA, riluzole, lamotrigine, and remacemide. A large multicenter study of high-dose coenzyme Q 10 is underway as an earlier trial indicated a trend for slower functional decline with 600 mg day^{-1} dose. Other trials aimed at efficacy in modulating disease progression in HD are evaluating creatine, phenylbutyrate, and minocycline. Studies, particularly of preHD, are limited by insensitivity of the assessment tools. There is no single biomarker to date that can be used to determine the onset and reliably track the progression of disease but several trials will use biomarkers along with clinical endpoints attempting to discover a more sensitive measure.

Symptomatic Therapy

Despite many multicenter, randomized, controlled trials in HD, there are no standard treatment recommendations that can be given. Recently, members of the Huntington Study Group were surveyed about treatment preferences for a number of symptoms in HD in an effort to develop a consensus of care statement based on expertise in the treatment of HD. Data suggest most patients with HD receive symptomatic treatment primarily for depression or other psychiatric manifestations. Individual management of the HD patient is based on the symptoms displayed over time and a knowledgeable team approach is invaluable. The team ideally consists of a physician, genetic counselor, psychologist or neuropsychologist, social worker, physical therapist, occupational therapist, speech therapist, and dietician. The patient then has a network of support as they struggle through diagnosis,

connecting with medical and social services, coping with family changes and job loss, as well as loss issues surrounding their own decline in function and loss of autonomy. The use of symptomatic treatments is largely based on clinical experience.

Motor

Chorea

Chorea should only be treated if bothersome to the patient or if it interferes with care or seating. Tetrabenazine, a dopamine depleting agent, is the first agent FDA approved to treat chorea in HD. There are good long-term benefits of the medication with dose adjustments. Titration should be done slowly as it takes several weeks for tetrabenazine to exert its full effect. Treating chorea may improve the accuracy of motor movements. Excessive dopamine depletion or blocking can dampen the personality, motivation, or worsen swallow function. The patient should be carefully monitored for behavioral changes, particularly for depression and suicidal ideation. Atypical and typical neuroleptics can also control choreiform movements and some aspects of the psychiatric disease; for example, severe anxiety, aggression, and psychosis. Clozapine has been well studied in HD but therapeutic dosages cause intolerable side effects. Olanzapine, risperidone, ziprasidone, and quetiapine have been reported to have some positive effects on movements and behaviors. Older typical neuroleptics are less expensive to use and less likely to cause weight gain or metabolic syndrome. Neuroleptic malignant syndrome has been reported with tetrabenazine and typical and atypical neuroleptics. It is recommended to treat with the lowest effective dose and decrease or stop treatment if chorea subsides. Dopamine 'stabilizers,' such as ACR 16, are being studied for their role in mood and movement.

Parkinsonism

Parkinsonism and bradykinesia may respond to levodopa or dopamine agonist therapy. Patients have to be observed for increased agitation, aggression, hallucinations, compulsions, and hypersexuality. Anticholinergic agents aggravate chorea and cause confusion, so they are generally not used.

Dystonia

Dystonia occurs mostly in younger onset disease and in those with longstanding HD. Physical therapy is used to relax muscle tone, to reduce secondary muscle contracture, to maintain muscle length through stretching, and to fit adaptive equipment. For focal dystonia causing discomfort or decreased functional use, botulinum toxin can be injected to reduce abnormal posturing and pain, improving the use in some cases. Generalized dystonia is best treated with medications, such as baclofen, tizanidine, or benzodiazepines.

Myoclonus

Some patients with HD have overwhelming myoclonic jerking. The movements interfere with all purposeful movements greatly hampering self-care and activities of daily life. Valproic acid, levetiracetam, carbamazepine, and benzodiazepines are the preferred agents to control this movement disorder.

Bruxism

Rarely, patients may show jaw clenching or teeth grinding present during the waking hours as well as at night. This is highly destructive to the teeth further compromising effective chewing and safe swallow. At times, there is a decrease in jaw opening excursion that further hampers efforts to feed the advanced patient. Botulinum toxin injections into the masseter muscles bilaterally relax the muscles generally without adverse effects on swallowing function.

Gait Dysfunction

The ataxia and gait abnormalities in HD are not responsive to medications. Patients are treated through physical therapy interventions, such as cueing and balance training. Gait safety is better with a wheeled walker than a cane. There comes a point that the patient must be confined to the wheelchair to prevent injury.

Psychiatric Disease

Identification of abnormal thought processes or behaviors is very important in management. It is advised to have a caregiver come with the patient to the office visit for a well-rounded discussion of how each is doing. At times, they must be interviewed separately to prevent repercussions for the caregiver. Obtain psychiatric and social work input for situations of possible neglect or abuse and do not hesitate to contact government social services to protect the patient and family. The practitioner should be familiar with emergency psychiatric services and suicide prevention hotlines in their community so that they can act quickly in times of crisis.

Depression is treated through counseling when the patient has insight as well as pharmacological medications. Most specialists prescribe selective serotonin reuptake inhibitors for mild to moderate depression. It is of great interest that in recent studies both sertraline and paroxetine have been found to prolong survival and increase brain-derived neurotrophic factor in the transgenic mouse model. Anxiety, panic, obsessive

compulsive disorders, irritability, and mania are treated with selective serotonin reuptake inhibitors or other mood stabilizing medications, including valproate, carbamazepine, lamotrigine, or lithium. If more severe manifestations of these disorders are accompanied by delusional thinking or psychosis, then neuroleptics should be used. Behavioral modification therapy can be successful in some patients with hostility, aggression, or compulsions.

Cognitive Disease

There are no medications that have reliably improved cognition in HD. A recent safety trial of dimebon gave hope for possible cognitive stabilization and a phase-3 trial is being planned. Treating behavioral and psychiatric problems should maximize the patient's capacity for cognitive performance.

Other Features

Start by treating sleep disturbance with lessons on good sleep hygiene practices and over the counter sleep aids. Rule out any psychiatric disturbance interfering with sleep onset or maintenance before using prescription sleep medications. Short-acting sedative hypnotics, such as eszopiclone, or zaleplon, are effective. The longer acting benzodiazepines (clonazepam) or sedating antidepressants (trazodone, nortriptyline) are also used. Clinicians can attempt regulation of the disturbance of circadian rhythm with a sleeping aid at night and a wake-promoting agent, like modafinil, in the morning.

An active lifestyle can improve sleep and may have long-term benefit in HD.

Special Situations

Endstage

Most patients ultimately require institutionalization to manage their care. It is harder to assess the advanced patient due to dementia and considerable difficulties in communication. The advanced stages of HD have particular management challenges either from excessive movement or too little movement. Special floor beds and Broda chairs have been developed to confine and pad flailing limbs. Lipped plates and trays on sticky mats prevent inadvertent scooting away during clumsy attempts at self-feeding. Because of significant weight loss, frequent meals and snacks should be offered. Ultimately, they require pureed foods and full assistance to feed. Patients continue to lose weight but usually do not choose to have a percutaneous gastrostomy tube placed for nutrition.

HD patients often refuse to use a bathtub or shower but will usually submit to a sponge bath. Patients may scream, hit, and be very unpredictable in behavior. Sometimes, a source of agitation can be found, as the patients do best with a routine accompanied by simple repeated explanation and the same caregivers. The secondary complications of an immobile state (pneumonia, urinary tract infections, venous thrombosis) are a common cause of death.

Juvenile HD

Juvenile HD, like adult onset HD, is treated using supportive care and symptom management. For generalized epilepsy, use typical anticonvulsant therapy in monotherapy, if possible. Rigidity, spasticity, and dystonia may be treated with antispasmolytics, such as baclofen, tizanidine, or benzodiazepines, or with antiparkinson medications, that is, levodopa or dopamine agonists. Depression, anxiety, oppositional behavior, and irritability are treated with standard medical and behavioral therapies. School failure can worsen feelings of isolation, and individualized educational plans for the children are helpful in dealing with schoolwork and adopting a 'no fail' strategy. Some parents will decide to home-school their children. A simple communication device can be very helpful as dysarthria grows severe to allow the child to express the needs. Timely discussion should be held about end of life issues and palliative care as children progress more rapidly with dysphagia and decline in mobility.

Prognosis

Prognosis is affected by many factors including age at onset, rate of disease progression, other genetic factors, weight, environment, and attentive care. Despite the advancements in research, survival is unchanged. Most patients require care in a long-term nursing facility at end stage of disease. The average duration of disease until death is estimated as 15–20 years after onset of chorea. The actual duration of disease is likely much longer as based upon biomarker studies and the clinical observations during phenoconversion into disease state.

See also: Chorea; Dentatorubropallidoluysian Atrophy; Huntington, George; Huntington's Disease: Genetics; Milkmaid's Grip; Motor Impersistence; Trinucleotide Repeat Disorders; Westphal Variant.

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www.hdfoundation.org – Hereditary Disease Foundation.
www.uihealthcare.com/depts/huntingtonsdisease/studies/hdmapstudy.html – HD Modifiers in Age of Onset in Pairs of Siblings (HD-MAPS).
www.hdsa.org – Huntington's Disease Society of America.
www.huntington-study-group.org – Huntington Study Group.
www.huntingtonproject.org – Systematic Evaluation of Treatments for Huntington's Disease (SET-HD).
http://WeMove.org

Hydrocarbons

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Glossary

Cytochromes – Membrane-bound hemoproteins that contain heme groups and carry out electron transport. They are found either as monomeric proteins (e.g., cytochrome *c*) or as subunits of bigger enzymatic complexes that catalyze redox reactions. They are found in the mitochondrial inner membrane and endoplasmic reticulum of eukaryotes, in the chloroplasts of plants, in photosynthetic microorganisms, and in bacteria.
Dopamine – A neurotransmitter occurring in a wide variety of animals, including both vertebrates and invertebrates. In the brain, this catecholamine functions as a neurotransmitter, activating the five types of dopamine receptors – D1, D2, D3, D4, and D5, and their variants. Dopamine is produced in several areas of the brain, including the substantia nigra and the ventral tegmental area.
Dyskinesia – Abnormal, involuntary movements. In the context of Parkinson's disease, dyskinesias are often the result of chronic levodopa (L-dopa) therapy.
Leukoencephalopathy – A disease, often due to degenerative, inflammatory, or toxic causes, that affects myelin (white matter) of the brain.
Neurotoxin – A toxin that acts specifically on the peripheral or central nervous system usually by interacting with membrane proteins such as ion channels.

Chemical Structure

Hydrocarbons are a heterogeneous group of organic substances that are primarily composed of carbon and hydrogen molecules and can be derived from either petroleum or wood. Petroleum distillates include kerosene, gasoline, and naphtha. *n*-Hexane and its derivates are common environmental contaminants, as they are also a constituent of many petroleum-derived products. However, *n*-hexane is present also in the human body as by-products of lipid peroxidation, independently of environmental pollution. Physiologically, *n*-hexane is converted by cytochrome P-450-dependent monooxygenases, mainly CYP2E1 and CYP 2B6 isomers, and by alcohol dehydrogenases into 2-hexanone, and subsequently, into 2,5 hexanedione and finally 2,5-dimethylpyrrole. Wood-derived hydrocarbons

include turpentine and pine oil. While most are liquids, some (e.g., butane) are gases, and others (e.g., waxes) are solids at room temperature. Hydrocarbons are quite abundant in modern society; their use includes fuels, paints, paint and stain removers, dry cleaning solutions, lamp oil, lubricants, rubber cement, and solvents. In addition, many volatile substances that contain hydrocarbons (e.g., glue, propellants) are commonly abused for their euphoric effects.

Hydrocarbons can be classified as being aliphatic or aromatic. Halogenated hydrocarbons are a subgroup of aromatic hydrocarbons, with one of the hydrogen molecules substituted by a halogen group. The most important halogenated hydrocarbons include carbon tetrachloride, trichloroethylene, tetrachloroethylene, trichloroethane, chloroform, and methylene chloride. Cigarettes contain large quantities of aromatic and aliphatic hydrocarbons, including *n*-hexane.

Environmental Exposures

Hydrocarbon exposure can be divided into the following four broad categories: Accidental ingestion, especially in children; recreational ingestion, where inhaling of hydrocarbons or other volatile solvents for the purpose of producing a transient state of euphoria; accidental exposure, more often industrial, where a worker gets either a dermal exposure to the liquid or an inhalational exposure to the vapors; and intentional. The toxicity of hydrocarbons is directly related to their physical properties, specifically the viscosity, volatility, surface tension, and chemical activity of the side chains. Many of the hydrocarbons that directly affect the central nervous system are able to cross the blood–brain barrier, because certain hydrocarbons are highly lipophilic. In addition, for individuals who deep breathe ('huffing') or rebreathe ('bagging'), hypercarbia can occur as well, contributing to a decreased level of arousal, and in severe cases, hypoxia or simple asphyxiation. In order to predict the intensity of inhalation, exposure to aromatic solvents among commercial painters, an exposure model for measurements that could be used as a tool in the historical exposure assessment in a health surveillance program has been developed. In this regard, toluene has been selected as a marker for solvent exposure, since hydrocarbon exposures appeared to be strongly correlated.

Clinical Signs of Intoxication

The most common CNS symptoms include headache, lethargy, and decreased mental status. Acute intoxication has been reported, and in such cases, has been associated with gait ataxia, tremor, dysarthria, limb weakness, myoclonus, and bradyphrenia, in various combinations. Treatment after acute hydrocarbon exposure consists in removing any contaminated clothing and washing the skin. Gastric emptying, which increases the risk of aspiration, is contraindicated. Patients who have symptoms are admitted and treated supportively.

There are several studies, albeit controversial, that suggest that hydrocarbons may be involved in the pathogenesis of neurodegenerative diseases. Exposure recall bias and other methodological issues make the extrapolation of epidemiologic studies difficult. However, prolonged abuse of hydrocarbons can result in white matter degeneration (leukoencephalopathy). Cases of parkinsonism have been repeatedly attributed to various hydrocarbons, mainly aliphatic and halogenated compounds. It has been demonstrated that ketonated compounds, such as 2,5-hexanedione, are able to bind neurofilaments selectively, forming accumulations of ubiquitin-positive material that resembles those found in many neurodegenerative diseases. Moreover, it has been suggested that the susceptibility to the development of Parkinson's disease (PD) may involve an isoform of cytochrome P450, CYP2E1, which metabolizes the hydrocarbon *n*-hexane, leading to the formation of its neurotoxic metabolite 2,5-hexanedione. In the only case reported in the literature with neuropathological findings, the nature of the lesions was intermediate between PD and multiple system atrophy, so that the neuropathologic picture did not clearly correspond to either diagnosis; no Lewy body inclusions were found. Neuronal loss was also observed in the periaqueductal gray matter, locus ceruleus, and pedunculopontine nucleus. These changes, if combined with moderate anemia due to marrow suppression, and a mild axonal neuropathy are suggestive of a hydrocarbon toxic insult.

In animal models, hydrocarbon exposure may induce parkinsonism and damage to the central nervous system characterized by an increase in lipid peroxidation and cytoskeleton alterations associated with accumulation of neurofilaments. Similar lesions have been described in PD and other neurodegenerative disorders. Compared with control mice, mice intoxicated with trichloroethylene presented significant dopaminergic neuronal death measured by the tyrosine hydroxylase inmnunoreactivity in the substantia nigra pars compacta.

A survey in elderly Canadians showed that patients with PD had been more exposed to resins, paints, and petroleum derivates, all containing hydrocarbon solvent compounds, compared to a healthy group. Furthermore, the incidence of PD is much higher among residents of Kibbutzim, where large quantities of chemical pollutants are present in drinking water and used in agriculture. Other studies have also found that the exposure to hydrocarbon-containing solvents was higher in parkinsonian patients compared to healthy controls or to any other patient population. McDonnell et al. investigated whether occupational exposure to metals or solvents was associated with an increased risk of death from or with PD. They found a significant exposure–response relationship for solvents and a nearly fourfold increase in the risk for employees exposed

for 30 years or more, suggesting a sustained cumulative exposure or stricter industrial environmental controls later in the twentieth century or exposure to older solvents such as trichloroethylene. Neurotoxic actions of trichloroethylene have been demonstrated in animal models showing that oral administration of such solvent for 6 weeks instigated selective complex 1 mitochondrial impairment in the midbrain with concomitant striatonigral degeneration and loss of dopamine neurons. Pezzoli et al. studied the exposure to hydrocarbon solvents and derivatives on PD symptoms in a cohort study of 990 patients with PD, using neuropharmacologic tests and imaging techniques. They found that exposure to hydrocarbon-containing solvents was detected in almost 20% of all patients. The exposed group was younger, and the length of the latency period inversely correlated with the degree of exposure to hydrocarbons. Further, the severity of PD symptoms was directly proportional to the duration and intensity of exposure. In addition, exposed patients had a poorer response to dopaminergic agents compared to nonexposed. This poorer response to dopaminergic agents could be due to pharmacodynamic differences between receptors in the two populations of patients following damage induced by hydrocarbon solvents. As a result, exposed patients with PD seems to have an earlier onset of disease, reduced response to treatment and greater immobility, and less levodopa-induced dyskinesias, although the mean dosage of levodopa was higher in exposed subjects.

Another distinguishing feature between exposed and nonexposed patients with PD is the MRI picture, with a higher number of focal lesions in the white matter on T2 among subjects exposed to hydrocarbons. The relatively circumscribed focal white matter alterations have been associated with chronic solvent exposure rather than heavier abuse. Different patterns of striatal dopamine transporter binding have also been documented in PD patients exposed or not exposed to hydrocarbons. In patients exposed to hydrocarbons, significantly decreased striatal uptake occurred compared with healthy controls and nonexposed PD patients, suggesting that exposure to hydrocarbons may modify the disease course and ultimately accelerate nigrostriatal denervation. Imaging and spectroscopic data have shown that, compared to normal subjects with no previous exposure to hydrocarbon-solvents, in PD patients exposed to hydrocarbons, *N*-acetylaspartate levels, as a marker of neuronal damage/loss, were normal in the lentiform nucleus of patients with low exposure as well as in patients with no exposure, whereas it was decreased in PD patients with higher exposure. According to these authors, clinical expression may be more severe in PD patients with a previous high level of solvent exposure, because of the associated postsynaptic damage of the nigrostriatal pathway, suggesting that dopaminergic neurons and their projections are particularly susceptible to organic solvents.

It has been hypothesized that metabolic changes may be seen in individuals with particular genotypes that can cause difficulties in metabolizing one or more environmental toxins and this 'poor metabolizer' status could make them more susceptible to developing PD following exposure of such toxins. In one study, the urinary levels of the main metabolites of *n*-hexane (2,5-hexanedione and 2,5-dimethylpyrroles) were measured in 108 patients and 108 healthy controls, matched by age and sex. Metabolite urinary excretion was significantly reduced in PD patients compared with controls and was inversely related to age in both groups, suggesting that aging and PD may be associated with a reduction in the capacity to eliminate the hydrocarbon *n*-hexane.

See also: Parkinson's Disease: Definition, Diagnosis, and Management.

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www.movementdisorders.org – Movement Disorder Society.
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Hyperekplexia

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Glossary

GLRA1 gene – α1 subunit of the glycine receptor.
Glycine receptor – Widely distributed inhibitory receptor in the central nervous system, especially in the spinal cord and brain stem.
Head-retraction reflex – The examiner applies a reflex hammer downward to the middle of the upper lip or the nose in order to effect a brisk bending of the head. When this reflex is positive, the patient answers with a quick retraction of the head.
Major form hyperekplexia – Combination of excessive startle reflexes, generalized stiffness at birth and stiffness related to the startle reflex.
Minor form hyperekplexia – Excessive startle responses without signs of stiffness.
SLC6A5 gene – Presynaptic glycine transporter-2 (GLYT2).

Definition and History

In 1958, the first family with exaggerated startle reflexes and unexpected violent falls was reported. In 1963, in a large Dutch family, this autosomal dominantly inherited disorder was named 'hyperekplexia' (HPX). The combination of the Greek words 'υπερ' and 'εκ-πλησσώ' means 'to startle excessively.'

In HPX or startle disease, two clinical forms have been recognized: the major and the minor form. For the diagnosis of the major form HPX, three features are required: excessive startle reflexes, generalized stiffness at birth, and stiffness related to the startle reflex. Patients with the minor form suffer from excessive startle responses without signs of stiffness.

In the major form HPX, the excessive startle reflexes to unexpected, especially auditory stimuli are present from birth. The frequency of startle responses can increase with emotional tension, nervousness, and fatigue, and can decrease while holding objects or drinking alcohol. The second cardinal feature is the generalized stiffness immediately after birth, normalizing during the first years of life. Handling increases the stiffness, and during sleep, it disappears. The third feature is a short period (seconds) of generalized stiffness after the startle response, making it impossible to stretch out arms and causes patients to fall while fully conscious. The stiff-baby syndrome, congenital stiff-person syndrome, and 'Kok disease' are other names for the major form HPX.

Neurological examination in newborns reveals a generalized stiffness and marked hypokinesia. Held horizontally, the child is as 'stiff as a stick.' In adults, in a clinical setting, startle reflexes are difficult to elicit as unexpected stimuli are required. A stiff-legged, mildly wide-based gait can be observed, but the most evident abnormality is an exaggerated head-retraction reflex elicited by tapping on the nose. It has been suggested as the hallmark of HPX.

Patients with the minor form HPX suffer from excessive startle reactions without stiffness. These exaggerated startle reflexes never start in the neonatal period, but the age of onset ranges from early infancy to adulthood. Neurological examination shows normal.

Genetics in HPX

The *GLRA1* gene is the major gene for the major form HPX. The *GLRA1* gene is located on chromosome 5q33–q35 and encodes for α-1 subunit of the inhibitory glycine receptor, located in the postsynaptic membrane of glycinergic and mixed γ-aminobutyric acid (GABA)ergic/glycinergic neurons. Dominant, recessive, and compound heterozygote mutations are identified in many individuals with the familial major form HPX and occasionally in sporadic cases. Glycine receptors are ligand-gated chloride channels causing postsynaptic hyperpolarization and synaptic inhibition in the brainstem and spinal cord. Glycine receptors are assembled into pentameric complexes and consist of combinations of α and β subunits. The combinations depend on the developmental stage and the brain region. The mutations in the gene often lead to compromised channel dynamics and impair the efficiency of glycinergic inhibition in the brainstem and spinal cord.

A second gene is the presynaptic glycine neurotransmitter transporter Glyt2 or *SLC6A5* gene (2006). Compound heterozygote inheritance of recessive alleles has mainly been described. The phenotype of Glyt2 patients closely resembles the phenotype of patients with the GLRA1 genotype except for a higher frequency of life-threatening neonatal apnea episodes in the Glyt2 positive patients. The *SLC6A5* gene codes for one of the glycine transporters (GlyTs), members of the Na^+/Cl^--dependent neurotransmitter transporter superfamily. GlyT2 is found in glycinergic axons, and the transporter functions are knocked out by

a process of nonsense mediated decay, the disruption of the glycine uptake or the inhibition of Na^+ ion coactivation.

Mutations in three other genes, encoding subunits, or binding proteins of GlyR complexes mutations have been reported. In each gene, single patients were identified: one had a compound heterozygous mutation in the GlyR β-subunit (GLRB); one showed a mutation in the *gephyrin* gene (GPHN); and the last one had an X-linked mutation in the collybistin gene (*ARHGEF9*). These three sporadic patients showed the classical major form HPX except for the patient with the *ARHGEF9* gene mutation, who died at the age of 4 and suffered from severe epilepsy and mental retardation.

In patients with the hereditary minor form HPX, no genetic cause has been detected until now. The minor form HPX patients have mainly been described in pedigrees also exhibiting the major form HPX. In a large Dutch family, all patients with the major form HPX carried a mutation of the *GLRA1* gene, but no patients with the minor form did. Only in a few small pedigrees with concisely described symptoms, *GLRA1* mutations were found in members who may possibly have had the minor form.

Several animal models display HPX-like phenotypes with autosomal recessive inheritance, indicating loss-of-function effects for these mutations. The *spasmodic (spd)* and the *oscillator* (spd^{ot}) harbor mutations in the *GLRA1* gene, whereas the *spastic (spa)* has a mutation in the β subunit. *Spd, spa*, and spd^{ot} have overlapping phenotypes with striking similarities to human HPX. Transgenic mutants resemble the human HPX phenotype even better. The targeted deletion of *gephyrin* (*Geph*) and glycine transporter subtype 2 (*GlyT2*) also resulted in HPX-like phenotypes in mice. A congenital recessive startle syndrome in Poll Hereford cattle has been described with mutations in the *GLRA1* gene and more recently, cattle with congenital muscular dystonia type 2 showed mutations in the Glyt2 gene.

Pathophysiology

The startle reflex is interpreted as the rapid accomplishment of a defensive stance with maximum postural stability. It consists of bilaterally synchronous shock-like movements, especially in the face and the upper part of the body. For the physiological details of the startle reflex.

In the major form HPX, the pattern of the startle reflex was identical with those of the normal startle reflex, although the latencies were shorter. Compared with controls, the motor response was more frequent and larger with repetitive stimuli and the auditory threshold was lower.

The abnormal startle reflex in HPX is suggested to originate in the brainstem. Arguments for this are that symptomatic HPX usually concerns brainstem damage. Furthermore, latencies of startle EMG responses point toward a brainstem origin as do eye movement recordings in HPX. Another argument is that glycine receptors in humans are concentrated in the brainstem and spinal cord.

Little is known about the background of stiffness in HPX. In the major form HPX with a proven GLRA-1 mutation, disynaptic reciprocal inhibition was absent similar to abnormalities in patients with pyramidal tract lesions. However, transcranial magnetic stimulation testing the pyramidal pathways was normal.

Startle responses in the minor form HPX differ substantially from those in the major form. EMG latencies are prolonged and habituation is lacking. Furthermore, the reciprocal inhibition of H-reflexes was found normal in the minor form HPX, consistent with their lack of stiffness.

Several hypotheses have been raised to explain how cases with the minor form HPX without a mutation in the *GLRA1* gene can occur in the same pedigrees as patients with the major form HPX with a mutation in the gene. One hypothesis is that the minor form startle response represents a learned behavior in subjects subjected to family members with organic startle reflexes. The prolonged EMG latencies can be an indication of a psychiatric or psychogenic origin of the exaggerated startle reflex, although the jerks do not have all characteristics of a psychogenic startle response. Alternatively, a polymorphism or a nonpenetrance of the *GLRA1* gene may underly the disorder. Finally, excessive startling may be much more common in the general population than previously thought, and the minor form HPX represents a common variant coincidentally found in some HPX families.

Epidemiology

The prevalence of hereditary HPX is low; over 70 pedigrees in many different nationalities have been described. The major form HPX mainly occurred in these pedigrees; occasionally the minor form was described. Sporadic HPX has been published in over 120 cases representing both the major and minor form HPX.

Clinical Features and Diagnostic Criteria

For the diagnosis of the major form HPX, three features are required: (1) generalized stiffness immediately after birth, normalizing during the first years of life, (2) an excessive startle reflex particularly to auditory stimuli that is present from birth, and (3) a short period (seconds) of generalized stiffness following the startle reflex. Patients with the hereditary minor form HPX suffer from an excessive startle response without signs of stiffness. Associated features are exaggerated head-retraction reflex, periodic limb movements in sleep, abdominal herniation, congenital dislocations of the hip, and sudden infant death.

Differential Diagnosis

In the following sections, a differential diagnosis of HPX is tabulated for each of the three main clinical features of hereditary HPX: excessive startle responses to unexpected stimuli, transient stiffness in relation to unexpected stimuli, and continuous stiffness in the neonatal period. A detailed discussion of all differential diagnoses is beyond the scope of this article.

Excessive Startle Responses to Unexpected Stimuli

Clinical observation alone is not sufficient to discriminate between excessive startle responses and startle-induced disorders. Still, Fwe divide the differential diagnosis of excessive startle reflexes into HPX, that is, defined as startle reflexes (**Table 1**), subsequently the differential diagnosis of the neuropsychiatric startle disorders (**Table 2**), and finally a group of stimulus-induced disorders (**Table 3**).

Excessive startle reflexes (HPX)

The most important discriminative factor among the three forms of HPX (hereditary, sporadic, and symptomatic) is the family history. HPX is usually hereditary, and a positive family history points toward this form. In sporadic HPX, the phenotype is similar to hereditary HPX, but a positive family history is lacking. In sporadic HPX, attacks of tonic neonatal cyanosis have frequently been described that can be stopped by the 'Vigevano' maneuver (forced flexion of the head and legs toward the trunk). Patients with a sporadic minor form HPX usually have an adult onset without other neurological signs. In these patients, a psychogenic etiology can be considered (see the following section). In symptomatic HPX, excessive startle responses are usually accompanied by other neurological signs arising especially from the brainstem. Causes of symptomatic HPX include cerebral or brainstem damage and encephalitis due to several causes (see **Table 1**). The symptomatic HPX cases have late-onset HPX without stiffness in the neonatal period. The discrimination between sporadic and symptomatic HPX is based on medical history and additional clinical and radiological information.

Table 1 Molecular genetic testing in hyperexplexia

Test method(s)	*Mutation detection rate*	*Inheritance pattern*
Sequencing of all exons and flanking introns	In familial: ±90% In sporadic: ±10%	
GLRA1 gene	>40 cases	AD, AR
GLRA1 deletions	6 cases	
SLC6A5 gene	>10 cases	AR
GLRB gene	Single case	AR
GPHN gene	Single case	
ARHGEF9 gene	Single case	X-linked

Table 2 Excessive startle reflexes (HPX)

Hereditary HPX	Major form
	Minor form
Sporadic HPX	Major form
	Minor form
Symptomatic HPX	Children with cerebral palsy
	Postanoxic encephalopathy
	Encephalomyelitis with rigidity
	Multiple sclerosis
	Gilles de la Tourette's syndrome
	Posttraumatic
	Paraneoplastic
	Cerebral abscess with encephalitis
	Brainstem infarct or haemorrhage
	Brainstem encephalopathy
	Creutzfeldt–Jakob's disease
	Subacute sclerosing panencephalitis
	Paraneoplastic syndromes

Neuropsychiatric startle syndromes

The main differential symptoms of the minor form HPX are the neuropsychiatric disorders, including the culture-specific syndromes, such as the 'Jumping Frenchman of Maine,' 'Latah,' and 'Myarichit,' startle neurosis, and hysterical jumps. Although startle responses are part of these syndromes, their motor patterns have not been defined in detail. Clinically, patients with an abnormal startle reflex as part of psychiatric symptoms show an inconsistent startle pattern with prolonged latencies. Anxiety disorders can also be accompanied by exaggerated startling possibly due to increased arousal.

Startle-induced disorders

In startle-induced disorders, the startle reflex triggers an abnormal movement, such as epilepsy, reflex myoclonus, paroxysmal kinesigenic dyskinesias, cataplexy, and occasionally a tic. Startle epilepsy concerns an epileptic seizure precipitated by a sudden stimulus. Clinically, usually an asymmetric tonic seizure is induced. Most startle epilepsy patients suffer from infantile cerebral hemiplegia.

Table 3 Neuropsychiatric startle syndromes

Culture-bounded	Jumping Frenchmen of Maine
	Latah
	Myriachit
	Leaping ague of Scotland
	Tigretetier of Abessynia,
	Imanenjana of Madagascar
Psychiatric	Startle neurosis
	Posttraumatic stress disorder
	Withdrawal periods anxiolytic drugs, opiates or alcohol
	Hysterical jumps

Progressive myoclonus epilepsy due to different causes is also a part of these epilepsy syndromes, each of which has a characteristic clinical picture. Reflex myoclonus, especially reticular and propriospinal myoclonus, can be discriminated from HPX by an EMG-reflex test. In paroxysmal kinesigenic dyskinesias, movements are luxated by an unexpected stimulus, but concern chorea or dystonia rather than a startle reflex. Patients with cataplexy have a loss of muscle tone due to unexpected stimuli rather than an increase in tone. Cataplexy is usually induced by laughter, but may occur after being startled. Incidentally, a normal startle reflex can induce a tic **Table 4**.

Transient Stiffness in Relation to Unexpected Stimuli

Transient stiffness in relation to unexpected stimuli can occur in the hereditary and sporadic major form of HPX. Strychnine poisoning mostly resembles HPX, but its incidence is very low. The startle-induced stiffness group mainly concerns stiff-person syndrome (SPS) characterized by progressive axial stiffness and intermittent spasms mainly evoked by stimuli. It usually starts in the fourth or fifth decade, and is frequently associated with diabetes mellitus. Antibodies against GABAergic neurones, especially antiglutamic acid decarboxylase (GAD), occur in many patients. The combination of stiffness and startle-induced falls closely resembles the major form of HPX; however, the stiffness in SPS is nearly continuous, contrasting sharply with the stiffness in adult HPX, which occurs only after a startle and lasts 1–2 s. The syndrome of 'continuous muscle fiber activity' of peripheral origin is Isaacs' syndrome, or neuromyotonia. Distal, proximal, and cranial muscles may be involved. The symptoms persist during sleep (**Table 5**).

Stiffness in the Neonatal Period

Continuous stiffness in the neonatal period can occur in the hereditary or sporadic major form HPX. Occasionally, stiff-man syndrome presents in the first months of life. Congenital generalized muscle hypertonia as a distinct autosomal recessive disorder was described in a Mexican family. The clinical description resembles HPX, but these children also suffered from cardiopulmonary distress. The most important differential diagnosis is formed by perinatal asphyxia. Pyramidal signs and irritability discriminate these newborns from HPX. Extrapyramidal signs, including stiffness, can occur in a child born to a mother using drugs such as phenothiazine and cocaine. Neonates with paroxysmal extreme pain disorder (familial rectal pain disorder) have tonic attacks associated with flushing and severe syncopes. These attacks are mainly triggered by perineal toilet, but also by bathing. The syndrome of continuous muscle activity of peripheral origin, Isaacs' syndrome, or neuromyotonia has already been discussed earlier. The Schwartz–Jampel syndrome, osteo-chondro-muscular dystrophy is a rare autosomal recessive syndrome. It consists of not only muscular stiffness but also abnormal facial appearance and skeletal abnormalities (**Table 6**).

Management

Clonazepam is the most effective drug for HPX for hereditary as well as for sporadic forms. Both the stiffness in the neonatal period and the stiffness related to the startle

Table 4 Stimulus-induced disorders

Epilepsy	Startle epilepsy
	Startle-provoked epileptic seizures
	Pyridoxine-dependent epilepsy
	Progressive myoclonus epilepsy due to different causes
Reflex myoclonus	Cortical
	Reticular
	Propriospinal
Rest group	Paroxysmal kinesigenic dyskinesias
	Gilles de la Tourette Syndrome
	Cataplexy

Table 5 Transient stiffness in relation to unexpected stimuli

HPX major form	Hereditary
	Sporadic
	Strychnine poisoning
Stiff-man and associated syndromes	Stiff-man syndrome
	Jerking stiff-man syndrome
	Progressive encephalomyelitis with rigidity
Rest group	Tetanus
	Magnesium deficiency
	Creutzfeldt–Jakob's disease
Peripheral origin	Isaac's syndrome, neuromyotonia

Table 6 Continuous stiffness in the neonatal period

Hereditary HPX, major form
Sporadic HPX
Stiffman syndrome
Congenital generalized muscle hypertonia
Perinatal asphyxia
Maternal medication use
Paroxysmal extreme pain disorder (familial rectal pain disorder)
Isaac's syndrome, neuromyotonia
Schwartz–Jampel syndrome (osteo-chondro-muscular dystrophy)
Cornelia De Lange syndrome
Autosomal recessive disorder with muscle contractions resembling neonatal tetanus

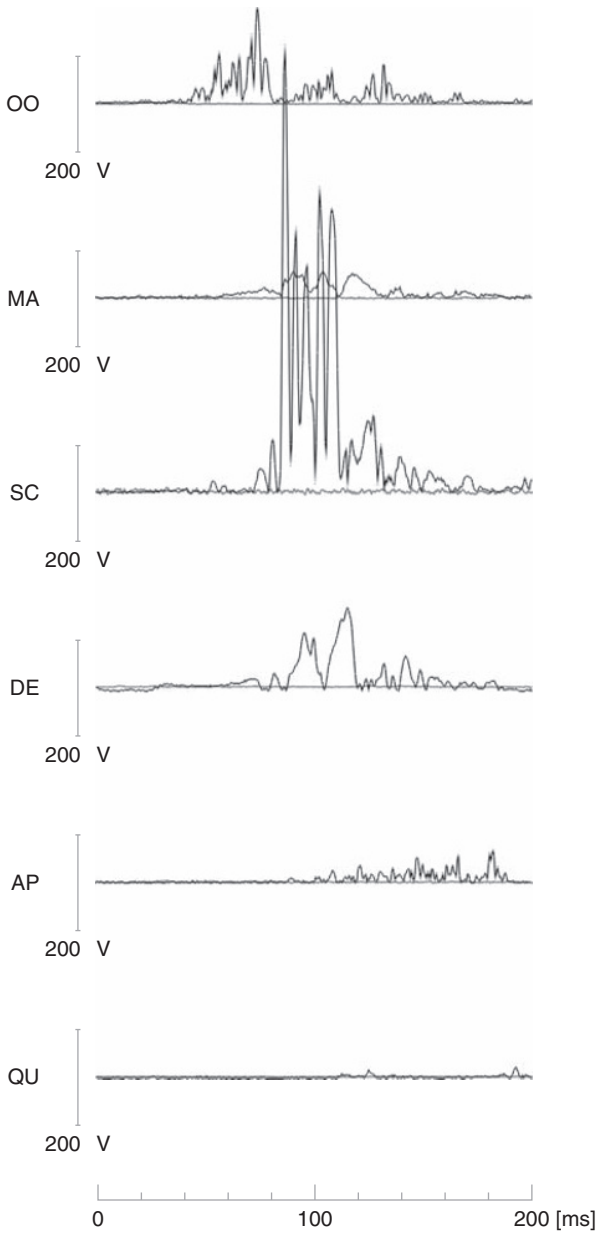

Figure 1

reduce with the treatment. Several other drugs have been tried with contrasting results mainly concerning case reports. Clonazepam potentiates the inhibitory neurotransmitter GABA. In various species, and presumably also in humans, GABA-A and glycine receptors show a widespread colocalization in the central nervous system.

Physical and cognitive therapy to reduce the fear of falling and, thereby, improving walking can be considered, but no randomized trial has been done.

Prognosis

In the major form hereditary HPX, the excessive startle reflexes to unexpected, especially auditory, stimuli are present from birth and throughout life. The frequency of startle responses varies between subjects, but also over the course of time. The generalized stiffness immediately after birth normalizes during the first years of life. The stiffness is still slightly visible while walking, manifesting as a mildly wide-based gait. The short period (seconds) of generalized stiffness after the startle response remains throughout life, but the frequency also varies largely between subjects. In patients with the minor form hereditary HPX, little is known on the prognosis.

See also: Jumping Frenchmen of Maine; Latah; Myriachit.

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Hypophonia

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Glossary

Fundamental frequency (F0) – Is the physical correlate of pitch. It is an acoustic measure that directly reflects the vibrating rate of the vocal folds and it also refers to the component in the vocal fold tone with the lowest frequency. The unit of measurement is Hertz (Hz).
Hypophonia – A breathy and hoarse vocal quality with reduced loudness that is mostly seen in the voice of patients with Parkinson's disease (PD). It is thought to be related to the rigidity in the laryngeal muscles.
Jitter and shimmer – Jitter or frequency perturbation refers to the cycle-to-cycle variability in the fundamental frequency of the vocal fold vibration while shimmer or amplitude perturbation refers to the cycle-to-cycle variability in the amplitude of the vocal fold vibration.
Lee Silverman Voice Treatment (LSVT/LOUD) – An evidence-based treatment method for hypophonia and hypokinetic dysarthria experienced by 89% of patients with IPD. It targets a single treatment target of loudness with high intensity in its delivery mode and sensory retraining.
Phonation – Is the physical-physiologic act of sound production: the oscillations of the vocal folds driven by the exhaled air stream.
Vocal intensity – The physical correlate of loudness. It varies as a function of both subglottal pressure (P_s) and vocal fold vibratory amplitude. It is measured in decibel (dB) and can be simply measured using a sound-level meter. Reduced intensity may be indicative of poor respiratory support, incomplete glottal closure, or reduced tissue pliability restricting the vocal fold vibratory amplitude.

Definition and History

Hypophonia refers to a vocal quality that is abnormally weak, soft, and breathy; it is mostly observed in patients with Parkinson's disease (PD). The word 'hypophonia' comes from the combination of the Ancient Greek prefix 'hypo,' meaning 'under,' and noun 'phōnia,' meaning 'voice.'

Pathophysiology

The pathophysiology underlying hypophonia in PD has been suggested to be the bowing of the vocal folds due to rigidity in the laryngeal musculature, while for atypical Parkinsonism, the pathophysiology may be bilateral vocal fold paresis or paralysis.

Epidemiology/Risk Factors

Epidemiology as Related to Different Etiologies

The underlying neurological disturbances most commonly associated with hypophonia are PD. However, acute onset of hypophonia has been reported to be associated with cerebrovascular diseases. Hypophonia may occur alone (45%) or as part of the symptoms of hypokinetic dysarthria (89%) in PD. Hypophonia is characterized by breathy and hoarse vocal quality with a significantly reduced vocal loudness. For patients with atypical Parkinsonism such as PSP or MSA, hypophonia may appear as one of the early symptoms of hypokinetic dysarthria. However, that may quickly change as the disease progresses. For example, the vocal quality of patients with PSP and Shy–Drager syndrome may change from initially extremely soft and breathy (sometimes even aphonic, i.e., no voice), a sign of hypophonia, to breathy strained and strangled. Articulation, resonance, and prosody may also be involved around the same time. These symptoms taken together indicate the presence of mixed spastic/hypokinetic dysarthria, which often develops within 1–5 years after the disease onset.

Risk Factors

In idiopathic PD, the most important risk factors for developing hypophonia are progression of the disease and disease severity level. In atypical Parkinsonism, however, when the symptoms of laryngeal dysfunction or hypophonia are present, they are usually much more severe and may be part of mixed dysarthrias rather than hypophonia alone. Risk factors in atypical Parkinsonism include fast disease progression and sleep-related disordered breathing with stridor.

Clinical Features/Diagnostic Criteria

Characterization

The main characteristic of hypophonia is that its symptoms are only in the laryngeal or phonatory subsystem.

Salient Voice Features

Perceptually, characteristics of hypophonia are limited to breathy and hoarse vocal quality, reduced loudness, and reduced pitch and loudness variability. There is no involvement of articulation or resonance. Even at early stages, the hypophonia due to IPD versus that resulting from atypical Parkinsonism may show qualitative difference: it is much more severe in atypical Parkinsonism. In addition, the selective abductor paralysis or paresis seen in atypical Parkinsonism could be life threatening due to glottic airway compromise.

Diagnosis of Hypophonia

Certified and licensed speech-language pathologists (SLP) are trained to diagnose *hypophonia*, using a combination of perceptual and instrumental tests. A typical evaluation has the following components: an in-depth medical history, including a voice history, voice handicap index (VHI), a complete oral motor examination, acoustic analyses of voice, and a videostroboscopy for direct examination of the laryngeal structure and vocal fold movement during phonation. Based on the findings, the SLP will be able to diagnose or rule out hypophonia.

Management

Medication

Hypophonia of PD usually appears early in the disease progression. The response to dopaminergic stimulation in hypophonia is very limited.

Deep Brain Stimulation

There is limited evidence indicating that unilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) in the nonlanguage dominating side (right side) in the right-handed speakers may increase the vocal intensity. However, bilateral STN DBS has been shown repeatedly to negatively impact on voice and speech and that is a common adverse effect of the procedure.

Speech Therapy

Speech therapy that has demonstrated clear efficacy is Lee Silverman Voice Treatment (LSVT/LOUD), an intensive treatment program for treating hypophonia and hypokinetic dysarthria in patients with IPD, targeting a single treatment target of loudness with high intensity in its delivery mode and sensory retraining. It works best when the main symptoms are soft, hoarse, and breathy voice. Symptoms such as inability to initiate speech, frequent hesitations, and palilalia seen in more advanced hypokinetic dysarthria are less responsive to LSVT/LOUD, but can be controlled by altered auditory feedback (AAF) provided by a wearable device.

Prognosis

Hypophonia in patients with IPD will worsen to become part of hypokinetic dysarthria when symptoms progress beyond phonation as the underlying disease progresses. Early onset of severe speech deficits such as palilalia in PD may indicate atypical Parkinsonism such as PSP or MSA especially when dysphagia, sleep-related breathing disorder, and stridor as well as gait disturbances are present.

Acknowledgments

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See also: Alzheimer's Disease and Parkinsonism; Basal Ganglia, Functional Organization; Corticobasal Degeneration; Deep Brain stimulation; Dyskinesias; Hoehn and Yahr Staging Scale; Levodopa; Multiple System Atrophy; Pallidotomy for Parkinson's Disease; Parkinson's Disease: Definition, Diagnosis, and Management; Progressive Supranuclear Palsy; Shy–Drager Syndrome; Spasmodic Dysphonia: Focal Laryngeal Dystonia; Unified Parkinson's Disease Rating Scale (UPDRS) and The Movement-Disorder Society Sponsored-unified Parkinson's Disease Rating Scale (MDS-UPDRS).

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Hypoprebetalipoproteinemia, Acanthocytosis, Retinitis Pigmentosa, and Pallidal Degeneration (HARP Syndrome)

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Glossary

Acanthocytosis – The microscopic appearance of spiculated erythrocytes. This should be a spikey appearance. Not to be confused with echinocytes that have more than 30 spurs.
Dystonia – A neurological movement disorder characterized by abnormal movements or postures.
Eye-of-the-tiger – The MRI finding (T2 weighted) of decreased signal intensity in the pallidal nuclei, with a centrally located area of increased intensity.
Globus pallidus – A major component of the basal ganglia. Pallidal degeneration is usually associated with abnormal movement.
Hallervorden–Spatz disease – A rare autosomal recessive disease characterized by an early onset of progressive dystonia and dementia, and pathologically by bilateral degeneration of the globus pallidus and substantia nigra reticulata associated with deposition of iron in the affected regions and more widely distributed neuronal axonal spheroids. Mutations in the *PANK2* gene are a common cause. This may then be referred to as PKAN.
HARP – The clinical syndrome of hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration. It is caused by homozygous mutations of the *PANK2* gene.
Hypoprebetalipoproteinemia – A reduction (or absence) in the intensity of the prebeta band on high-resolution lipopoprotein electrophoresis, reflecting a reduction in predominantly very low density lipoprotein (VLDL).
NBIA – Neurodegeneration with brain iron accumulation (NBIA) is a rare group of neurodegenerative conditions, which include PKAN (Hallervorden–Spatz disease). Other forms of NBIA include infantile and adult neuroaxonal dystrophy, acerulopasminemia, and neuroferritinopathy
PANK2 – The pantothenate kinase 2 gene (*PANK2*). Mutations in PANK2 cause PKAN (Hallervorden–Spatz disease and related syndromes, including HARP).
PKAN – Pantothenate kinase-associated neurodegeneration (PKAN) is the neurodegenerative condition, often with clinical features of Hallervorden–Spatz disease, and other features, caused by mutations in the *PANK2* gene.
Retinitis pigmentosa – A pigmentary disorder of the retina, leading to a progressive loss of vision.

Definition and History

Higgins et al. reported a patient with features of Hallavorden–Spatz disease, distinguished by the presence of a lipoprotein abnormality (hypoprebetalipoproteinemia), acanthocytosis, retinitis pigmentosa, and pallidal degeneration. Orrell et al. reported a further patient.

Both of these patients have now been found to have mutations of the *PANK2* gene, with autosomal recessive inheritance. The clinical syndrome of HARP is a variant of Hallervorden–Spatz disease, PKAN, or neurodegeneration with brain iron accumulation (NBIA).

Pathogenesis/Pathophysiology

HARP is an autosomal recessive disorder with mutations of the *PANK2* gene. The precise pathogenesis of neurodegeneration is unknown, but relates to that of PKAN. There is bilateral degeneration of the globus pallidus and substantia nigra pars reticulata, with deposition of iron in the affected regions (as demonstrated on MRI scan) and more widely distributed neuronal axonal spheroids (demonstrated in PKAN but there is no neuropathological report of HARP). The significance of the lipid changes and acanthocytosis is uncertain.

Epidemiology/Risk Factors

HARP is very rare, with only two reported patients. Other possible variants include two patients with acanthocytosis, retinitis pigmentosa and pallidal degeneration (ARP) with no lipid abnormality. HARP is an inherited condition, autosomal recessive, with no other specific risk factors known.

Clinical Features and Diagnostic Criteria

The clinical features are those of a variant of Hallervorden–Spatz disease, with an early onset (3 and 16 years) and prominent orofacial dyskinesia or dystonia. There may be pyramidal signs, including spasticity. Plantar responses may be flexor or extensor. There may be progressive dementia. Hypoprebetaliproteinemia on lipoprotein electrophoresis, acanthocytosis on a blood film, or preferably electron microscopy, and retinitis pigmentosa, which may include circumferential restriction of visual fields, are key features of the syndrome.

Differential Diagnosis

The differential diagnosis of the movement disorder includes other types of dystonia. The clinical features of Hallervorden–Spatz disease, or PKAN, are typical with predominant orofacial dystonia. Other forms of neuroacanthocytosis may be considered as well as other lipid-related movement disorders.

Diagnostic Workup/Test

Sequencing of the *PANK2* gene should demonstrate mutations in both alleles. MRI scan of the brain should show the 'eye-of-the-tiger' sign. Lipid abnormalities may be present on standard laboratory lipid analysis, but high-resolution lipoprotein electrophoresis is required for full definition. Electrooculography may identify features of tapetoretinal degeneration. The assessment of acanthocytosis is more complex than a standard examination of a blood film, and specialized assessment, including electron microscopy, is needed to fully define the nature of the spiculed cells to quantify and exclude artifact. Pedantically, many cells that have been termed acanthocytes may be echinocytes.

Management

The management is of the dystonic condition. Additional management may be needed for dementia and other related conditions. In the patient described by Orrell et al., we tried putative neuroprotective agents (selegiline and antioxidants) with no clear benefit. *PANK2* is one of the four human genes that encode pantothenate kinase. This enzyme is important in the synthesis of coenzyme A from pantothenate (vitamin B5). As coenzyme A is central to cell function, including phospholipid and membrane synthesis, we sought to overcome the PANK2 enzyme defect by giving a supplement of pantothenic acid 1 g twice daily. When reassessed, there was no clinical, laboratory, or radiologic improvement. There is no curative or preventive treatment available at present. Symptomatic treatment is given as appropriate.

Prognosis

Only two patients with the full presentation of HARP have been described. The patient of Higgins et al. had a disease onset age of 11 years and was severely disabled at age 11 years. The patient of Orrell et al. had a disease onset age of 16 years, and was significantly disabled at age 29 years, although with a relatively stable condition.

See also: Dystonia; Eye-of-the-Tiger Sign; Hallervorden–Spatz Syndrome (PKAN); Neuroacanthocytosis Syndromes.

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Idebenone and Friedreich Ataxia

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Glossary

Aconitase – An enzyme in the tricarboxylic acid cycle (Krebs cycle) that catalyzes the isomerization of citrate to isocitrate via *cis*-aconitate. It is also an iron–sulphur protein involved in iron homeostasis.
Cardiomyopathy – A disease of the heart muscle which occurs frequently in Friedreich's ataxia (FRDA) patients. Presentations most frequently include concentric thickening of the left ventricle (LV) of the heart but also asymmetric LV thickening or dilated LV.
Ejection fraction (EF) – A measure of the pumping function of the heart, which can be assessed by echocardiography.
Electron transport chain (ETC) – The ETC couples a chemical reaction between an electron donor (such as NADH) and an electron acceptor (such as O_2) to the transfer of H^+ions across a membrane, through a set of mediating biochemical reactions, with the goal of these H^+ions to produce adenosine triphosphate (ATP), the main energy intermediate in living organisms.
Endomyocardial biopsy – A procedure by which a small piece of heart muscle tissue can be obtained for morphological or biochemical analysis.
8-Hydroxy-2′deoxyguanosine – An oxidative DNA damage product excreted in urine.
Iron–sulfur (Fe–S) clusters – These clusters are prosthetic groups commonly found in various proteins that participate in oxidation–reduction reactions. Iron–sulfur clusters are found in a variety of metalloproteins, such as NADH dehydrogenase, succinate dehydrogenase, cytochrome reductase. Best known for their role in the oxidation–reduction reactions of mitochondrial electron transport.
Krebs cycle – Also known as the tricarboxylic acid cycle. It is a series of enzyme-catalyzed chemical reactions that uses oxygen as a part of cellular respiration. The cycle is part of a metabolic pathway involved in the chemical conversion of carbohydrates, fats, and proteins into carbon dioxide and water to generate energy.
Lipoperoxidation – The oxidative degradation of lipids and process whereby free radicals 'steal' electrons from the lipids in cell membranes, resulting in cell damage.
Mitochondrial complexes – Five membrane-bound complexes identified in mitochondria that consist of an extremely complex transmembrane structure embedded in the inner membrane: Complex I (NADH dehydrogenase), Complex II (succinate dehydrogenase), Complex III (cytochrome reductase), Complex IV (cytochrome oxidase), and Complex V (ATP synthase). Complexes I–III contain Fe–S clusters.
Oxidative stress – An imbalance between the production of reactive oxygen and a biological system's ability to readily detoxify the reactive intermediates or easily repair the resulting damage.
Ubiquinone – A component of the electron transport chain and involved in aerobic cellular respiration, generating ATP. Also known as coenzyme Q_{10}, ubidecarenone, coenzyme Q, and abbreviated at times to CoQ_{10}, CoQ, Q10, or Q. A benzoquinone, where Q refers to the quinone chemical group and 10 refers to the isoprenyl chemical subunits.

Definition and History

Idebenone (6-[10-hydroxydecil]-2,3-dymethoxy-5-methyl-1,4-benzoquinone) is a quinone analogue, which is used in the treatment of several neurological disorders: Friedreich ataxia (FRDA), mitochondrial encephalomyopathies, senile dementia, and Huntington disease. Idebenone acts as an

antioxidant through the action of its quinone ring and diffuses more rapidly than ubiquinone across biological membranes due to the modification of the composition and length of its side chain. Besides being a potent antioxidant, idebenone also functions as an electron transport carrier and has been reported to have various other effects, including stimulation of nerve-growth factor production and blockade of voltage-sensitive calcium channels. Idebenone is rapidly absorbed and has a plasma half-life of 14.9 ± 0.7 h. It crosses the blood–brain barrier. Within 48 h, most of the compound is excreted as metabolites in urine and faeces.

In vitro Studies of Idebenone

FRDA is an autosomal recessive disorder characterized by progressive neurological impairment (ataxia, dysarthria, weakness, and sensory loss), cardiac dysfunction (left ventricular hypertrophy), diabetes mellitus, and skeletal abnormalities (scoliosis and pes cavus). The causative mutation is an expansion of a GAA repeat within the first intron of the *FXN* gene, leading to decreased levels of the corresponding transcript and of the mitochondrial protein frataxin. Frataxin has been demonstrated to be involved in the assembly of the iron–sulfur (Fe–S) clusters. Decreased levels of frataxin decrease the activity of the iron–sulfur enzymes, such as complexes I–III of the mitochondrial electron transport chain, and mitochondrial and cytosolic aconitase.

When frataxin deficiency was demonstrated to cause mitochondrial iron accumulation and oxidative stress in the yeast model of FRDA, idebenone was considered a potential therapeutic tool for FRDA. In 1997, Rustin et al. showed in heart homogenates that reduced iron (Fe^{2+}), but not oxidised iron (Fe^{3+}) decreased the activity of respiratory complex II and increased lipoperoxidation. Addition of ascorbate increased lipoperoxidation by reducing Fe^{3+} to Fe^{2+}. Desferoxamine protected complex II from iron injury, but the activity of the Krebs cycle enzyme aconitase was decreased. Only idebenone protected complex II and lipids from iron injury in heart homogenates without modification of aconitase activity. A normalization of mitochondrial complexes I, II, III, and aconitase has been reported in a repeated endomyocardial biopsy after 5 years of 5 mg kg^{-1} day^{-1} idebenone treatment.

Idebenone and Mouse Models

Animal models with frataxin deficits have been used to test the efficacy of idebenone. A conditional knock-out model, in which frataxin was specifically deleted in cardiac muscle, resulted in a rapidly progressive disease. The murine cardiomyopathy is characterized by an early onset of dilatation with development of left ventricle (LV) hypertrophy followed by reduced systolic function. In this animal model, high dose idebenone (90 mg Kg^{-1} day^{-1}) delayed disease onset, slowed progression, and prolonged survival by 10%, with an average survival rate of 79 ± 9 days versus 71 ± 9 days for placebo treated mutant animals. Of note, this dose was 18-fold greater than the dose usually given to FRDA patients.

Human Studies of Idebenone in FRDA

Low Dosage

The 'in vitro' findings described above prompted a trial on three patients with FRDA and LV hypertrophy. The treatment with idebenone 5 mg Kg^{-1} day^{-1} for 4–9 months was accompanied by substantial decreases in interventricular septum and LV posterior wall thickness and in left ventricle mass (LVM) index. Most open-label and one randomized placebo-controlled trial with idebenone 5 mg kg^{-1} day^{-1} confirmed the effect on LV hypertrophy. While most of these trials included neurological endpoints, only one small, open-label trial with 5 mg kg^{-1} day^{-1} found in pediatric patients a significant improvement, which was related to idebenone plasma concentration.

A large open-label prospective survey has been recently reported. The trial included a total of 104 FRDA patients, 88 of whom received idebenone 5 mg Kg^{-1} day^{-1} and 16 of whom preferred not to be treated. The patients were followed for a median time of 5 years. The neurological picture, as measured by international cooperative ataxia rating scale (ICARS), worsened in both groups but there was a trend towards clearer deterioration in those who were not treated (1.93 ± 0.25 vs. 4.43 ± 1.56 per year). The cardiac hypertrophy decreased in the treatment group (LVM index decreased by -4.1 ± 1.5 g m^{-2} per year), but the cardiac function did not improve as the ejection fraction decreased by -1.3 ± 0.3 per year (**Table 1**).

High Dosage

The safety of high dosages of idebenone has been shown in two phase I studies. In the first trial, 78 patients completed a dose escalation to a maximum of 75 mg kg^{-1} without evidence of dose limiting toxicity. The most common adverse effect was transient mild nausea. Plasma levels of total idebenone were found to increase proportional to the drug dose up to 55 mg kg^{-1}. The second trial included 15 patients who received 60 mg Kg^{-1} day^{-1} for a month. One child experienced nausea and diarrhea, and the drug was discontinued. Urine discoloration was frequently reported.

On the basis of these results, a randomized, placebo-controlled, double-blind, phase II study was designed to

Table 1 Idebenone trials in FRDA

	Design	*Number*	*Idebenone dose*	*Treatment period*	*Cardiac outcomes*	*Neurological outcomes*
Rustin et al.	OL	3	5 mg kg^{-1} day^{-1}	4–9 months	↓ IVS ↓ LVPW ↓ LVMi	Ataxia not quantified
Hausse et al.	OL	38	5 mg kg^{-1} day^{-1}	6 months	↓ LVMi	Ataxia not quantified
Artuch et al.	OL	9	5 mg kg^{-1} day^{-1}	12 months	No change LVPW No change IVS	50% ↓ ICARS in pediatric patients
Rustin et al.	OL	40	5 mg kg^{-1} day^{-1}	6 months	↓ IVS ↓ LVPW ↓ LVMi	No change of ataxia
Mariotti et al.	DBPC	29	5 mg kg^{-1} day^{-1}	12 months	↓ IVS ↓ LVM	No change
Buyse et al.	OL	8	5 mg kg^{-1} day^{-1}	12 months	↓ LVMi ↓ Cardiac strain ↓ Strain rate	↑ CAG
Ribai et al.	OL	88	5 mg kg^{-1} day^{-1}	60 months	↓ LVMi ↓ EF	↑ ICARS
Di Prospero et al.	DBPC	48	~5 mg kg day 15 mg kg^{-1} day^{-1} 45 mg kg^{-1} day^{-1}	6 months	Not reported	↓ ICARS in ambulatory patients, no change in FARS and ADL
Pineda et al.	OL	24	5–20 mg kg^{-1} day^{-1}	36–60 months	No change in pediatric or adult patients	ICARS no change in pediatric patients, ↑ in adult patients

OL, open-label; DBPC, double-blind placebo-controlled; IVS, interventricular septum; LVPW, left ventricule posterior wall; LVMi, left ventricule mass index; EF, ejection fraction; ICARS, international cooperative ataxia rating scale; CAG, Cooperative Ataxia Group; FARS, Friedreich ataxia rating scale; ADL, activities of daily living; ↑ of ataxia scores (ICARS, CAG) indicates worsening.

further assess tolerability and to obtain initial efficacy data. Forty-eight FRDA patients were enrolled in a 6-month, double-blind, placebo-controlled trial. The patients received either placebo or three doses of idebenone (ca 5, ca 15, ca 45 mg kg^{-1}). Urinary 8-hydroxy-2′deoxyguanosine, a peripheral marker of oxidative DNA damage, was chosen as the primary end point. It was not increased in patients and did not significantly change during treatment. The secondary endpoints included change in the ICARS, the Friedreich ataxia rating scale (FARS), and a survey of activities of daily living (ADL). After 6 months of treatment, there was no significant difference among the groups in the degree of change from baseline in the ICARS, FARS, or ADL, even though an indication of dose-dependent improvement was present in the ICARS. A second prespecified analysis excluding patients, who required wheelchair assistance, showed a significant improvement in ICARS and suggested a dose-related response in ICARS, FARS, and ADL scores (**Table 1**). Changes in eye movements and speech contributed the most to the overall change in score. The changes in ICARS and FARS scores at high doses were modest. With regard to safety, one patient receiving the high dose developed neutropenia that resolved shortly after discontinuation of the drug.

Several phase III studies examining high dose idebenone in FRDA are currently underway. A phase III multicenter randomized, placebo-controlled, double-blind study is currently in progress in adult FRDA patients in Europe. FRDA patients will be randomized to one of the same three idebenone doses described above and followed for 1 year. The study will investigate the efficacy of idebenone on hypertrophic cardiomyopathy, as measured by LVM index, and on neurological signs, as measured by ICARS. A shorter 6-month, phase III trial in pediatric patients is in progress in the US. This trial uses a midrange dosage (450–900 mg day^{-1}) and a high dosage (1350–2250 mg day^{-1}), according to body weight $\leq$45 kg or $>$45 kg. The primary endpoint of this trial is the ICARS score. New quinone analogues such as mito-Q are promising molecules but have not yet been tested in clinical trials.

See also: Ataxia with Isolated Vitamin E Deficiency; Complex I Deficiency; Friedreich's Ataxia and Variants; Friedreich's Ataxia Rating Scale (FARS); International Cooperative Ataxia Rating Scale (ICARS); Mitochondrial Dysfunction; Spinocerebellar Ataxias Genetics.

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Immunophilin Ligands

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Glossary

Cyclophilin – Cyclic undecapeptide, a high-affinity receptor for the immunosuppressant cyclosporine A.
FK506 – Macrolide antibiotic with immunosuppressant activity, prototypic ligand for FKBP immunophilins.
FKBP – FK506 binding protein, a high-affinity receptor for the immunosuppressant FK506.
GPI 1046 – 3-(3-Pyridyl)-1-propyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinedinecarboxylate, a nonimmunosuppressant immunophilin ligand.
Immunophilin – FKBP and cyclophilin, the high-affinity receptor proteins for immunosuppressants FK506 and cyclosporine respectively.

Definition and History

Immunophilins are ubiquitous cellular proteins that display a peptidylprolyl cis–trans isomerase (PPI'ase) enzymatic activity and are broadly classified into two major groups: the cyclophilins (cyclosporine A binding protein; CyP) and the FKBPs (for FK506 binding protein). These immunophilin proteins, named for their interactions with the immunosuppressant molecules cyclosporine A and FK506, respectively, catalyze the rotamerization of X-Proline bonds in proteins. The FKBPs are often listed as FKBP, followed by the apparent molecular weight of the protein, such as FKBP 12. Numerous FKBP proteins have been characterized in humans, including FKBP 12, 12.6, 13, 25, 36, 38, 51, 52, 63, 65, and FKBPL protein. These FKBPs have very different functions and act as calcineurin inhibitors, molecular chaperones, and endoplasmic reticulum, nuclear, and mitochondrially targeted proteins. The cyclophilins include cyclophilin A, B, C, D, E, F, H, 40, and NK, which are localized to cytoplasm, nuclear, and microsomal fractions, and also have diverse functions as listed earlier for the FKBP immunophilins.

The mechanism of immunophilin-mediated immunosuppression regulated by FK506 and cyclosporine A (CsA) is now well understood. Although FK506 and CsA are structurally very distinct, both interact with their respective immunophilin protein and then target and inhibit the protein phosphatase, calcineurin. Calcineurin inhibition regulates transcription of genes for interleukin-2 (IL-2) protein and blocks Ca^{2+}-dependent signaling pathways in T-cells. Initially, it was thought that the FK506-FKBP12 and CsA-CyPA binding, and the subsequent inhibition of the immunophilin's PPI'ase activity, was responsible for immunosuppression, but synthetic derivatives of FK506, while potent PPI'ase inhibitors, were not able to inhibit T cell proliferation. Thus, inhibition of the PPI'ase activity of the immunophilin was not required for immunosuppression.

Neuroprotective/Neuroregenerative Effects

Immunophilin proteins, such as FKBP12, are highly enriched in the nervous system and are distributed with their target proteins, suggesting that they may perform a significant function in the brain. In early studies in neuronal cultures, Dawson and colleagues demonstrated that the immunosuppressive drugs FK506 and CsA protected primary cortical neurons from glutamate toxicity with nanomolar potency. The proposed neuroprotective mechanism of action of FK506 in these cultures was to maintain neuronal NOS in a highly phosphorylated and therefore inactive state. These effects on NOS were mediated primarily via calcineurin inhibition, since the neuroprotective effects of FK506 were antagonized by rapamycin, an FK506 antagonist. Low nanomolar concentrations of FK506, CsA, and rapamycin promoted neurite outgrowth from PC12 cells, rat sensory ganglion cells, and hippocampal neurons, demonstrating a neurotrophic and neuroregenerative action of these compounds.

The neurotrophic and immunosuppressive effects of FK506 and CsA were separated when nonimmunosuppressive derivatives of each compound were similarly neuroprotective. The prototypic nonimmunosuppressive immunophilin ligand, GPI1046, elicited an increased neurite outgrowth from embryonic and adult sensory neuronal explant cultures. GPI-1046 also protected organotypic spinal cord cultures of motor neurons from excitotoxic lesions and promoted survival of mesencephalic dopamine neurons from cell death induced by MPP+ and 6-OHDA. In SY5Y neuroblastoma cells, Gold and colleagues found that FK506 and FK1706 promoted neurite outgrowth. The work of Costantini and Isacson demonstrated a significant effect of FK506 and V-10 367 on increased neurite length in mesenchephalic dopamine neurons and protection against MPTP and 6-hydroxydopamine (6-OHDA) in rodents. More recent studies including JNJ460 and FK1706 demonstrate the neuroprotective effects of these immunophilin ligands in vitro and in vivo.

Parkinson's Disease Models

Immunophilin ligands have demonstrated significant neuroprotective and neuroregenerative actions in animal models of Parkinson's disease. In mouse MPTP models, both FK506 and GPI 1046 afforded a significant protection of dopaminergic cells, which was accompanied by increased striatal dopamine levels. Remarkably, when GPI1046 treatment was initiated after 90% of nigrostriatal DA neuron degeneration had occurred, a significant increases in tyrosine hydroxylase (TH) immunostaining in the striatum of lesioned mice was measured. These effects were the result of regenerative actions of the GPI1046, since the nigral cell counts following drug treatment were unchanged. In the 6-OHDA model of Parkinson's disease, significant increases in striatal TH immunoreactivity were found in rats treated with GPI1046 up to 1 month after lesioning. The protective effects of GPI1046 on sparing dopamine neurons and striatal innervation by dopaminergic projections were also evident in MPTP-lesioned rhesus monkeys. In this study, the GPI1046, administered prior to and during MPTP infusion, resulted in the protection of dopaminergic cell bodies in SNc and in improved clinical rating scores when all of the treated animals were evaluated as one treatment group compared with MPTP/Vehicle control, even though individual dose groups were not significantly neuroprotective.

Effects on Peripheral Nerve Models

Immunophilin ligands (FK506, L-685818, GPI1046, V-13670, FK1706) also demonstrated significant effects when evaluated in rats with crushed sciatic nerves, where immunophilin ligand treatment resulted in an increased number of larger-sized axons, significantly increased myelination levels and a more rapid functional recovery of the injured hindlimb following immunophilin ligand treatment. In a rodent cavernous nerve crush model that mimicked the urogenital nerve damage that occurs as a result of radical prostatectomy surgery, these immunophilin compounds have also demonstrated a striking neuroprotective efficacy.

Potential Neurotrophic/Neuroprotective Mechanism(s) of Action

The neurotrophic/neuroprotective mechanism of action of immunophilin ligands remains unclear. Some of the effects of FK506 and CsA may be mediated by the inhibition of calcineurin. The nonimmunosuppressive compounds may have multiple modes of action and multiple FKBPs as targets. FKBP12 is not likely the primary target, since neurotrophic effects of FK506 and GPI1046 persist even in neuronal cultures devoid of FKBP12. Instead, the neurotrophic target of these compounds may be FKBP52 via steroid hormone signaling, since FKBP52 is an integral part of the unliganded steroid hormone receptor. Activation of these receptors by steroid ligand causes dissociation of FKBP52 from the receptor complex and may lead to activation of MAP and ERK kinases. Addition of FK506 and GPI 1046 to neuronal cells in culture leads to upregulation of heat shock proteins 70 and 27, which in turn may provide cytoprotective effects.

Tanaka's studies show that treatment of neurons and glial cells in culture and intact animals with these compounds has demonstrated heightened levels of the

antioxidant glutathione, thus reducing the level of reactive oxygen species. In addition, treatment of neurons in culture and MPTP-intoxicated mice with FK506 and GPI 1046 resulted in increased levels of neurotrophins, BDNF and GDNF in dopamine neurons, within the nigrostriatal pathway.

Recently, two immunophilin proteins, FKBP12 and 52, were found to interact with multiple distinct transient receptor potential (Trp) C channels and modulate calcium influx. Immunophilin ligands can dissociate interactions and restore calcium homoeostasis. These results suggested that immunophilins are TRPC channel accessory proteins that play an important role in the mechanism of channel activation following receptor stimulation.

Lastly, Fischer and colleagues have discovered that immunophilin ligands may target FKBP 38 and calmodulin to elicit their neuroprotective effects. They found that GPI 1046 treatment disrupted the interaction of FKBP-38/calmodulin with the antiapoptotic protein Bcl-2, at the mitochondrial outer membrane. By promoting the dissociation of the FKBP38-Bcl-2 complex, GPI 1046 treatment freed Bcl-2 to interact with and bind up all of the apoptotic BH3-containing proteins, such as Bad, Bax, and Bak. The projected beneficial role of immunophilin ligands in this model then was to facilitate Bcl-2 mediated antiapoptotic effects.

See also: 6-OH Dopamine Rat Model; GDNF (including Nurturin); Mitochondrial Dysfunction; Movement Disorders: Overview; MPTP; Neuroprotection in Movement Disorders; Parkinson's Disease: Animal Models.

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Indirect Pathway

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Glossary

Axon collateral – A side branch of a neuronal axon that can give rise to multiple terminals either in the main target structure of the axon, in a secondary structure, or in the structure from which the axon originates.

Basal ganglia – A group of interconnected subcortical nuclei, including the striatum, globus pallidus, subthalamic nucleus, and substantia nigra, that play a role in motor, limbic, and cognitive functions.

Dopamine – A monoamine neurotransmitter produced mainly in the substantia nigra and ventral tegmental area, known to be important for motor control, reward, and learning; it stimulates two families of receptors: the excitatory D1 family and the inhibitory D2 family.
Dyskinesia – Abnormal involuntary movements commonly associated with progressive motor side effects of chronic administration of dopaminergic drug treatments for Parkinson's disease.
GABA – γ-Aminobutyric acid, the main inhibitory neurotransmitter in the central nervous system.
Parkinson's disease – The second most common neurodegenerative disease, after Alzheimer's disease, characterized by severe, often idiopathic, degeneration of the nigrostriatal dopaminergic projection. Symptoms include bradykinesia, akinesia, muscle rigidity, resting tremor, cognitive impairment, and depression.

Definition

Indirect pathway is a major route of information flow through the basal ganglia circuitry. The classical view of the indirect pathway relies on the following connectivity network. Extrinsic information from the cerebral cortex and thalamus enters the basal ganglia circuits via the striatum (input nucleus), reaching D2 dopamine receptor-containing GABAergic medium spiny neurons (MSN), which send projections to the external globus pallidus (GPe). In turn, the GPe extends a massive GABAergic projection to the subthalamic nucleus (STN), which then provides glutamatergic innervation of the basal ganglia output nuclei, the internal globus pallidus (GPi), and the substantia nigra pars reticulata (SNr). Collateral projections of pallidosubthalamic axons that end in the GPi and SNr, without a relay in the STN, are also part of this system. The indirect pathway is parallel to the 'direct pathway' of the basal ganglia, in which D1 dopamine receptor-containing striatal neurons project directly to the GPi/SNr. The following discussion will pertain to different basal ganglia nuclei that are part of the primate indirect pathway; subtle differences exist in rodents.

Striatum

More than 90% of the total striatal neuronal population is made up of one main type of projection neuron, called MSN, because their distal dendrites are densely covered with spines. Striatal MSNs can be divided equally into two groups based on their distinct chemical phenotypes and main projection targets. Indirect pathway (GPe-projecting) MSNs preferentially express D2 dopamine receptors, adenosine A2A receptors, and the neuropeptide enkephalin, whereas direct pathway (GPi/SNr-projecting) MSNs preferentially express D1 dopamine receptors and the neuropeptides substance P and dynorphin. Other subtle, though functionally important, differences exist in the physiology and morphology of direct and indirect pathway MSNs. D1-containing MSNs are less excitable than D2-containing MSNs, which is likely due to the larger dendritic area of D1-containing MSNs.

The segregation between these two populations of striatal MSNs has been challenged based on evidence for significant coexpression of D1 and D2 dopamine receptors in subsets of striatofugal neurons and the existence of axonal projections from individual MSNs that innervate both the GPe and GPi/SNr. The exact degree of functional segregation and the significance of D1/D2 coexpression remains a controversial issue that generates continued interest in basal ganglia research. It is also important to note that direct and indirect pathway MSNs communicate with each other via local axon collaterals in the striatum.

In any case, indirect pathway striatal neurons project preferentially to the GPe in a topographic fashion, where they form dense bands of axon terminals that completely ensheath the dendritic tree of pallidal neurons with GABAergic symmetric synapses, thereby providing the most massive inhibitory input to the GPe.

External Globus Pallidus (GPe)

The next step in the indirect pathway is the projection from the GPe to the STN. However, this projection is not a simple linear connection, but rather made up of a highly collateralized set of axons that connects the GPe not only with the STN, but also with the GPi, SNr, or both. In nonhuman primates, four major types of GPe projection neurons have been characterized based on their projection targets. About half of all GPe neurons project to the STN and SNr, while the remaining half is split about evenly between neurons projecting to the STN and GPi; the STN, GPi, and SNr; or to the striatum. Most GPe projection neurons also give rise to local axon collaterals that terminate on the cell bodies of other GPe neurons.

Projection neurons of the first, most prevalent type send axons that form a highly focused, dense field of terminals that innervate the whole extent of the somatodendritic domain of individual STN neurons. Axon collaterals from this projection descend into the SNr, where they form dense pericellular baskets around the somata of SNr output neurons. The next two types of GPe projection neurons follow a similar path, creating highly focused pericellular projections to GPi output neurons. These GPe projections are distributed in a highly specific and topographic fashion with respect to functional regions in the target structures. A specific subset of GPe neurons

also sends reciprocal connections to the striatum that terminate in a widespread fashion throughout the structure, where they give rise to GABAergic terminals that preferentially target interneurons, at least in rodents.

Subthalamic Nucleus (STN)

The final step in the indirect pathway is the glutamatergic projection from the STN to the output nuclei. Like other projections in the indirect pathway, STN projection neurons have axons that collateralize and terminate in multiple structures. In addition to GPi and SNr, STN efferents contact the striatum, the substantia nigra pars compacta, the pedunculopontine nucleus, the spinal cord, and send reciprocal projections to the GPe. In nonhuman primates, the most common types of STN projection neurons are those collateralizing to both GPi and GPe (comprising about half), followed by neurons contacting GPe, GPi, and SNr (comprising about 20%), striatum only (~17%), and GPe only (~10%). The STN terminals have a similar morphology in all target nuclei and form asymmetric synapses with dendrites and perikarya. The STN projections to the output nuclei and GPe are highly topographic and functionally organized such that neurons related to the same functional modality remain connected through segregated loops. In addition to the striatum, the STN is another site of entry of extrinsic information into the basal ganglia circuitry, receiving direct inputs from the cerebral cortex (so-called the 'hyperdirect pathway'), thalamus, and brainstem.

Indirect Pathway Neurons and Basal Ganglia Disorders

Imbalanced activity between the indirect and direct striatofugal pathways is one of the key pathophysiological features of Parkinson's disease (PD). In patients with PD, degeneration of the nigrostriatal dopaminergic projection oppositely changes the level of activity in 'direct' versus 'indirect' striatal MSNs, due to their differential expression of dopamine receptors. D1-containing direct pathway neurons, which are normally excited by dopamine, decrease their activity, whereas D2-containing indirect pathway MSNs, normally inhibited by dopamine, display an increased activity in PD. The increased striatal GABAergic outflow to the GPe reduces inhibitory pallidal influences on the STN which, in turn, provides an increased glutamatergic drive to the output nuclei. Together with the decreased inhibition from the direct pathway, this increased glutamatergic drive from the STN leads to an overactive inhibitory basal ganglia outflow to thalamocortical neurons, thereby contributing to reduced motor cortex activity and inhibition of voluntary movements (**Figure 1**).

Current pharmacological treatments for PD largely focus on replacing the diminished striatal dopamine in order to balance the activity between the direct and indirect pathways. However, long-term dopamine therapy often results in the progressive development of dyskinesias and other nonmotor side effects. Consequently, intensive ongoing research aims at testing nondopaminergic drugs that could normalize the activity of the basal ganglia

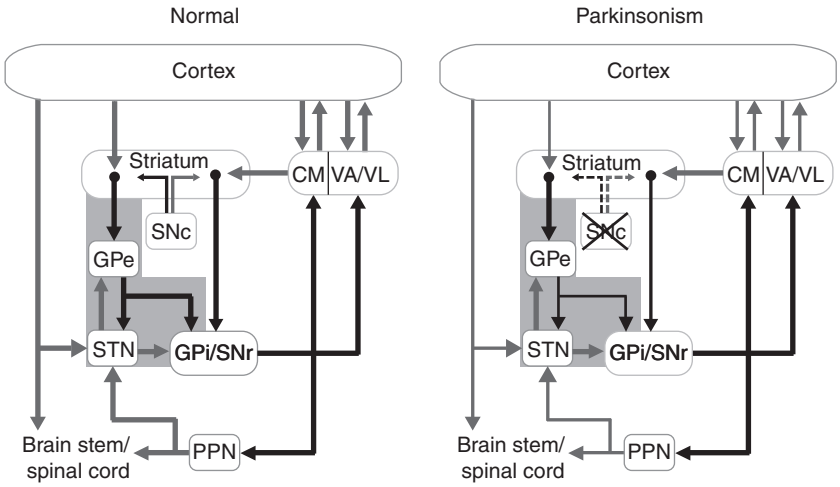

Figure 1 Schematic diagram of the basal ganglia under normal and parkinsonian conditions. Black arrows represent inhibitory projections, and gray arrows represent excitatory projections. In the parkinsonian condition, the weight of the arrows represents the level of neuronal activity relative to the normal state. The connections that makes up the indirect pathway are shaded in gray. CM, centromedian thalamic nucleus; GPe, external globus pallidus; GPi, internal globus pallidus; PPN, pedunculopontine nucleus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; VA/VL, ventral anterior/ventral lateral thalamic nuclei. Adapted from Wichmann and DeLong (2003) Pathophysiology of Parkinson's disease: The MPTP primate model of the human disorder. *Annals of the New York Academy of Sciences* 991:199.

output nuclei. Although an optimal compound remains to be developed, there is good preclinical and clinical evidence that the antagonism of adenosine A_{2A} receptors, which are selectively expressed on indirect pathway MSNs, is a good strategy to reduce Parkinsonian motor symptoms. In addition, knowledge gained from many years of electrophysiological and anatomical studies in animal models has lead to development of surgical interventions for PD aimed at lesioning or stimulating the STN or GPi.

Huntington's disease (HD) is a genetic disorder in which a mutation in the huntingtin protein leads to protein aggregation and death of striatal MSNs (as well as cortical neurons), resulting in chorea, psychiatric problems, cognitive decline, and eventually death. Postmortem studies from HD brains showed that indirect pathway neurons are more sensitive to degeneration than direct pathway neurons, which could explain the chorea and unwanted movements seen in HD; a situation, opposite to that in PD, where an underactive indirect pathway leads to reduced inhibitory basal ganglia outflow to thalamocortical neurons, thereby increasing cortical excitability and problems controlling movements.

Acknowledgments

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See also: Basal Ganglia; Basal Ganglia, Functional Organization; Chorea; Direct Pathway; Dopamine; Dopamine Receptors; Dopamine Transporter: Aging and Parkinson's Disease; Dyskinesias; GABA and Movement Disorders; Huntington's Disease; Parkinson's Disease: Definition, Diagnosis, and Management; Substantia Nigra; Subthalamic Nucleus.

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Inflammation and Parkinson's Disease

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Glossary

BDNF – Brain-derived neurotrophic factor is a trophic factor that can be released by glial cells and that can support the survival of dopaminergic neurons.

GDNF – Glial cell line-derived neurotrophic factor is a potent neurotrophic factor that can be released by reactive astrocytes and activated microglia and protects catecholaminergic neurons from toxic damage and induces fiber outgrowth.

Glial cells – Glial cells are nonneuronal cells that represent at least half the volume of the human brain and outnumber neurons by about ten to one. Glia is mainly composed of macroglia, which includes astrocytes and oligodendrocytes, and microglia. Glial cells have traditionally been considered to provide structural support and nutrition to neurons. However, it is now known that glial cells are also critical for the development of the nervous system and have a wide range of functions, including the control of synapse formation and function, the regulation of brain vasculature and blood–brain barrier or the optimization of environmental conditions for neuronal function.

LPS – Lipopolysaccharide are large molecules constituted by a lipid and a polysaccharide joined by a covalent bond that are found in the outer membrane of gram-negative bacteria, act as endotoxins and elicit strong inflammatory responses in animals.

MPTP – 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine is a by-product of the chemical synthesis of a meperidine analog, with potent heroin-like effects, that can induce a parkinsonian syndrome in humans and nonhuman primates almost indistinguishable from PD on both clinical and neuropathological standpoints. Over the years, MPTP has been used in a host of different animal species, especially in mice, to recapitulate the hallmark of PD cellular pathology, namely the degeneration of the nigrostriatal dopaminergic pathway.

NOS – Nitric oxide synthase is the enzyme of synthesis of nitric oxide (NO), a short-lived, endogenously produced gas that acts as a signaling molecule in the body. So far, three distinct NO-synthesizing isoenzymes have been purified and molecularly cloned: neuronal NO synthase (nNOS), inducible NOS (iNOS), and endothelial NOS. nNOS is the main NOS isoform in the brain, as its catalytic activity and protein are identifiable throughout the central nervous system. In contrast, iNOS normally is not or is minimally expressed in the brain. However, in pathological conditions, iNOS expression can increase in brain glial cells and invading macrophages in response to a variety of injuries. Endothelial NOS is mainly localized in the endothelium of blood vessels and to a minimal extent in different discrete regions of the brain.

ROS – Reactive oxygen species such as superoxide and hydroxyl radicals are constantly produced during normal cellular metabolism, primarily as by-products of the mitochondrial respiratory chain. At high levels, however, these species may damage cellular components, including lipids, proteins and DNA, leading to cellular dysfunction and cell death.

Definition and History

The loss of nigral dopaminergic neurons in PD has long been associated with a marked inflammatory response, mainly composed of activated microglial cells and reactive astrocytes. Astrocytes are crucial to the homeostatic control of the neuronal extracellular environment, while microglia are the most efficient and aggressive phagocytes of the central nervous system. In contrast, oligodendrocytes, which are involved in the process of myelination, have not been so far implicated in PD. In addition to the glial response, T-lymphocyte infiltration has also been identified in PD, indicating an involvement of the adaptive immune system in the inflammatory process seen in the disease.

The glial response in PD was initially regarded as irrelevant to the pathogenic process of the disease. More recently, however, human epidemiological studies have suggested that inflammation may increase the risk of developing PD. In addition, studies in experimental PD models have shown that the inflammatory response can modulate nigrostriatal dopaminergic neuronal death. In particular, it is believed that inflammatory events secondary to the initial neuronal damage could influence the fate of compromised neighboring neurons, thus contributing to the amplification and progression of the neurodegenerative process.

Inflammatory Reaction in PD

In normal brains, resting astrocytes and microglial cells are not evenly distributed. The density of microglial cells is remarkably higher in the substantia nigra compared to any other brain region. In contrast, the density of astrocytes is moderate in the substantia nigra and higher in areas least affected by PD, such as the gray substance.

In PD, glial reaction occurs in both substantia nigra pars compacta (SNpc) and striatum. However, while the damage to dopaminergic elements is consistently more severe in the striatum than in the SNpc, the response of glial cells is consistently more robust in the SNpc than in the striatum. This discrepancy probably reflects the fact that dopaminergic structures are in dominance in the SNpc, whereas in the striatum dopamine synapses represent only a small percentage (about 10–15%) of the entire pool of synapses.

Regarding the magnitude of the astrocytic and microglial responses occurring in PD, SNpc postmortem PD samples only exhibit a mild increase in the number of astrocytes, most of which appear with a resting-like morphology with thin and elongated processes, with only a few having a true reactive aspect with hypertrophic cell body and short processes. In contrast, the activation of microglial cells in PD is consistently more dramatic. Using positron emission tomography imaging techniques, widespread microglial activation can be detected in living PD patients. Microscopical examination of postmortem PD samples indicates that the microglial response in the SNpc mostly occurs in the subregions most affected by the neurodegenerative process. Moreover, activated microglial cells are predominantly found in close proximity to free neuromelanin in the neuropil and to remaining neurons, onto which they sometimes agglomerate to produce an image of neuronophagia.

In addition to the glial reaction, a marked accumulation of CD8+ and CD4+ T lymphocytes has been observed in the SNpc of PD patients, either in close contact with blood vessels or having migrated deep into the brain parenchyma close to neuromelanin-containing dopaminergic neurons.

Similar to sporadic PD, postmortem examination of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-intoxicated individuals also reveals a marked glial reaction

in the SNpc, the magnitude of which seems to parallel that of dopaminergic neuronal loss. In these autopsy cases, the SNpc exhibits both reactive astrocytes and activated microglial cells, as well as images of neuronophagia, indicative of an active, ongoing process of cell death, even if the acute intoxication with MPTP occurred several years before. These results indicate that a single acute insult in the SNpc could set in motion a self-sustaining cascade of molecular events with long-lasting deleterious effects on dopaminergic neurons.

While human postmortem studies do not provide information about the temporal relationship between inflammatory reaction and dopaminergic neuron cell death, experiments in MPTP-intoxicated mice indicate that reactive astrocyte formation parallels dopaminergic degeneration in both the striatum and the SNpc and that it remains increased even after the main wave of neuronal death has occurred. In contrast, activation of microglial cells in MPTP-intoxicated mice occurs much earlier than that of astrocytes and reaches a maximum before the peak of dopaminergic neurodegeneration. These results indicate that the response of both astrocytes and microglial cells in the SNpc occurs within a timeframe compatible with these glial cells to influence the fate of dopaminergic neurons following MPTP intoxication, and possibly in PD. When compared with the time course of glial cell activation, the T cell brain infiltration following MPTP intoxication to mice was found to arise after the increase of microglial cells and concomitantly with astrogliosis. Such dynamics are compatible with a possible role of activated microglial cells in the brain region-specific recruitment of T cells.

Role of Inflammation in PD

Studies in experimental models of PD have demonstrated that inflammation may have either neuroprotective or neurotoxic effects on dopaminergic neurons.

Neuroprotective Effects of Inflammation in PD

Various types of glia and T cells can provide trophic factors that are essential for the survival of dopaminergic neurons. Among those, glial-derived neurotrophic factor (GDNF), which can be released by reactive astrocytes and activated microglia, seems to be the most potent factor in supporting SNpc dopaminergic neurons during their period of natural developmental death in postnatal ventral midbrain cultures. Moreover, ablation of GDNF in adult mice results in pronounced catecholaminergic cell death, mostly affecting the locus coeruleus and the substantia nigra, thus indicating that GDNF is indispensable for adult catecholaminergic neuron survival. Intracerebral administration of GDNF induces dopaminergic nerve fiber sprouting in the injured rodent striatum and has been shown to attenuate dopaminergic neuronal death and to boost dopaminergic function within injured neurons in both MPTP-treated monkeys and mice. In PD patients, however, repetitive intraventricular injections of recombinant GDNF has been poorly tolerated and failed to halt the progression of the disease. Brain-derived neurotrophic factor (BDNF) and mesencephalic astrocyte-derived neurotrophic factor (MANF) are other trophic factors that can also be released by glial cells and that can support the survival of dopaminergic neurons.

Glial cells could also exert a neuroprotective effect in PD by scavenging toxic compounds released by dysfunctional and dying neurons. Dopamine can produce reactive oxygen species (ROS) through different routes, and glial cells may protect remaining neurons against the resulting oxidative stress by metabolizing dopamine via monoamine oxidase-B and catechol-*O*-methyltransferase present in astrocytes, as well as by detoxifying ROS through the enzyme glutathione peroxidase, which is detected almost exclusively in astrocytes.

Finally, glia can take up extracellular glutamate, which could mitigate the presumed excitotoxic effects resulting from the hyperactivity of the subthalamic input into the substantia nigra that occurs in PD.

Deleterious Effects of Inflammation in PD

Many compelling findings indicate that glial cells, in particular activated microglia, could be harmful for dopaminergic neurons in PD. Stereotaxic injection of bacterial endotoxin lipopolysaccharide (LPS) into the SNpc causes a strong activation of microglia throughout the substantia nigra, followed by a marked degeneration of dopaminergic neurons. Conversely, pharmacological inhibition of microglial activation prevents LPS-induced SNpc neuronal death.

Activated microglial cells can produce a variety of noxious compounds, including ROS, reactive nitrogen species, proinflammatory prostaglandins, and cytokines. Significant attention has been given to reactive nitrogen species, due to the prevalent idea that nitric oxide (NO)-mediated nitrating stress could be pivotal in the pathogenesis of PD. So far, however, none of the characterized isoforms of nitric oxide synthase (NOS) has been identified in SNpc dopaminergic neurons. In contrast, numerous glial cells in the SNpc of both PD patients and MPTP-treated mice express high levels of inducible NOS (iNOS). This NOS isoform, upon its induction, produces high amounts of NO for a prolonged period of time, as well as superoxide radicals, two reactive species which can either directly or indirectly promote neuronal death by inflicting oxidative damage. Supporting an instrumental role for glial-derived NO in PD, ablation of iNOS in mutant mice has been shown to attenuate MPTP-induced neurodegeneration.

Another major source of glial-derived ROS emanates from the microglial enzymatic complex NADPH-oxidase, which upon its induction and activation can produce large amounts of superoxide radicals. NADPH-oxidase is activated in the SNpc of both PD patients and MPTP-intoxicated mice and its genetic inactivation has been shown to attenuate MPTP-induced neurodegeneration in mice.

Prostaglandins and their synthesizing enzymes, such as cyclooxygenase type 2 (Cox-2), constitute a second group of potential deleterious effectors of inflammation. In both PD and MPTP-intoxicated mice, the expression of Cox-2 and its products, such as prostaglandin E2, is significantly increased. In MPTP-injected mice, Cox-2 is induced via a c-Jun N-terminal kinase-dependent pathway, the blockade of which, like that of Cox-2 itself, has been shown to attenuate neurodegeneration.

A third group of glial-derived compounds that can inflict damage in PD is constituted by proinflammatory cytokines, several of which, such as tumor necrosis factor-α and IL-1b, are increased in both SNpc tissues and cerebrospinal fluid of PD patients. These cytokines may act in PD by stimulating the activation of other astrocytes and microglia, thus amplifying the inflammatory response, or by directly binding to specific cell surface cytokine receptors in dopaminergic cells, leading to the activation of apoptotic molecular pathways in these neurons.

A deleterious role of the adaptive immune response has also been reported in experimental PD models. For instance, MPTP-induced dopaminergic cell death is markedly attenuated in the absence of mature T lymphocytes in immunodeficient mouse strains. This protection is specifically associated with a lack of CD4+, but not CD8+, T cells. In addition, PD-associated oxidative protein modifications, such as nitration of α-synuclein, can create novel antigenic epitopes capable of a peripheral adaptive T cell response that exacerbates MPTP-induced nigrostriatal degeneration in mice.

In order to reconcile the inherent protective role of glial cells with a potential detrimental action, it has been proposed that, during normal aging or in pathological situations, glial cells may become progressively disabled and lose their functional capacity to support neurons, which would consequently result in neuron cell death. Whether such a scenario is relevant to PD, however, remains to be determined.

Therapeutic Implications

Potential therapeutic strategies for PD based on targeting inflammation should aim at balancing the protective versus the deleterious roles of glial cells.

If the effects of inflammation in PD are mainly considered as deleterious, then attempts to prevent the glial reaction, and more specifically microglial activation, may be envisaged. Along this line, several preclinical studies in MPTP and 6-OHDA models of PD have succeeded in attenuating dopaminergic neurodegeneration by preventing microglial activation with a variety of agents, including the antibiotic minocycline, the peroxisome proliferator-activated receptor-γ agonist pioglitazone, the vasoactive intestinal peptide, and some opiate receptor antagonists. Alternatively, potential therapeutic strategies could be aimed at blocking the effects of specific proinflammatory mediators, such as iNOS-derived NO or NADPH-oxidase-derived ROS.

Other strategies aiming at targeting the adaptive arm of the immune system in PD may involve the development of vaccines for antigens that promote cell-mediated antiinflammatory responses or the blockade of the migration of immune cells across the blood–brain barrier. For instance, in the MPTP mouse model of PD, immunization strategies with CNS antigens expressed at the lesion site have been shown to reduce dopaminergic neurodegeneration by inducing T cells to enter inflamed CNS tissue, attenuate innate glial immunity, and increase local neurotrophic factor production. These data suggest that vaccination strategies with antigens derived from proteins at the site of neurodegeneration may be potentially used as a therapeutic approach for PD. However, a note of caution is necessary, as the use of proteins that are prone to nitrate modifications can result in a deleterious, rather than protective, peripheral adaptive T cell responses in experimental models of PD.

Conversely, because of the inherent supportive role of glial cells, strategies to boost or preserve glial functions may also be proposed to protect neurons from degenerating. Along this line, it has been reported that the beneficial effect on MPTP-induced behavioral alterations in monkeys obtained by implanting undifferentiated human neural stem cells (hNSCs) in the nigrostriatal pathway may result from the differentiation of hNSCs into GDNF-producing astrocytes rather than its differentiation into dopaminergic neurons. However, whether such a strategy may be applicable to PD remains to be demonstrated.

See also: Glial Cell Activation in PD; MPTP; Neuroimaging, Parkinson's Disease; Nitric Oxide; Parkinson's Disease: Animal Models; Substantia Nigra.

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International Cooperative Ataxia Rating Scale (ICARS)

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Glossary

Ataxia – Literally (Greek) absence of order. Clinically referred to as a specific motor syndrome with difficulty to stabilize the trunk against gravity, difficulty to stabilize gaze, and difficulty in goal-directed limb movements and dysarthria.
Cerebellar sign – Neurological sign attributed to lesions of the cerebellum.
Clinical rating scale – Assessment tool used to document and compare disease status, for example, in clinical trials that are based on a standardized clinical examination of selected disease features. Standardization refers to instructions of test performance and rating.
Outcome parameter – Type of assessment that is chosen to document and compare the effects of an intervention in clinical trials. This can be a clinical scale or any instrumental or laboratory test known to change with disease severity.
Reliability – Accuracy of an assessment tool, that is, how consistent or repeatable the measurements are. For clinical rating scales, reliability is usually documented by good internal consistency and minimal variance between different raters (interrater) or between test and retest.
Sensitivity – Ability of an assessment tool to pick up differences between different disease states. Sufficient sensitivity (or responsiveness) to change over time is a prerequisite for use of a clinical rating scale as an outcome parameter in clinical trials.
Validity – Appropriateness of content of an assessment tool, that is, does it measure what it is intended to measure what it is intended to measure. It is usually documented by good correlations with other assessments of the same construct: for example, a clinical scale supposed to measure disease severity could be compared to other measures known to change with disease severity.

Definition and History

The conduct of multicenter therapeutic trials depends on reliable and sensitive assessment tools. Consequently, clinical rating scales have been established for different diseases for the testing of potential therapeutic agents. Ataxia disorders are diseases characterized by prominent ataxia due to lesions of the cerebellum or its afferent or efferent connnections. In these disorders, ataxia is often

accompanied by other neurological symptoms. Ataxia research has recently focused on the hereditary neurodegenerative ataxias, rare disorders that are clinically and genetically heterogeneous, and are often slowly progressive. For clinical research in ataxia disorders, three clinical rating scales have been published to date: the International Cooperative Ataxia Rating Scale (ICARS), the Friedreich Ataxia Rating Scale (FARS), and the Scale for the Assessment and Rating of Ataxia (SARA). Of these, ICARS, published in 1997, was the first standardized clinical rating scale for ataxia (**Figure 1**).

Development of the Scale

The World Federation of Neurology formed an ad hoc Committee, in 1993, to develop a practical standard tool for the evaluation of cerebellar ataxia suitable for clinical trials. The group aimed to propose a scale that would describe and quantify cerebellar ataxia symptoms, and could be administered in a relatively short time. The authors of the scale acknowledged that the presence of noncerebellar symptoms in ataxia patients (they use the term ataxia as equivalent to cerebellar syndrome) may

International Cooperative Ataxia Rating Scale

I. Posture and gait disturbances

1. Walking capacities
(Observed during a 10 m test including a half-turn, near a wall, at about 1,5 m)

0 normal
1 almost normal naturally, but unable to walk with feet in tandem position
2 walking without support, but clearly abnormal and irregular
3 walking without support but with considerable staggering; difficulties in half-turn
4 walking with autonomous support no longer possible, the patient uses the episodic support of the wall for a 10 m-test
5 walking only possible with one stick
6 walking only possible with two special sticks or a stroller
7 walking only with accompanying person (wheelchair)

2. Gait speed
(Observed in patients with preceding scores 1-3; preceding score 4 and up gives automatically score 4 in this test)

0 normal
1 slightly reduced
2 markedly reduced
3 extremely slow
4 walking with autonomous support no longer possible

3. Stance
(The patient is asked first to try and stay on one foot, if impossible, to stand with feet in tandem position; if impossible, to stand with feet together; for the natural position, the patient is asked to find a comfortable standing position)

0 normal; able to stand on one foot more than 10s
1 able to stand with feet together, but no longer able to stand with feet in tandem position
2 no longer able to stand with feet together, but able to stand in natural position without support, with no or moderate sway
3 Standing in natural position without support, with considerable sway and corrections
4 Unable to stand in natural position without strong support of one arm
5 Unable to stand at all, even with strong support of two arms

4. Spread of feet in natural position without support, eyes open
(The patient is asked to find a comfortable position; then the distance between medial malleoli is measured)

0 normal (<10 cm)
1 slightly enlarged (<10 cm)
2 clearly enlarged (25 cm<spread<35 cm)
3 severly enlarged (>35 cm)
4 standing in natural position impossible

Figure 1 (Continued)

hamper the assessment of ataxia severity. ICARS claims to assess only ataxia, even in the context of a more complex neurological syndrome. Items included in the ICARS were selected according to the assumed specificity for ataxia with reference to the early clinical reports.

Scale Structure

The ICARS is a 100-point, semiquantitative, examination-based clinical assessment of 19 items that are grouped into four subscales: (1) posture/gait disturbance (seven items, maximum 34 points), (2) kinetic functions (seven items, maximum 52 points), (3) speech disorder (two items, maximum eight points), and (4) oculomotor disorder (three items, maximum six points). Kinetic functions are assessed separately for both right and left sides the ratings of which are then added for the proposed subscale score. The subscales are assumed to correspond to anatomically defined regions of the cerebellum concerning the vermis and hemispheres. The authors propose adding the ratings of each subscale to form the subscore for each of the four sections and subsequently,

5. Body sway with feet together, eyes open

0 normal
1 slight oscillations
2 moderate oscillations (<10 cm at the level of the head)
3 severe oscillations (>10 cm at the level of the head), threatening the upright position
4 immediate falling

6. Body sway with feet together, eyes closed

5 normal
6 slight oscillations
7 moderate oscillations (<10 cm at the level of the head)
8 severe oscillations (>10 cm at the level of the head), threatening the upright position
9 immediate falling

7. Quality of sitting position
(Thighs together, on a hard surface, arms folded)

0 normal
1 with slight oscillations of the trunc
2 with moderate oscillations of the trunc and legs
3 with severe dysequilibrium
4 impossible

II. Kinetic functions

8. Knee-tibia test (decomposition of movement and intention tremor)
(The test is performed in the supine position, but teh head is tilted, so that visual control is possible. The patient is requested to raise one leg and place the heel on the knee, then slide the heel down the anterior tibial surface of the resting leg towoards the ankle. On reaching the ankle joint, the leg is again raised in the air to a height of approx. 40 cm and the action is repeated. At least three movements of each limb must be performed for proper assessment)

0 normal
1 Lowering of heel in continuous axis, but the movement is decomposed in several phases, without real jerks, or abnormally slow
2 Lowering jerkily in the axis
3 Lowering jerkily with lateral movements
4 Lowering jerkily with extremely strong lateral movements or test impossible

9. Action tremor in the heel-to knee test
(Same test as preceding one: the action tremor of the heel on the knee is specifically observed when the patient holds the heel on the knee for few seconds before sliding down the anterior tibial surface; visual control is required)

0 no trouble
1 tremor stopping immediately when the heel reaches the knee
2 tremor stopping in less than 10s after reaching the knee
3 tremor continuing for more than 10s after reaching the knee
4 uninterrupted tremor or test impossible

Figure 1 (Continued)

summing all subscores to compute a total score of the ICARS, which reflects a global measure for the severity of ataxia, ranging from zero (= no ataxia) to 100 (= most severe ataxia).

Metric Properties and Validation Studies

The ICARS was originally published without validity assessment. Since then, however, several groups have contributed to validate the ICARS construct and define its metric properties and reliability. These studies are highlighted in this section.

Internal consistency was found to be excellent in a sample of 50 patients with multiple system atrophy, and factorial analysis supported the four subscores of the scale. However, the items nystagmus and Archimedes' spiral had a low factor loading for their subscales and ICARS total. Parkinsonian features such as gait impairment and limb

10. Finger-to-nose test: decomposition and dysmetria
(The subject sits on a chair; the hand is resting on the knee before the beginning of the movement; visual control is required. Three movements of each limb must be performed for proper assessment)

0 no trouble
1 oscillating movement without decomposition of the movement
2 segmented movement in 2 phases and/or moderate dysmetria in reaching the nose
3 segmented m vement in more than 2 phases and/or considerable dysmetria in reaching the nose
4 dysmetria preventing the patient from reaching the nose

11. Finger-to-nose test: intention tremor of the finger
(The studied tremor is that appearing during the proximal ballistic phase of the movement; the patient is sitting comfortably, with his/her hand resting on his/her thigh; visual control is required; three movements of each limb must be performed for proper assessment)

0 no trouble
1 simple swerve of movement
2 moderate tremor with estimated amplitude <10 cm
3 tremor with estimated amplitude between 10 and 40 cm
4 severe tremor with estimated amplitude >40 cm

12. Finger-finger test (action tremor and/or instability)
(The sitting patient is asked to maintain medially his/her index fingers pointing at each other for about 10s, at distance of about 1 cm, at the level of the thorax, under visual control)

0 normal
1 mild instability
2 moderate oscillations of finger with estimated amplitude <10 cm
3 considerable oscillations of finger with estimated amplitude between 10 and 40 cm
4 jerky movements >40 cm of amplitude

13. Pronation-supination alternating movements
(The subject, comfortably sitting on a chair, is asked to rais his/her forearm vertically and to make alternative movements of the hand. Each hand is moved and assessed separately)

0 normal
1 slightly irregular and slowed
2 clearly irregular and slowed, but without sway of the elbow
3 extremely irregular and slowed movement, with sway of the elbow
4 movement completely disorganised or impossible

14. Drawing of Archimedes' spiral on a predrawn pattern
(The subject is comfortably settled in front of a table, the sheet of paper being fixed to avoid artefacts. The subject is asked to perform the task without timing requirements. The same conditions of examination must be used for follow-up: same table, same pen. The dominant hand is examined. For rating see examples in original publication.)

0 normal
1 impairment and decomposition, the line quitting the pattern slightly, but without hypermetric swerve

Figure 1 (Continued)

bradykinesia seemed to contaminate the ataxia assessment with ICARS in this patient group. In a study of 22 patients with different hereditary ataxias rated using video assessments, interrater and test–retest reliability were high, notably without rater training other than written test instructions. The interrater reliability for ICARS total was higher than that of the subscores, and lowest in the speech subscale. The authors of that study found scoring instructions of the kinetic items potentially confusing. In a sample of 77 Friedreich ataxia patients, only the ICARS total and posture/gait subscore satisfied established psychometric test criteria. Specifically, the criterion of internal consistency was not met by the two items, finger–finger-test and fluency of speech; and the speech and oculomotor subscales had low test–retest reliability. Further evaluations questioned the proposed grouping of the ICARS items into subscales. Thus, the authors of that study questioned the proposed grouping of the ICARS items into subscales and did not recommend the use of ICARS in Friedreich ataxia. Factorial analysis in a different sample of 96 FRDA patients resulted in four factors, but only of them loaded for a single ICARS subscale (oculomotor function).

2 line completely out of the pattern with recrossings and/or hypermetric swerves
3 major disturbance due to hypermetria and decomposition
4 drawing completely disorganised or impossible

III. Speech disorders

15. Dysarthria: fluency of speech
(The patient is asked to repeat several times a standard test sentence, always the same,...)

0 normal
1 mild modification of fluency
2 moderate modification of fluency
3 considerably slow and dysarthric speech
4 no speech

16. Dysarthria: clarity of speech

0 normal
1 suggestion of slurring
2 definite slurring, most words understandable
3 severe slurring, speech not understandable
4 no speech

IV. Oculomotor disorders

17. Gaze-evoked nystagmus
(The subject is asked to look laterally at the finger of the examiner: the movements assessed are mainly horizontal, but they may be oblique, rotatory or vertical)

0 normal
1 transient
2 persistent but moderate
3 persistent and severe

18. Abnormalities of ocular pursuit
(The subject is asked to follow the slow lateral movement performed by the examiner)

0 normal
1 slightly saccadic
2 clearly saccadic

19. Dysmetria of saccades
(The two index fingers of the examiner re placed in each temporal visual field of the patient, whose eyes are in the primary position; the patient is asked to look laterally at the finger, on the right and on the left; the average overshoot or undershoot of the two sides is then estimated)

0 absent
1 bilateral clear overshoot or undershoot of the saccade

Figure 1 International Cooperative Ataxia Rating Scale.

In the same sample ICARS was correlated with disease duration, and with both SARA and FARS (part III) sum scores. The ICARS was also validated in a sample of 156 spinocerebellar ataxia patients and 8 controls. The mean time to complete the scale was 21 min. Interrater and test–retest reliability were high, and internal consistency was excellent although it increased when the oculomotor items were deleted. Correlations with different functional ratings supported validity. However, factorial analysis again did not support the use of subscores as proposed in the original publication. The authors noted difficulties with overlapping and interdependent ratings in the posture/gait subscale. In conclusion, they questioned the usefulness of the scale for this ataxia patient group, but noted that ratings in a small number of controls differed from the patient group. In an evaluation of scale responsiveness in Friedreich ataxia patients, the effect sizes of the ICARS total were moderate, while the FARS performed superiorly in this respect. One publication supported face validity by association of ICARS total with the expected clinical course after surgery of the cerebellum. Factorial analysis in this sample of 136 patients with focal cerebellar lesions revealed five factors that coincided with the proposed four subscales of ICARS, while the fifth factor accounted for the laterality of the kinetic items. The authors concluded that ICARS subscales may be used in patients with focal cerebellar lesions, whereas in degenerative ataxias, only the ICARS sum score should be reported.

Clinical Trials

The ICARS has been used as a secondary outcome measure in a NIH trial of high-dose idebenone in Friedreich ataxia. In a sample of 47 patients with mean baseline scores of 40.4, mean changes in the treatment and placebo arm over a 6-month interval were reported between 0 and −4.5 (estimates from figures in the original publication). As no treatment effect was detected, these data can be seen as an estimate of the 'natural' progression in Friedreich ataxia. In a prospective 5-year follow-up of 104 Friedreich ataxia patients, yearly ICARS changes were significant with an increase of 4.4 ± 1.6 in 16 untreated subjects and 1.9 ± 0.3 in 88 idebenone-treated subjects. Changes were also significant for all subscores except for the oculomotor subscore in this patient group. Estimates of progression rates were higher in the subgroup with earlier onset, thereby suggesting of higher discriminant ability of the scale in less severely affected patients. Of note, the authors noted a plateau in ICARS ratings despite further clinical deterioration in late-stage (wheelchair-bound) Friedreich ataxia patients. In an observational study in 34 patients with Machado–Joseph disease, a mean yearly increase of +5.1 was found, and progression rates were not dependent on disease duration, age at onset or number of CAG repeat in this sample. The ICARS has been used as a secondary outcome measure in a NIH trail of high-dose idebenone in Friedreich ataxia. As no treatment effect was detected, the mean changes in the treatment and placebo arm over a 6 month interval of 0 and −4.5 (estimates from figures in the original publication) give a different estimate of the "natural" progression in Friedreich ataxia. The ICARS has also been used as a primary outcome measure in several pilot studies of, for example, branched-chain amino acid therapy ($n = 16$), L-carnitine ($n = 16$), and ondansetron ($n = 46$), gabapentin in SCA6 (n = 11), Coenzyme Q10 and vitamine E (n = 50) or idebenone (n = 24) in FRDA. It was chosen as secondary outcome measure for the ongoing pilot study of Lithium in spinocerebellar ataxia type 1 and a phase II trial of high-dose idebenone in FRDA.

Criticism

Although the scale was developed as a general measure for cerebellar ataxia, subsequent validation trials revealed limitations in samples with substantial noncerebellar involvement like multiple system atrophy or some spinocerebellar ataxias. Although the time to administer the scale is acceptable for clinical trials, some difficulties were noted in the test and rating descriptions even by trained raters. Importantly, the proposed subscale structure was not supported by different trials in Friedreich ataxia and spinocerebellar ataxias. Thus, the reporting of subscores does not seem justified in these particular patient groups. In addition, in Friedreich ataxia patients, the scale did not seem to discriminate well in more severely affected patients. Like many other clinical scales, the ICARS is not well characterized in terms of sensitivity to change or clinical relevance of score differences.

Conclusion

ICARS was the first standardized clinical rating scale for ataxia published in 1997 by an international consortium, and is now widely used. Its metric properties were only determined in later studies, and revealed several shortcomings for its use in clinical trials. Some scoring instructions were found potentially confusing, and they underline the need for rater training. The reporting of subscores, though supported in patients with focal cerebellar lesions, may not be well suited for Friedreich ataxia and spinocerebellar ataxia patients. Furthermore, the presence of parkinsonian features may affect the use of ICARS in multiple system atrophy. Therefore, new ataxia scales have recently been developed for ataxia in general (the SARA) or for specific diseases (the Unified Multiple System Atrophy Rating Scale, UMSARS, or the Friedreich Ataxia Rating Scale, FARS) with the aim to address such concerns.

See also: Ataxia; Friedreich's Ataxia Rating Scale (FARS); Multiple System Atrophy; Rating Scales in Movement Disorders; Scale for the Assessment and Rating of Ataxia (SARA).

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Interspike Interval

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Glossary

Action potential train – A single action potential is a very large and rapid rise in the cell membrane potential that lasts ~1 ms before the membrane potential returns again close to its resting potential. A train of action potentials refers to consecutive action potentials, which are sometimes referred to as 'spikes.'

EPSP – Excitatory postsynaptic potentials result from excitatory inputs from another neuron or neurons that depolarize the cell membrane (resting potential becomes less negative).

Histogram – It is a graphical display that indicates the proportion of cases that fall into each of several categories (time or frequency bins).

Interspike interval – The time between successive action potentials discharged by a neuron.

Motor unit – The spinal motor neuron and all of the muscle fibers that it innervates.

Motor unit synchronization – When interspike intervals from two motor units are compared, synchronization indexes can be obtained, which reflect the common input from higher centers. These common inputs can be quantified in the time (short-term synchronization) or frequency (coherence) domain.

Definition and History

Interspike interval (ISI) refers to the time between successive action potentials discharged by a neuron. Dr. Edgar D. Adrian (1928) was most likely the first physiologist, who demonstrated that the ISI is a communication tool for the nervous system.

A single action potential is a very large and rapid rise in the cell membrane potential that lasts ~1 ms before the

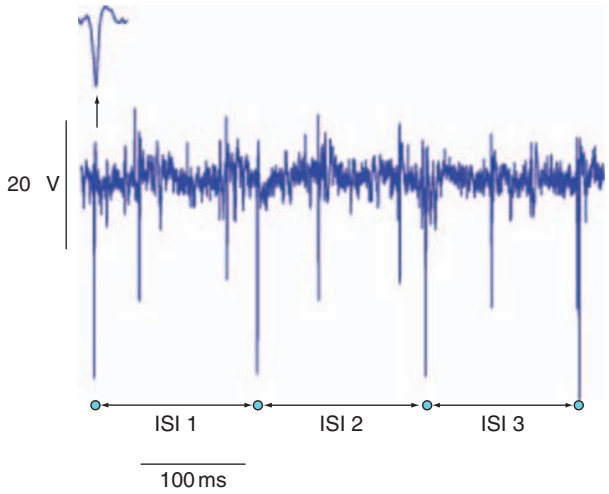

Figure 1 Recording of action potentials from a human motor unit. This recording shows two different motor units recorded at the same time from fine wires inserted into the first dorsal interosseous muscle. The ISI of the motor unit with the largest action potential is identified by quantifying the time between two successive spikes (action potentials).

membrane potential returns again close to its resting potential (∼−70 mV; potential difference between the inside of the cell and the external environment). It typically results from excitatory inputs (EPSP; excitatory postsynaptic potentials) from another neuron or neurons, which depolarize the cell membrane (resting potential becomes less negative). The action potentials (often called 'spikes') propagate along the neuronal axon to reach the nerve terminal to release chemical signals (neurotransmitters) and consequently excite or inhibit other neurons. The train of action potentials is a very important way by which neurons carry information. Therefore, neurophysiologists are interested in the pattern of the action potential discharge. The amplitude of the action potential is not so important, because the cell membrane will either depolarize or not (all-or-none phenomenon).

The simplest way to examine the pattern of the action potential discharge is to record from a single neuron and construct a histogram of the time intervals. In humans, this is typically achieved by recording the extracellular action potentials from a single motor unit using fine wire electrodes placed in the muscle of a subject. Since a motor unit is defined as the spinal motor neuron and all of the muscle fibers that it innervates, the recording of fiber action potential provides a window into the behavior of the spinal motor neuron in vivo. The action potentials that come from the same motor neuron are often discriminated by amplitude and shape algorithms. The time between two consecutive action potentials is calculated (e.g., ISI 1, ISI 2, ISI 3; **Figure 1**) and then a histogram (**Figure 2**(**a**)) is constructed of all the time intervals recorded. For the construction of a good histogram, ∼1000 such time intervals are needed, which would require the recording of

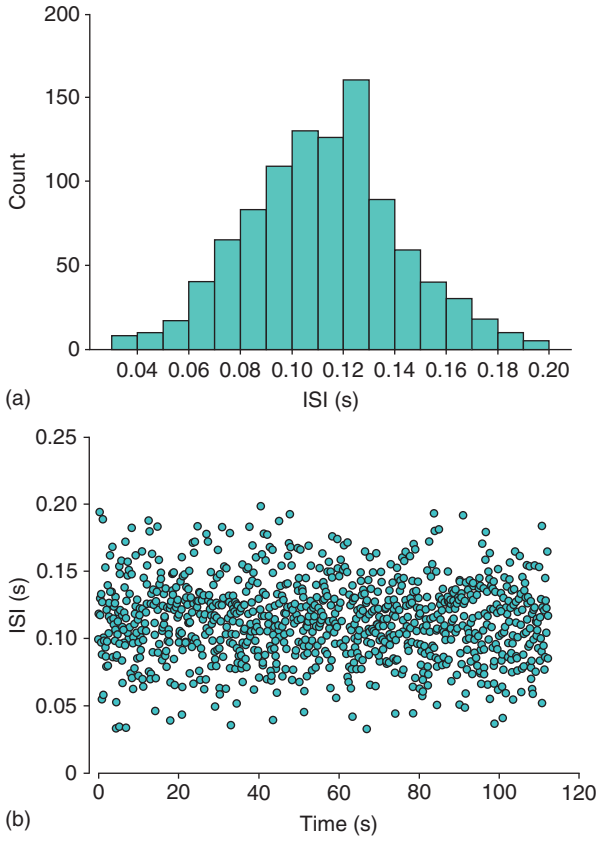

Figure 2 Graphing of ISI, (a) demonstrates a histogram from the recording of a train of action potentials (112 s), whereas (b) shows the ISI as a function of time.

action potentials from 2 to 3 min (assuming an average discharge rate of 6–8 actions potentials per second). Another way to visualize the ISI is to graph it against time (**Figure 2**(**b**)). Basic statistics such as the mean, standard deviation, and coefficient of variation are calculated from the recorded train of action potentials to identify the mean discharge rate and the variability of discharge rate. Furthermore, when ISI from two motor units are compared, synchronization indexes can be obtained. Such synchronization of motor unit discharge times have been attributed to common input that has been delivered to spinal motor neurons either by branched axons from last order neurons or by presynaptic synchronization of efferent fibers from the motor cortex.

See also: Motor Output Variability; Motor Unit; Motor Unit Synchronization.

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Intra-Individual Variability in Movement

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Glossary

Interindividual variability – The variation from moment to moment or trial to trial that arises from the same individual attempting to perform the same movement or postural outcome.
Noise – The random processes that create the unexplained observed variability in movement and posture. Most behavioral accounts of noise are based on an analysis of the system output that is measured in distributional and frequency properties. There are many different kinds of noise but most analyses of movement variability use white noise when they estimate the levels of system noise.
Tremor – It is an unintentional, somewhat rhythmic, muscle movement involving to-and-fro movements (oscillations) of one or more body parts.

Definition and History

Variability within and between species has been a construct of longstanding theoretical significance in many fields of biology. Nevertheless, in the human movement domain, variability has traditionally been interpreted, largely without experimental examination, as merely noise leaving the theoretical focus to the invariance rather than the variance of movement control. It is only in recent years that the variability of movement in disordered systems has received direct theoretical, experimental, and clinical attention.

There are many measures and interpretations of intraindividual variability in human movement that can also vary with the time scale (within-trial, across trials, and/or movement sessions) over which the intraindividual movement variation is determined. The standard approaches to the analysis of variation used linear measures but more recent analysis of variability, including those in movement disorders, are motivated by the constructs, and hence the measures of nonlinear dynamics and chaos theory.

Measures of Movement Variability

In behavioral motor control, the measures of movement variability tend to focus on three aspects: (1) the outcome of the action in relation to the task goal (the most prevalent); (2) properties of the movement trajectories of the limbs and torso; and (3) coordination measures of the movement relations between body segments. In each category, the intraindividual variability of a movement property can be determined often with multiple indices. Nevertheless, the traditional emphasis to variability has been on the dispersion of the respective movement variable as reflected in distributional descriptive statistics such as standard deviation (SD) and coefficient of variation (SD/M).

A general finding across a range of motor tasks and population groups has been the SD scales with the parameter value of each variable. Thus, the SD of movement outcome and trajectory properties whether measured in space, time, or force tends to be higher as the scaling demands on those respective dimensions are increased. This is the essence of the movement speed-accuracy trade-off, which is a classic example of the scaling of movement variability.

In general, the SD of a movement property, such as peak velocity or movement extent, is s-shaped over the full range of scaling though approximations to linearity in the change of SD tend to be obtained in the middle range of movement scaling. The coefficient of variation (relative variability) of movement properties is, thus, not constant over the full range of movement conditions. This scaling property of the amount of variation over movement conditions leads to the position that the amount of system noise and the structure of movement variability is task dependent.

The time- and frequency-dependent properties of the within-subject variability also provide a way to characterize movement variation as a function of conditions and population group. These measures of the structure of variability provide insight into the nature of the movement variability that can be independent of the dispersion

estimates of the amount of variation. For example, spectral analysis and its variants can provide clues as to the nature of system control through signal decomposition of the frequency regimen. Time-dependent analysis of the sequential structure of variability (autocorrelation, ApEn, SampEn, recurrence) can reveal aspects of the attractor dynamics of the movement or posture time series.

Analysis of the structure of movement variability in either the outcome or the movement trajectory rarely approximates white Gaussian noise (Gaussian amplitude, equal contribution of frequencies, and independence of sequential points). Instead, there is systematic time- and frequency-dependent structure to the movement variability of a time series. Enhanced variation in the time- and frequency-dependent structure is adaptive in some tasks, whereas the opposite is the case in other tasks. Thus, the structure and amount of movement variability, together with their relation, is dependent on the confluence of the performer, environmental, and task constraints.

There is also variation in the coupling between body and limb segments in movement as a function of the different time scales of measurement and movement conditions. Enhanced variation in coupling measures, such as relative phase, has been used as an index of the stability of the motor system and the onset of coordination mode changes. On the other hand, in some tasks, enhanced variability but with covariation between effectors can lead to a reduced amount of variation in the movement outcome. Thus, the direction and nature of change in the variability of coordination measures is also specific to the constraints on action and the movement property investigated.

The variability of movement output has also been related to the variability in the output at other system levels, including muscle (EMG), heart (EKG), and brain (EEG). Indeed, many of the measures and outcomes outlined above for the behavioral aspects of movement can also be applied to these other levels of analysis. A central question has been the degree of coherence in the variability across systems in the execution of posture and movement. Experimental findings show the adaptive- and task-dependent nature to this variability relation within a bounded range and that variability can be adaptive as opposed to necessarily a negative process.

Variation and Theories of Motor Control

It is generally presumed that there is noise at all levels of the sensorimotor system, though measures of variability have been limited to only certain levels of analysis during movement and action. Early physiological and psychological accounts of movement variation, such as in tremor, were signal plus noise models in which the noise was additive to the system output. These models tend to accommodate well the findings on the scaling of amount of movement outcome and trajectory variability but not the systematic changes in the time- and frequency-dependent structure of variability. This is because the variability of motor output is clearly not white noise though a very small contribution of white noise is present in the motor output, including that from the experimenter's measuring instrument(s).

A number of recent studies have shown the structure of the different timescales of movement and posture variability to reflect 1/f-like properties. 1/f noise (pink noise) is a signal or process with a frequency spectrum such that the power spectral density is proportional to the reciprocal of the frequency. White noise with equal frequency contributions is $1/f^0$, brown noise is $1/f^2$, and black noise is $1/f^3$. The exponent can take non integer values leading to what is called fractal noise. 1/f-like noises are prevalent in a range of physical systems and they have been increasingly shown in a range of human performance tasks and movement disorders. These estimates of the noise are on the motor output and it is likely that noise in the system is filtered prior to influencing the movement outcome.

The range of 1/f-like scaling processes in movement and posture variability holds a number of theoretical implications for motor control. It provides evidence against the simple signal plus noise additive models of variation, such as those traditionally postulated for tremor. It reveals interesting mixes of deterministic and stochastic processes that need to be examined more directly in movement and posture variability. It is consistent with the idea that noise is multiplicative rather than additive in system control.

A final point to note is that the measures of the time- and frequency-dependent variability in movement and posture have been shown to be more sensitive to change in clinical movement disorder conditions than standard measures of the amount of variability. The faster time scale of moment-to-moment variation in movement execution reflects a different time scale of influence to the variability of performance than the between-trial variation. In summary, the study of intraindividual variation in movement and posture is revealing new insights into motor control and movement disorders.

See also: Tremor.

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Jumping Frenchmen of Maine

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Glossary

Coprolalia – Pathological use of foul language.
Culture-specific syndrome – Forms of abnormal behavior restricted in distribution to defined racial or social groups, discrete areas of the world, or particular historical periods.
Echolalia – Pathological repetition of words just spoken.
Echopraxia – Pathological repetition of the acts of other people.

Definition and History

The Jumping Frenchmen of Maine was first mentioned in an article in the *Journal of Nervous and Mental Disease* from 1880, written by the American physician George Beard. Dr. Beard described 50 cases of French Canadians from the Beauce region, living in the Moosehead Lake region in Maine. According to Beard, the individuals were not able to prevent themselves from starting, striking, dropping, jumping, and repeating words or sounds once another person startled them with sudden exclamations or commands. Some, when addressed quickly in a language foreign to them, would echo the phrase, even to the point of quoting from the Odyssey or Iliad. If one person was suddenly asked to strike another, he would do so without hesitation, even when it was his mother and he had an axe in his hand. Beard felt that the disorder was a 'fixed psychological state,' 'a survival of habits,' and 'a remarkable demonstration of involuntary life.'

The symptoms and classifications of presently living subjects are very similar to Beard's description. The Jumping Frenchmen of Maine is a syndrome consisting mainly of nonhabituating excessive startle responses combined with various behavioral responses like *echolalia*, *echopraxia*, suggestibility, and 'forced obedience' (involuntary, immediate obedience to commands). As the features of the matching behavior and forced obedience are prominent, the Jumping Frenchmen of Maine is also referred to as startle-matching syndromes. There are several other similar syndromes, for example, Latah in Indonesia/Malaysia and Myriachit in Siberia. The clinical details of the three syndromes are given in **Table 1**. For each society affected, the presentation of characteristics varies only slightly. In addition to these three syndromes, there are other rare entities like 'Yaun of Burma,' 'Bah-Tsche of Thailand,' 'Mali-Mali in the Philippines,' 'Lapp panic,' 'The raging Cajuns of Louisiana' (related to the Jumpers of Maine'), 'Ainu in Japan,' 'Leaping ague of Scotland,' 'Tigretetier of Abessynia,' 'Imanenjana of Madagascar,' etc. However, as the literature contains no recent references to them, these syndromes are mainly of historical interest. The Jumping Frenchmen of Maine and other culture-specific startle syndromes are most often classified as a neuropsychiatric startle syndrome, although some authors claim that they are merely cultural phenomena.

Epidemiology

There is no information available other than that the condition is very rare; less than 70 cases have been described. A decreased prevalence of the present-day Jumping Frenchmen of Maine compared with that of the earlier times has been attributed to the reduced boredom and isolation experienced by the lumberjacks.

Pathophysiology

Jumping Frenchmen of Maine, Latah, and Myriachit present with an excessive startle or startle-like response,

Table 1 Culture-specific startle disorders

	Jumping Frenchmen of Maine	*Latah*	*Myriachit*
Gender	M > F	F > M	F > M
Onset	Childhood	Adult	Adult
Familial	Yes	Yes	No
Local terms	Yes	Yes	Yes
Excessive startle-like response	+	+	+
Coprolalia	?	+	?
Echolalia	+	+	+
Echopraxia	+	+	+
Forced obedience	+	+	+

M = male, F = female.

echolalia, *echopraxia*, and forced obedience (involuntary, immediate obedience to commands). Only descriptive, but neither functional nor electrophysiological, studies have been performed in these patients. The neurophysiological background of the excessive startle responses remains, therefore, largely unknown.

The onset, occurrence, and nature of the symptoms in the culture-specific syndromes seem to be influenced by both psychological and cultural factors. There is an ongoing debate on whether culture-specific startle syndromes should be seen as behavioral phenomena belonging in the cultural or anthropological realm or whether they represent a somatic neuropsychiatric disorder in which only the actual expression is open to local cultural influences. There is a striking cross-cultural similarity of behaviors of startle syndromes. The Latah paradox is a term first used by Geertz and refers to the contrast of the connection between Latah behavior and the norms of Malayo–Indonesian culture on the one side and the occurrence of similar syndromes in completely different cultures on the other side. Therefore, in general, an underlying universal neuropsychiatric basis is likely. Gilles de la Tourette saw resemblance between the Jumping Frenchmen of Maine and the syndrome to date known as Gilles de la Tourette. He suggested that the syndromes shared a similar etiology. Nowadays we know that tics are suppressible, in contrast to the initial startle response in culture-specific startle syndromes. However, although a nonhabituating startle response is described to be part of the jumping syndrome this has not yet been confirmed with electromyographical studies. Therefore, similarities in etiology of Gilles de la Tourette and culture-specific startle syndromes should not be ruled out. Yap compared culture-specific startle syndromes with reflex-like fright reactions in German soldiers in the First World War. Heightened arousal or anxiety elicits exaggerated startle responses, and therefore, may indeed explain the symptoms. Accordingly, anxiety or mood disorder symptoms and negative or intense life events are associated with the onset of culture-specific startle syndromes. However, the behavioral features related to the startle response of patients with culture-specific startle syndromes are clearly more complex than in patients with anxiety disorders. The initial brainstem-mediated motor startle response phase, which is roughly uniform from time to time and from individual to individual, is followed by a secondary phase occurring at a longer latency, which shows more variation. This secondary phase contains variable, more complex behaviors, possibly under the influence of psychological factors. It consists of orienting toward the stimulus source by postural adjustments and autonomic changes and may include emotional and voluntary components. A prolonged series of 'orienting' and even vocalizations following a startle response is common and considered normal. Culture-specific startle syndromes may be an abnormal exaggeration of the late, secondary phase of the startle response. Accordingly, a recent observational study described that the startle-associated behavior such as echolalia and forced obedience can be suppressed. (like tics in Gilles de la Tourette). There is evidence suggesting that an exaggerated startle response can be part of a learned response. The 'minor' form of hyperekplexia occurs in families of individuals affected with the 'major' form of hyperekplexia, an organic condition. However, clinically, electromyographically and genetically the 'minor' form differs from the 'major' form. Finally, the behavioral symptoms of the culture-specific startle syndromes may be seen as an exaggerated dependency on the environment for behavioral cues. Such behavior, in the form of utilization and imitation behavior, is also observed in frontal lobe syndromes. Frontal dysfunction has the potential for releasing brain-stem centers normally under inhibitory control, for example, circuits within the brainstem.

Specifically for the French Jumpers of Maine, the occurrence of Jumping Frenchmen is related to specific conditions in lumber camps in the nineteenth and the beginning of the twentieth century. That is, as the isolated life of the French–Canadian lumberjacks was quite boring, jumping seemed to have a clear entertaining function. Beard described that after a long day's work, the loggers engaged in mutual tickling, punching, and startling of the fearful, and he thought that this repeated horseplay eventually resulted in the condition.

Clinical Features and Diagnostic Criteria

There are no clear diagnostic criteria other than the clinically stimulus-induced responses. The individuals

startle excessively to unexpected stimuli, and when startled, may jump, scream or swear, throw objects, strike out at objects or others, assume defensive postures, and obey commands (such as 'dance,' 'jump,' or 'run'). *Echolalia* is also common and *echopraxia* has been described. There is some disagreement whether *coprolalia* is part of the syndrome. Therefore, the swearing following a startle in the jumpers may somewhat different from the blurting of obscene language reported to occur in Latah. Some of the behaviors, such as throwing knifes, striking hot stoves, or jumping into fire, were potentially dangerous or injurious. Jumping is elicited by loud noises, sudden gestures or commands, and unexpected physical sensations such as the sudden arrival of someone from behind. The subjects are typically adult male lumberjacks from the Beauce region of Quebec or from Maine. In contrast to Latah in Indonesia/Malaysia, the Jumping Frenchmen of Maine usually starts in childhood. In six of the eight cases described by Saint-Hilaire, the onset coincided with the start of work as a lumberjack. Similar to Latah in Indonesia/Malaysia, anxiety and depressive symptoms are mentioned as comorbidity simultaneously with the onset of the disorder. The startle responses become more exaggerated with increased frequency of startling.

Prognosis

The condition is usually chronic. Beard described the Jumping Frenchmen of Maine as lasting throughout life.

Differential Diagnosis and Diagnostic Work-up Tests

Detailed history taking will exclude hyperekplexia (major form) and other neurological causes of exaggerated startle reflexes. Further, this may reveal the behavioral features typical of culture-specific startle syndromes. EMG studies for the pattern of the startle reflexes in the Jumping Frenchman of Maine have never been performed, and therefore, have no diagnostic value.

A prominent difference with Gilles de la Tourette is that the Jumping phenomenon is externally driven or stimulus-induced. In contrast, the tics in Gilles de la Tourette syndrome are considered to be due to an internal urge. Further, the onset of Gilles de la Tourette is during childhood. Hysterical jumps, pyschogenic startle, and the minor form of hyperekplexia clinically resemble the culture-specific startle syndromes, but are not culture-specific.

Management

In the past, both serotinergic and dopaminergic agents have been suggested with little effect. As culture-specific startle syndromes are considered neuropsychiatric startle syndromes, psychiatric treatment is indicated. There are a few brief reports describing the effect of psychiatric treatment on neuropsychiatric startle syndromes. The excessive startle reflexes of one patient described as 'latah' (although he did not belong to a certain cultural group) were successfully treated by psychiatric therapy including both suggestion (known to be effective in conversion disorders) and exposure elements (known to be effective in anxiety disorders). Similar treatments are described for (other) psychogenic startle syndromes.

See also: H-reflex; Hyperekplexia; Latah; Myriachit.

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Jumpy Stumps and Phantom Dyskinesias

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Glossary

Jumpy stump – Sudden, jerking movements of the amputation stumps, often but not always, associated with stump pain.
Phantom dyskinesias – Involuntary movements that the patient perceives to be occurring in the phantom limb itself.
Segmental myoclonus – Brief, involuntary, twitching, or 'shock-like' contractions of a muscle or muscle group innervated by the affected spinal cord segments or peripheral lower motor neurons.

Definition

Jumpy stumps are 'spasms' or sudden jerking movements of the amputation stump.

Phantom dyskinesias refer specifically to involuntary movements (often choreic) that the patient perceives to be occurring in the phantom limb itself, and not just in the amputation stump.

History

Neurological sequelae after amputation have been well described. Commonly, amputees experience stump pain and phantom limb sensation. Much less frequent are persistent, abnormal movements that occur in the amputation stump. These movements have been referred to as 'spasms,' 'jumping,' or 'convulsive movements' of amputation stumps, or '*trepidation du moignon*.' In 1875, Weir Mitchell compiled a group of patients with abnormal amputation stump movements among amputees from the American civil war. Since that time, there have been a few case reports of these types of movements in the literature. When these cases are published, standardized reporting and follow up are often lacking, leaving many questions regarding these movements unanswered.

Pathophysiology

The pathophysiology underlying jumpy stumps remains poorly understood. Some have suggested that these movements are a form of segmental myoclonus. The mechanisms postulated include injury-related structural reorganization of local neuronal circuitry by axonal sprouting, resulting in disinhibited intraspinal reflex pathways or hyperexcitable motor neurons. Others have suggested that the disorder is due to alterations of either cortical or subcortical central nervous system function. Proponents of the concept that peripheral trauma can induce a centrally organized movement disorder often use the example of the postamputation stump movements to support this concept, postulating that peripheral injury alters the processing of afferent sensory input to central cortical and subcortical structures and leads to central reorganization.

Studies have demonstrated changes in both the somatosensory system and in the motor cortex after amputation. There are several experiments involving both primates and humans that have shown that digit amputation causes the cortical representations of adjacent digits to expand topographically and to occupy most of the cortical territories formerly representing the amputated digit. However, firm evidence defining the mechanism underlying peripherally induced movement disorders is still lacking. While the 'jumpy stump' has always been taken at face value to represent an organic entity, at least one case report in the literature suggests that jumpy stumps may also, at times, be psychogenic.

Risk Factors

Because the literature is so sparse, the prevalence of 'jumpy stumps' is unknown and no risk factors other than amputation have been identified. In the cases reported, common (but not uniform) themes include traumatic amputation, infection of the limb and/or amputation stump, central nervous system trauma, and severe pain preceding development of abnormal movements.

Clinical Features

Typically, postamputation stump movements consist of sudden jerking of the stump associated with severe stump pain although abnormal movements in the absence of pain have been reported as well. 'Jumpy stumps' have been reported in lower and upper extremity amputees and are often characterized by alternating flexion and extension or abduction and adduction of the stump. In three

cases, choreic movements have been described. However, two of these cases had movements, aptly termed 'phantom dyskinesias' and the stump movements occurred in the context of tardive dyskinesias in the setting of D2 blocking agents. These cases not only developed choreic movements of the amputation stump, but they also perceived constant choreic movements of the phantom limb itself.

Postamputation stump movements begin at variable time periods following amputation. Sometimes, they occur in the immediate postoperative period, but they may also develop gradually following a variable latent period, with the longest latency from amputation to development of movements reported as 10 years. Most reports do not comment on whether these movements typically persist during sleep, but in at least some cases, movements occur in both wakefulness and sleep. While jerking can occur spontaneously when the stump is at rest, it is usually precipitated by voluntary movement of the stump, and can be triggered by cutaneous stimuli. In one case, talking provoked the movements. Often there are no alleviating factors but some patients report temporary relief by putting pressure on the stump, such as a 'strong vibration on the thigh.' Other modifying maneuvers include applying counter stimulation on the side opposite, a noxious stimulation, and 'vigorously squeezing' the stump. Intense concentration was temporarily helpful in one report, and in one case, clearly thought to be psychogenic in origin, distraction also resulted in the cessation of abnormal stump movements.

Differential Diagnosis

The differential diagnosis of abnormal movements in the stump is limited. Based on appropriate history, seizures may feature in the differential diagnosis.

Diagnostic Work up

No standardized work up has been defined for jumpy stump. A history and detailed examination should include assessment of distractibility, entrainability, and variability in the amplitude and frequency of the movement. Ancillary studies can include electrophysiology, including electromyography (EMG) and multichannel EMG with back averaging, electroencephalography, and spinal and brain MRI.

Management and Prognosis

In most cases, treatment of the jumpy stump is unsatisfactory. The movements can diminish without intervention over time, but in many, the movements persist unabated. Many previously published cases either do not mention treatment trials or report efficacious treatments. In two case reports by the same author, local and epidural anesthesia were temporarily effective, but multiple other interventions including diphenylhydantoin, diazepam, carbamazepine, lumbar sympathetic blockage, intrathecal saline, and direct injection of saline into the sciatic nerve failed to alleviate either the pain or the movements. More recent single case reports have suggested some level of success with baclofen, clonazepam, doxepin, gabapentin, and topiramate. There is a single report of a patient with stump pain and dyskinesias who benefited from centromedian–parafascicular complex thalamic deep brain stimulation. Spontaneous and complete resolution has been reported in only one patient who developed a jumpy stump 3 days postamputation. The movements began to improve 2 weeks later and by 1 year, they had disappeared entirely.

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Relevant Websites

www.movementdisordrs.org – Movement Disorder Society.

Junctophilin

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Glossary

Afterhyperpolarization (AHP) – Hyperpolarizing potential observed in many neurons following a train of action potentials.
Ca^{2+}-activated K^+ channels – K^+-conducting channels activated by increased cytoplasmic Ca^{2+}; classified as small-conductance (SK), intermediate-conductance (IK), and big-conductance (BK) channels.
Ca^{2+}-induced Ca^{2+} release (CICR) – Ryanodine receptor-mediated Ca^{2+} release from intracellular stores, which is usually activated by Ca^{2+} influx.
Junctional membrane complex (JMC) – An ultrastructure showing close association between the endoplasmic reticulum and the plasma membrane, that is a proposed platform for functional communication among intracellular and cell-surface channels and transporters in excitable cells.
Ryanodine receptor (RyR) – Ryanodine-sensitive Ca^{2+} release channel on the endoplasmic reticulum that is usually activated by increased cytoplasmic Ca^{2+}.
Ryanodine – A plant alkaloid that binds to open ryanodine receptor channels.

Definition and History

Junctional Membrane Complex and Junctophilin

The junctional membrane complex (JMC) is characterized by a close association between the plasma membrane (PM) and the endoplasmic/sarcoplasmic reticulum (ER/SR) in excitable cells, and it is a predicted structural platform for functional crosstalk between ionic channels on both membrane systems. In striated muscle, the SR and the transverse tubule of the invaginated PM form JMCs, called the 'triad' in skeletal muscle and the 'diad' in cardiac muscle. Electron-microscopic analysis has also detected JMCs in other excitable cell types, such as the 'subsurface cistern' in neurons and the 'peripheral coupling' in immature striated muscle and smooth muscle. Of several proteins identified from skeletal muscle triads in our screening, junctophilin (JP) contributes to JMC formation. JP is composed of two major parts: a carboxyl-terminal hydrophobic segment that spans the ER/SR membrane, and a remaining cytoplasmic domain that interacts with the PM (**Figure 1(a)**). MORN motifs of 14 amino acid residues appear eight times in the cytoplasmic region and probably bind to phospholipids as membrane components. Indeed, JP effectively constructs JMC similar to the subsurface cistern and peripheral coupling in an amphibian embryonic cDNA expression system (**Figure 1(b)**). To date, four JP subtypes (JP1–JP4) have been identified in mammalian excitable tissues.

During the contraction of striated muscle, JP subtypes are essential for JMC formation to establish the functional coupling between L-type voltage-gated Ca^{2+} channel subtypes (Cav1.1 and Cav1.2) on the PM and ryanodine receptor subtypes (RyR1 and RyR2) on the SR. JP1 is predominantly expressed in skeletal muscle, and JP1-knockout mice show sucking failure and die immediately after birth. In mutant muscle lacking JP1 showing a deficiency in triad formation, low efficiency in excitation–contraction coupling is observed, that is presumably due to impaired communication between Cav1.1 and RyR1. In cardiomyocytes expressing JP2, functional coupling between Cav1.2 and RyR2 in diads converts the depolarization signal into the cellular Ca^{2+} signal through the Ca^{2+}-induced Ca^{2+} release (CICR) mechanism. JP2-knockout mice exhibit embryonic lethality because of cardiac failure, and the mutant cardiomyocytes exhibit poor formation of the peripheral coupling and random SR Ca^{2+} release likely due to disconnected crosstalk between Cav1.2 and RyR2.

JPs in Hippocampal Pyramidal Neurons

In the central nervous system, both JP3 and JP4 are expressed in all neuronal sites and probably contribute to the formation of the subsurface cistern. Knockout mice lacking either JP3 or JP4 do not show severe abnormalities, suggesting functional redundancy between the subtypes. Although double-knockout mice lacking both JP3 and JP4 (JP-DKO mice) retain normal brain histology, they show severe growth retardation and lethality 3–4 weeks after birth under normal housing conditions. This lethality is likely caused by a feeding defect due to the dysfunction of salivary secretion, because JP-DKO mice can be rescued when their diet is switched from normal pellets to hydrated paste. Mature JP-DKO mice exhibit an aberrant behavior known as the 'foot-clasping reflex,' that has been reported in several mutant animals with neurological defects, including Huntington's disease

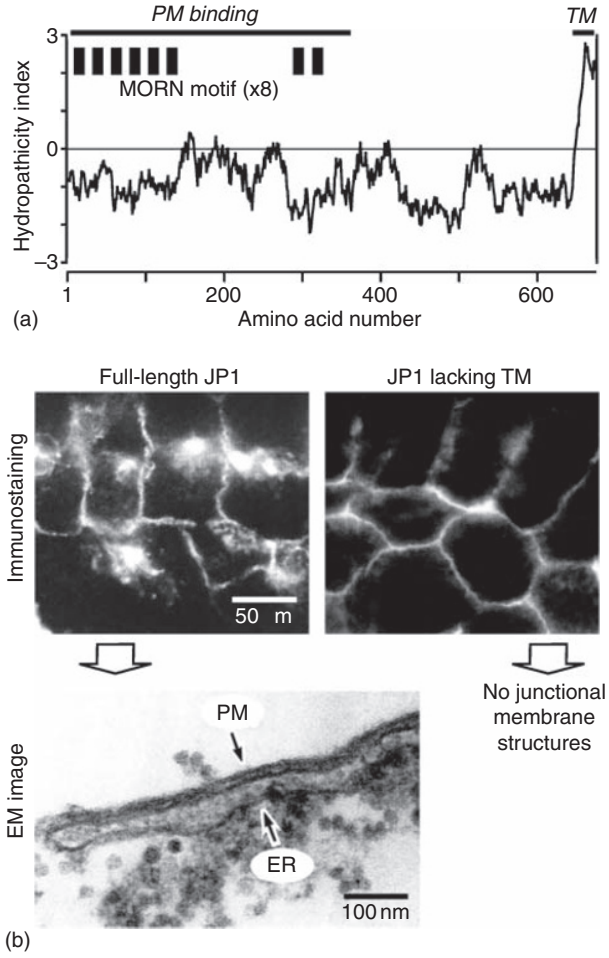

Figure 1 Structure and basic function of JP. (a) Hydropathicity profile of rabbit JP1: the Kyte–Doolittle algorithm with a window size of 19 residues is used for the analysis. MORN motifs for interacting with the PM and the C-terminal transmembrane segment spanning the ER/SR membrane (TM) are indicated. (b) JP-mediated JMC formation: in amphibian embryos injected with the full-length rabbit JP1 cRNA, expressed JP1 was detected at the cell periphery by immunofluorescent staining (upper panels), and JMCs were frequently constructed as shown in the electron-microscopic image (lower panel). When mutant protein lacking the C-terminal transmembrane segment was expressed, this truncated JP1 was detected on the PM but could not construct JMCs.

(HD) model mice. When normal mice are suspended by the tail, their lower limbs remain opened. In contrast, JP-DKO mice always cross their legs when hung upside-down (**Figure 2**). Therefore, JP-DKO mice seem to bear abnormal neural circuits for controlling the salivary and hindlimb reflexes.

JP-DKO mice show impaired performance in learning and memory tasks. Despite a lack of abnormal histological features, hippocampal neurons display corresponding abnormal excitability and synaptic plasticity in JP-DKO mice. CA1 neurons generate the afterhyperpolarization (AHP) phase following action potentials. This phase is

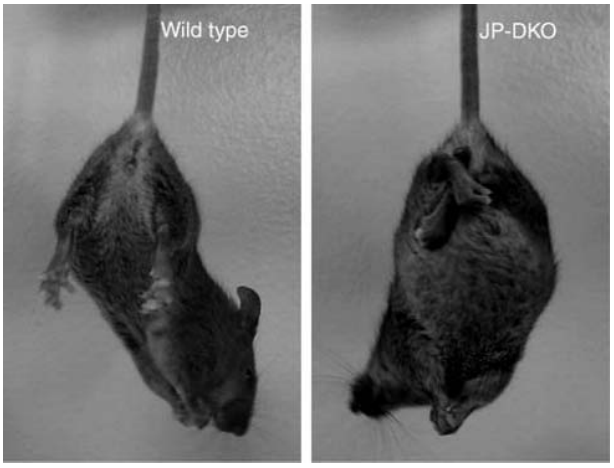

Figure 2 Foot-clasping reflex in JP-DKO mice. When hung upside-down, control mice open their hindlimbs but JP-DKO mice cross their legs.

sensitive to apamin, an inhibitor of small-conductance Ca^{2+}-dependent K^+ channels (SK channels). However, JP-DKO CA1 neurons completely lack apamin-sensitive AHP. Pharmacological examinations indicate that SK channel opening in CA1 neurons requires Ca^{2+} influx through *N*-methyl D-aspartate receptors (NMDARs) and subsequent RyR-mediated Ca^{2+} release. Therefore, NMDAR-mediated Ca^{2+} influx seems to activate RyR-mediated Ca^{2+} release by the CICR mechanism, and then Ca^{2+} released from intracellular stores likely opens SK channels to generate AHP (**Figure 3**). In JP-DKO CA1 neurons, the functional crosstalk between NMDARs, RyRs, and SK channels is probably abolished in under JMC-deficient conditions. On the other hand, long-term potentiation (LTP) in CA1 is closely linked with learning and memory. With an accompanying hyper activation of Ca^{2+}/calmodulin-dependent protein kinase II, a key enzyme for LTP induction, JP-DKO CA1 neurons demonstrate impaired LTP.

JPs in Cerebellar Purkinje Cells

Cerebellum-dependent tasks detect impaired motor coordination and learning in JP-DKO mice. Cerebellar Purkinje cells (PCs) receive distinct types of excitatory inputs from parallel fibers (PFs) and climbing fibers (CFs). Individual PF synapses are weak, but one PC establishes roughly $\sim 10^6$ PF synapses. In contrast, PCs are innervated by single CFs, but CFs form strong excitatory synapses on proximal PC dendrites. The JP-DKO cerebellum retains the normal properties of PF-PC and CF-PC synapses, but it exhibits severe electrophysiological abnormalities in PCs.

CF stimulation elicits a complex spike in PCs, consisting of a fast initial spike, several subsequent slow spikelets, followed by slow afterhyperpolarization (sAHP). However,

JP-DKO PCs lack this sAHP generated by apamin-sensitive SK channels. In addition to SK channels, PCs contain another type of Ca^{2+}-activated K^+ channels known as big-conductance Ca^{2+}-activated K^+ channels (BK channels). Ca^{2+} influx through P/Q-type voltage-gated Ca^{2+} channels activates both SK and BK channels in control PCs, and normal levels of BK channel activity are detected in JP-DKO PCs. Therefore, both Ca^{2+} influx through P/Q-type channels and subsequent Ca^{2+} release through RyRs are essential for the activation of SK channels, whereas Ca^{2+} influx directly activates BK channels (**Figure 3**). It may be that SK and BK channels are localized in distinct cell-surface microdomains, and that neural JPs functionally connect RyRs to SK channels by constructing specific JMC in PCs.

Long-term depression (LTD) at PF-PC synapses is presumably the cellular basis of cerebellar motor learning. After our LTD-inducing conjunctive stimulation (CJS) of CF and PF, the amplitude of PF inputs is consistently decreased by ~25% from the baseline level in control PCs. In contrast, an opposite change in the PF-induced current, recognized as LTP, is induced by the same stimulation in JP-DKO PCs. This reversed synaptic plasticity in the JP-DKO cerebellum is mainly due to sAHP deficiency, because a weak reversion of plasticity can be induced by apamin application to control cerebellar slices.

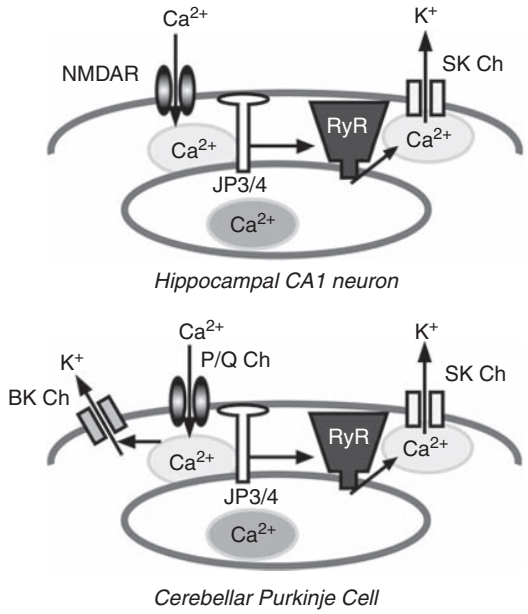

Figure 3 JP-mediated channel communication in neurons. In hippocampal CA1 neurons, JPs support Ca^{2+}-mediated channel crosstalk between NMDARs, RyRs, and SK channels to generate AHP following action potentials. In cerebellar PCs, JPs establish crosstalk between P/Q-type voltage-gated Ca^{2+} channels, RyRs, and SK channels to produce the slow AHP following CF-mediated complex spikelets. In both neurons, the JP deficiency, ryanodine application, or apamin treatment abolishes AHP generation.

In addition to impaired sAHP, the hyper activation of protein kinase Cγ and the altered expression of transcription regulators are predicted in JP-DKO PCs and may further aggravate the reversed plasticity.

HDL-2 and JP3 Gene

Similar to authentic Huntington's disease (HD), Huntington's disease-like 2 (HDL2) is an adult onset, progressive, neurodegenerative, autosomal dominant disorder clinically characterized by abnormal movements, dementia, and psychiatric syndromes. HDL2 is generally rare, accounting for only a few percent of total HD/HDL patients. HDL2 is caused by a CTG/CAG expansion mutation on the JP3 gene, but is not a typical polyglutamine disease. On the basis of the available evidence, HDL2 mutations accompanying triplet repeat expansion might disrupt the functional JP3 gene or reduce gene expression. Our studies demonstrated that JPs are essential for modulating neural excitability and plasticity by providing a structural platform for channel crosstalk. Indeed, JP-DKO mice show abnormal reflexes, motor discoordination, impaired memory, and diminished motor learning. In HDL2 patients, reduced JP3 expression together with age-related neural changes may lead to functional abnormalities, such as unstable membrane potentials or hyperactivation of Ca^{2+}-dependent enzymes. These abnormalities might further induce cell death in a certain set of damaged neurons.

See also: Huntington's Disease: Genetics; Huntington's Disease-like 2; Huntington's Disease.

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Juvenile Myoclonic Epilepsy

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Glossary

Electroencephalogram (EEG) – A recording of electrical activity produced spontaneously by neurons in the brain, commonly used in the diagnosis and management of seizure disorders.
Myoclonic – Large, brief contractions of a muscle or group of muscles such as the arms, legs, or proximal muscles. Myoclonus may be a normal occurrence or, as in the case of juvenile myoclonic epilepsy, a seizure-related finding.
Seizure – Paroxysmal abnormal electrical activity produced by nerve cells in the central nervous system. These discharges may result in overt clinical symptoms or signs which may be experienced by the patient or observed by others.
Tonic–clonic – A type of seizure (also known as 'grand mal') consisting of a phase of tonic stiffening of muscles typically preceding or coinciding with repetitive jerking movements (clonic phase).

Definition and History

Juvenile myoclonic epilepsy (JME) is one of the most common of the idiopathic generalized epilepsy syndromes. It is characterized by myoclonic seizures (which define the disorder), generalized tonic–clonic seizures, and frequently absence seizures. As the name implies, onset is typically in the adolescent years. A clear genetic abnormality associated with JME has been known for some time.

A clinical description of JME was first recorded by Herpin in 1867, describing a 13 year old patient with myoclonic jerks who subsequently developed tonic–clonic seizures. Though similar patients were described by other physicians in the intervening years, it was not until 1955 and 1957 that Janz and colleagues in Germany carefully described a number of cases of JME, labeling the syndrome 'impulsive petit mal' epilepsy. This was subsequently known as JME (of Janz). The international league against epilepsy in 1989 settled on the current term 'juvenile myoclonic epilepsy' which had been proposed by Lund and colleagues several years earlier.

Pathogenesis/Pathophysiology

A genetic basis for JME has long been suspected based on the typically strong family history, with some reports describing up to half of all JME patients having family members with epilepsy. Several genes have been reported in association with JME, though none have been identified in all cases. Several researchers have reported a strong link to abnormalities on the short arm of chromosome 6, and mutations on chromosome 5, 10, and 15 have also been identified. Isolated abnormalities associated with JME have also been described in several cellular ion channels including γ-aminobutyric acid (GABA) receptors and chloride channels. It appears that JME may have a complex and polygenic etiology.

Epidemiology/Risk Factors

JME is the most common of the idiopathic generalized epilepsy syndromes. It is estimated that JME represents

between 4% and 10% of all cases of epilepsy. The prevalence in the general population is estimated at up to 0.1%. However, as it is frequently pointed out, this number may be underestimating the true prevalence as the diagnosis is frequently delayed or missed. Prevalence across all population groups appears similar. There is approximately equal division between males and females, with females having slightly increased risk in some studies. There is a hereditary preponderance in family members of patients with JME being at slightly higher risk of having JME compared with the normal population. The occurrence of other genetic epilepsies in patients' families is common.

Clinical Features and Diagnostic Criteria

The diagnosis of JME is made clinically. Supportive data from testing may be useful but is not always required. As suggested by its name, JME has onset during adolescence, typically between ages 12 and 18 but with a range of 8–30. Myoclonic seizures are the predominant and defining feature, and thus are present in all cases. These consist of sudden, large amplitude jerks, most commonly seen in the arms and upper body. Rarely there may be loss of consciousness with these jerks. They typically occur within 1–2 h of awakening in the morning. Frequently, patients will not think about mentioning these jerks unless specifically asked, leading to delayed or missed diagnoses. In a minority of patients with JME (~2–10%), this may be the only seizure type. However, generalized tonic–clonic seizures occur in the majority (90%) of patients with JME, often months to years after onset of the myoclonic seizures. Usually these seizures prompt a medical evaluation. The tonic–clonic seizures also have a propensity to occur after awakening and sometimes to occur at the end of a cluster of myoclonic seizures. Absence seizures also occur in about a third of patients with JME and have even been reported as occurring prior to the onset of myoclonus in some cases. The absence seizures tend to be relatively mild compared with the typical seizures seen in absence epilepsy of childhood. As with many other seizure disorders, seizures in JME are often precipitated by lack of fatigue and sleep deprivation, stress, alcohol intake, and missed medications.

Patients with JME have normal intelligence, development, and neurological examinations. No decline in neurological status occurs.

Differential Diagnosis

The symptoms of JME can overlap with a number of other epileptic disorders as well as nonepileptic syndromes. Included in the differential diagnosis are the other forms of idiopathic generalized epilepsies (childhood absence epilepsy, juvenile absence epilepsy), epilepsy with generalized tonic–clonic seizures on awakening, absence syndromes, progressive myoclonic epilepsies, epilepsy with myoclonic–astatic seizures, Unverricht–Lundborg disease, frontal lobe epileptic syndromes, and symptomatic localization-related epilepsies.

Diagnostic Work up/Tests

The most helpful diagnostic tool is a thorough and detailed history. Neuroimaging with MRI is typically normal and is often not required, though some studies have shown suggestions of minor cortical developmental abnormalities. The electroencephalogram (EEG) is the diagnostic tool of choice, as there are characteristic findings on the EEG recordings of patients with JME. Bursts of generalized, bisynchronous polyspike, and polyspike-wave discharges are superimposed on a normal or nearly normal electrographic background. The frequency of spike/polyspike-wave discharges is 3.5–6 Hz, which is faster than those seen in childhood absence epilepsy, though they may occasionally occur at slower frequencies. A high proportion of patients (20–40%) with JME demonstrate photosensitivity. Hyperventilation may also trigger epileptiform activity. Both of these findings are diagnostically helpful. During stage II sleep, there is often suppression of discharges, in contrast to many other forms of epilepsy. Myoclonic seizures are invariably associated with bursts of polyspike and polyspike-wave discharges.

Management

Treatment with antiepileptic medication is necessary in JME, and due to the low remission rate, it may need to be continued for many years and possibly for life. Valproic acid, lamotrigine, zonisamide, topiramate, and more recently levetiracetam have been used with success. Lamotrigine in some cases may worsen myoclonus. For many patients, excellent seizure control may be achieved with relatively low doses of antiepileptic medications.

Prognosis

Currently there is no cure for JME. Although antiepileptic drug treatment usually controls the seizures, long term, possibly lifetime therapy appears to be necessary. Unlike the case with some other epilepsies, there is a high risk of recurrence (~80%) with medication withdrawal even after several years of seizure freedom. Avoidance of

excessive alcohol and sleep deprivation is crucial for successful control of seizures.

See also: Cortical Myoclonus; Electroencephalography (EEG); Epilepsia Partialis Continua; Magnetoencephalography (MEG); Myoclonus, Epileptic.

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Juvenile Parkinsonism

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Glossary

Bradykinesia – Slowing of voluntary movements.
Dystonia – Involuntary muscle contractions causing abnormal movements.
Juvenile parkinsonism – Defined as onset of parkinsonian symptoms prior to age 21.
Parkinsonism – A syndrome involving symptoms of rest tremor, rigidity, motor impairment and postural instability.
Parkinson disease – A degenerative disorder of the central nervous system that often impairs the sufferer's motor skills and speech.
Postural instability – Impaired ability to maintain an upright posture.
Tremor – Involuntary oscillatory movements.

Definition and History

Juvenile parkinsonism (JP), first described nearly a century ago, is defined as onset of parkinsonian symptoms prior to age 21. In contrast, young-onset Parkinson disease (YOPD) encompasses those patients with onset of typical parkinsonian symptoms between 21 and 39 years of age. Some sources use the term early-onset parkinsonism to describe onset before age 40. JP is relatively rare and is typically due to secondary or hereditary causes. YOPD is more common and tends to more closely resemble idiopathic Parkinson disease (PD), except for slower progression, longer disease duration and earlier onset of motor fluctuations and dyskinesias.

Pathogenesis/Pathophysiology

JP is a syndrome that encompasses many underlying etiologies; thus, the pathogenesis and pathophysiology will depend upon the specific diagnosis and cannot be succinctly summarized. Rather, the individual diagnoses will be discussed further below in the sections on Differential Diagnosis and Diagnostic Work-up/Tests. Typical Lewy body pathology is rarely observed in JP cases that come to autopsy, suggesting that idiopathic PD is not a common cause of JD.

Epidemiology/Risk Factors

JP comprised 0.6% of 918 parkinsonian patients seen over a 6 year period at a movement disorders center. The mean age of onset was 12.5 with a range from 7 to 19. Incidence of JP has been reported at 0.8 per 100 000 per year for ages 0–29. In another group of 149 patients presenting with apparent idiopathic PD onset prior to age 40, 10 of these patients had onset prior to age 21. The risk of mortality was noted to be threefold that of the general population. A positive family history of parkinsonism was reported in 50% of cases of JP in this group. There was a 4:1 male predominance. The mean age of onset was 17, with a

range of 5–19. JP is reported to occur more frequently in Japan, this is presumed to be due to the high historical rate of consanguinity because of the increased incidence of recessive early-onset parkinsonism.

Clinical Features and Diagnostic Criteria

Cardinal features of JP include bradykinesia, rigidity, and postural instability. Dystonia is a common presenting symptom of JP and tremor is also commonly observed. Non-parkinsonian symptoms such as supranuclear opthalmoparesis, dementia, seizures, myoclonus, diminished reflexes, and pyramidal signs suggest structural causes or one of the childhood encephalopathies. In pure parkinsonian syndromes, dopaminergic medications typically produce improvement of motor symptoms; however, dyskinesias and motor fluctuations tend to occur earlier (after an average of 6 months) and with greater severity than in similarly treated late-onset PD patients. JP patients tend to have relatively preserved cognitive function and postural stability compared to late-onset PD patients with similar disease duration. Dystonia is a presenting symptom in as many as 60% of JP patients, a finding that is probably more common in this group than in YOPD. The onset is with tremor in ~50% of JP patients and with an akinetic-rigid syndrome in 20%. Both JP and YOPD typically have an excellent response to levodopa (L-dopa).

Differential Diagnosis

The differential diagnosis of JP is broad and includes genetic, toxic, metabolic, infectious/inflammatory, and structural causes; these are further discussed below.

Diagnostic Work-Up/Tests

Potentially treatable causes of JP should be ruled out. Screening tests for Wilson disease includes urine and serum copper, serum ceruloplasmin and slit lamp examination for Kayser–Fleischer rings. Dopa-responsive dystonia–parkinsonism can be evaluated by looking for an immediate and impressive resolution of the associated dystonia with L-dopa therapy. Drug-induced parkinsonism may be caused by dopamine-receptor blocking medications such as neuroleptics, antiemetics, certain calcium-channel blockers and others. Structural lesions, such as stroke, tumor, extrapontine myelinolysis and hydrocephalus are rare causes of JP and can be evaluated by brain MRI or CT.

JP without associated atypical non-parkinsonian features is likely to be genetic in nature. The most common genetic cause of JP is a mutation in the *Parkin* gene (PARK 2), with 77% of JP cases found to have a *Parkin* mutation in one study. Other mutations known to cause JP, albeit less commonly, are *PINK1* (PARK6) and *DJ1* (PARK7), both of which are autosomal recessive. Commercial testing is available for *Parkin* and *PINK1*.

Other genetic causes of JP, particularly when there are associated atypical features, include Huntington disease (Westphal variant), spinocerebellar ataxia (SCA 2 and 3), neuroacanthocytosis, rapid onset dystonia-parkinsonism, X-linked dystonia-parkinsonism (Lubag), mitochondrial disorders, Niemann Pick type C, juvenile neuronal ceroid lipofuscinosis, Gaucher's disease, neurodegeneration with brain iron accumulation, neuroferritinopathy, cerebrotendious xanthanomatosis, and Fahr's syndrome.

Management

In those with secondary causes, treatment should first be tailored to the underlying cause. Symptomatic treatment of the component of parkinsonian symptoms is also indicated in those cases. Medications used in the treatment of idiopathic PD may be employed, with adjustment to pediatric dosing as required. Anticholinergics (trihexyphenidyl, benztropine) may be particularly helpful in cases with prominent dystonia. L-dopa in combination with a dopa decarboxylase blocker (carbidopa or benserazide) is the gold standard dopaminergic medication; however, it is associated with a higher incidence of dyskinesias and motor fluctuations than dopamine agonists, such as pramipexole and ropinirole. Dopamine agonist use has been associated with excessive daytime somnolence and neuropsychiatric complications, such as psychosis and impulse control disorders, although L-dopa can also cause these side effects. A trial of amantadine, selegiline or rasagiline (the latter two being monoamine oxidase B inhibitors) can be considered for early, mild symptoms or later as an adjunct to L-dopa or a dopamine agonist. Entacapone and tolcapone (catechol-*O*-methly transferase inhibitors) prolong the duration of L-dopa response, but tolcapone requires liver function monitoring.

Anti-parkinsonian medications can cause multiple side effects, including orthostasis, nausea, sedation, confusion/mental status changes, dyskinesias, motor fluctuations, and psychosis. Orthostatic hypotension may respond to dietary salt supplementation, fludrocortisone, or midodrine. Nausea can be treated with additional carbidopa or domperidone. Modafinil is useful to combat sedation. Psychosis and hallucinations may respond to atypical antipsychotics, such as quetiapine or clozaril; however, clozaril requires frequent monitoring due to the risk of agranulocytosis. Clozaril and amantadine may help control dyskinesias. Motor fluctuations and dyskinesias may improve with smaller, more frequent L-dopa doses. A reduction in total dosage of anti-parkinsonian medications may ultimately be necessitated by intractable side effects.

Surgical treatment of JP has not been systematically studied. Deep brain stimulation surgery has been shown to be effective in the treatment of adults with both Parkin-related and idiopathic PD and is also used in the treatment of dystonia.

Prognosis

As discussed above, mortality is significantly increased compared to the general population. Initial response to dopaminergic medications is good; however, efficacy is often limited by early and severe dyskinesias and motor fluctuations. As in all forms of parkinsonism, disability supervenes over time. After a mean disease duration of 6.5 years, 83% of JP patients were recently found to require assistance with activities of daily living. Data on JP is somewhat limited due to its relative rarity. Patients with early-onset parkinsonism have a shorter life expectancy than those with late-onset PD. Elucidation of the specific etiology underlying a particular case of JP allows a more definitive statement regarding expected morbidity and mortality.

See also: DYT6, Mixed Phenotype Primary Dystonia; Huntington's Disease; PARK2, parkin; Parkinson's Disease: Definition, Diagnosis, and Management; Wilson's Disease.

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http://www.yopa.org – Young Onset Parkinson's Association.

K

Kainic Acid Model of Dystonia

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Motor Phenotype

Low-dose microinjections of kainic acid into the cerebellum induce a motor disorder in both rats and mice that closely resembles generalized dystonia in humans. Approximately 10–20 min after injection, mice exhibit transient hindlimb adductions that are generally preceded by volitional movements. Shortly thereafter, the dystonic movements become sustained and spread to involve the entire body to include the trunk, forelimbs, head, neck and even tail. Truncal flexion often causes the perineum to be pressed downward while the hindlimbs frequently exhibit paddling motions. Furthermore, although kainate is commonly used to induce seizures in rodents, no abnormalities are detected with EEG following intracerebellar microinjections of kainate, which is inconsistent with epileptic seizures.

Neuroanatomy

The dystonia observed in rodents following cerebellar microinjections of kainate arises from the local effects of the drug, since injections into other brain regions do not induce the dystonia. Moreover, microinjections of kainate into the cerebellar vermis result in bilateral dystonia, but injections into the cerebellar hemispheres generate ipsilateral symptoms, consistent with the ipsilateral wiring of the cerebellum. Furthermore, kainic acid does not induce dystonia in mice lacking Purkinje cells, demonstrating that output from the cerebellar cortex is necessary for expression of the dystonia.

Kainate-induced dystonia likely results from a gross distortion of cerebellar output. Assessments of c-*fos* mRNA expression demonstrate that the dystonia is associated with abnormal increases in neuronal activation almost exclusively within the cerebellum and the red nucleus, which is a prominent efferent target of the deep cerebellar nuclei. In contrast, the striatum exhibits significant decreases in both neuronal activation and extracellular dopamine levels. Partial lesions to the striatum exacerbate the dystonia in this model, arguing that the basal ganglia may actually exert a protective influence in cases of dystonia originating from cerebellar dysfunction.

Neurochemical Mechanisms

Kainate-induced dystonia is dose and time dependent. The dystonia produced by 25 $\mu g\ ml^{-1}$ is mild to moderate, whereas the dystonic postures produced by 100 $\mu g\ ml^{-1}$ are much more severe and prolonged. The dystonia probably does not arise from a mechanism involving excitotoxic cell death, as injections over consecutive days reliably induce the disorder (**Figure 1**). Furthermore, the doses of kainic acid that kill neurons are 10-fold higher than those used to elicit dystonia.

Kainic acid, which is a potent agonist at AMPA and kainate-sensitive glutamate receptors, likely elicits dystonia through excessive excitation of glutamatergic signaling within the cerebellum. Indeed, intracerebellar administration of domoic acid, another glutamatergic agonist, also induces generalized dystonia. The dystonia does not arise from simply perturbing glutamatergic signaling within the cerebellum, as microinjections of NBQX, a kainate and AMPA receptor antagonist, do not elicit the disorder. However, coadministration of the glutamatergic antagonist with kainate prevents the induction of dystonia, indicating that excessive activation of glutamate signaling within the cerebellum is necessary to produce the dystonia.

See also: Dystonia; Dystonia in Amish-Mennonite and Mennonite Families; Dystonia, Task-specific; Dystonia, Traumatic; Dystonic Storm; DYT1; DYT2, Autosomal Recessive Generalized Dystonia; DYT3, X-linked Dystonia-parkinsonism (Lubag); DYT4, Autosomal Dominant Type Dystonia or Whispering Dysphonia; DYT5; DYT6, Mixed Phenotype Primary Dystonia; DYT7, Autosomal

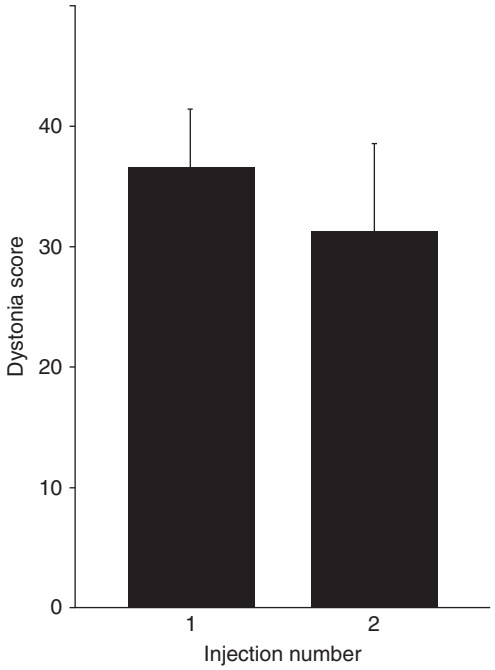

Figure 1 Repeated intracerebellar microinjections of kainate reliably induce dystonia in mice. Mice (n = 3) with implanted cannula were administered 0.5 μl of 100 μg ml^{-1} kainic acid on two consecutive days. Mice were scored for the severity of dystonia once every 10 min over a 2 h time period following injection whereby 0 = normal motor behavior; 1 = slightly slowed or abnormal movements; 2 = mild impairment, limited ambulation unless disturbed or transient abnormal postures; 3 = moderate impairment, limited ambulation unless disturbed and frequent abnormal postures; 4 = severe impairment, almost no ambulation and sustained abnormal postures. The mean dystonia severity scores were not statistically different (Student's t-test; $p > 0.5$).

Dominant Focal Dystonia; DYT11, DYT15, Myoclonus-dystonia; DYT12, Rapid Onset Dystonia-parkinsonism; DYT13, Cranio-Cervical-Brachial; Generalized Primary Torsion Dystonia.

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Kayser–Fleischer

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Introduction

The Kayser–Fleischer ring is an ocular finding defined by a pigmented ring of copper deposition in the peripheral corneal secondary to a dysfunction in copper metabolism. The most common systemic condition associated with a Kayser–Fleischer ring is Wilson's disease; however, this finding has been reported in other hepatic disorders and with intraocular copper foreign bodies.

Background

A brownish pigment in the corneal periphery was first described by Bernhard Kayser in 1902 in a patient with

multiple sclerosis. In 1912, Bruno Fleischer linked the peripheral coloration to Wilson's disease. The composition of the corneal deposits was first thought to be related to a breakdown in hemoglobin. Heavy metal deposition then became the leading theory as silver and copper were found in large amount in the viscera of patients with Wilson's disease. In 1936, Policard, Bonnet, and Bonnamour demonstrated the absence of silver and the sole presence of copper in the area of peripheral corneal pigmentation in patients with Wilson's disease. This work was supported by others including Harry and Tripathi in 1970 using electron microscopy to demonstrate copper deposition in the corneal periphery of a patient with Wilson's disease.

Ocular Anatomy

The cornea is an optically clear lens located in the anterior globe which bends and directs light to the posterior retina. Histologically, it is composed of five layers: epithelium, Bowman's layer, stroma, Descemen's membrane, and endothelium. The epithelium functions as a barrier and provides a smooth refractive surface to refract light. Bowman's membrane is made up of type I collagen and is found between the epithelium and stroma. The stroma is the thickest layer and is composed of collagen, keratin sulfate, glycosaminoglycans, and numerous cells including keratocytes, melanocytes, and Langerhans' cells. Below the stroma, Descemen's membrane is a basement membrane composed of type IV collagen secreted by the endothelium. The endothelium is a monolayer of cells that actively pumps water out of the stroma and keeps the cornea clear. It is in the posterior lamella of Descemen's membrane that copper is deposited to form the Kayser–Fleischer ring.

Copper Physiology

Copper is absorbed by cells in the small intestine. Approximately 25–60% of ingested copper is absorbed by the gastrointestinal system and transported to the liver by the portal vein. Copper is taken up by hepatocytes in the liver and is acted upon by the transmembrane protein ATPase ATP7B encoded by the gene *ATP7B*. ATP7B has at least two functions related to copper metabolism. One is to transport intracellular copper into the Golgi apparatus where it is incorporated into plasma protein to form ceruloplasmin. Copper, as part of ceruloplasmin, accounts for 90–95% of plasma copper. ATP7B also acts intracellularly to transport copper to the bile canaliculus for excretion into bile. Thus, the ATP7B transporter has dual synthetic and excretory roles in copper metabolism. In the eye, copper is found in the aqueous humor, which fills the anterior chamber, at a concentration equal to that of plasma ($\sim$1 mg ml^{-1}).

Pathophysiology

As stated above, the most common condition associated with a Kayser–Fleischer ring is Wilson's disease. Wilson's disease is an autosomal recessive disorder of copper metabolism characterized by hepatic and neurologic disease. It is caused by a defect in the *ATP7B* gene which as described above codes for the ATP7B protein that is essential for the incorporation of copper into ceruloplasmin and excretion of copper into bile. Without proper functioning of this protein, copper begins to accumulate in the liver in toxic levels. Toxic injury occurs by formation of free radicals, binding of sulfhydryl groups to cellular proteins, and displacing other metals in hepatic metalloenzymes. This can lead to fatty changes, acute hepatitis, chronic hepatitis, cirrhosis, and liver necrosis. Once the liver is saturated, nonceruloplasmin bound copper begins to spill into the systemic circulation and accumulates in other tissues such as the brain, eye, and kidneys. It is believed that the source of copper found in the Kayser–Fleischer ring comes from the aqueous humor in the anterior chamber of the eye and is either passively or actively introduced by the endothelial cells into Descemen's membrane.

Other hepatic disorders that cause a rise in unbound copper and intraocular containing copper foreign bodies are presumed to have a similar mechanism of creating a pigmented peripheral corneal ring.

Clinical Findings

Wilson's disease may present with symptoms related to hepatic dysfunction, neurologic dysfunction, or a combination of both. Hepatic disease may manifest with signs of coagulopathy or encephalopathy. Ascites, portal hypertension, and splenomegaly may be presenting signs of cirrhosis. Neurological dysfunction may present with behavioral changes, psychosis, or mild dementia and seizures. Often a Parkinson's like picture is evident or other movement disorder; these are generally the first signs and symptoms that present as copper deposits in the liver and brain. Ocular findings may not be present at this time.

The timing of ophthalmic findings in Wilson's disease is variable. Often changes in the cornea can only be seen by slit lamp examination or using a specially designed goniolens to examine the very corneal periphery. Liver stores must be saturated before copper begins to deposit in other tissues: this fact may be the reason that not all patients with hepatic dysfunction and a diagnosis of Wilson's disease have a Kayser–Fleischer ring on exam.

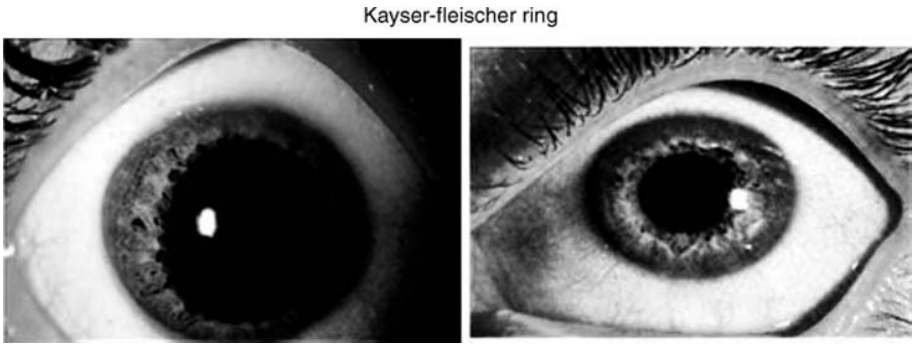

Figure 1 Peripheral corneal deposition as seen in Kayser-Fleischer ring.

Figure 2 Classic Kayser-Fleischer ring.

However, by the time most patients develop neurological dysfunction, a Kayser–Fleischer ring can be observed. The ring can appear to be different colors but generally it is described as golden brown, dark red, or green in pigmentation. The deposits often begin in the superior cornea first, then the inferior cornea, and extend until the full circumference of the peripheral cornea is affected. The deposition begins in the far periphery and extends centrally. As the disease is treated and the copper levels decrease, the ring can fade and even disappear.

Other conditions that should be considered include primary biliary cirrhosis, hepatitis, cryptogenic cirrhosis, multiple myeloma, alcoholic liver disease, and intraocular copper foreign body. A pigmented peripheral corneal ring has been reported in each of these diseases. However, only Wilson's disease has decreased levels of ceruloplasmin and the unique neurologic symptoms described above.

Treatment

The copper deposition in the cornea does not interfere with the function of the eye and as such, treatment is not aimed at eliminating the Kayser–Fleischer ring. The ring is a sign of elevated copper levels due to a disruption in copper metabolism and therapy is directed at correction of the underlying disorder and at reducing systemic copper levels.

See also: DYT4, Autosomal Dominant Type Dystonia or Whispering Dysphonia; Wilson, Samuel Alexander Kinnier; Wilson's Disease.

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Kernicterus

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Glossary

Exchange transfusion – Simultaneous withdrawal of the recipient's blood and transfusion with the donor's blood in the treatment of extreme hyperbilirubinemia.
Hyperbilirubinemia – The presence of an excess of bilirubin in the blood.
Jaundice – Yellowish pigmentation of the skin, tissues, and body fluids caused by the deposition of bile pigments.
Kernicterus – A rare neurological disorder that occurs in some newborns with severe hyperbilirubinemia, marked by the deposition of bile pigments in the nuclei of the brain and spinal cord and by degeneration of the nerve cells.
Phototherapy – The application of light for therapeutic purposes.

Definition and History

The term kernicterus was initially applied to the yellow staining of the basal ganglia found at the autopsy of severely jaundiced infants who died with severe erythroblastosis fetalis. Currently, the term kernicterus has come to be used interchangeably with both the acute and chronic findings of bilirubin encephalopathy. To avoid confusion, the American Academy of Pediatrics (AAP) recommends that in infants the term 'acute bilirubin encephalopathy' be used to describe the acute manifestations of bilirubin toxicity seen in the first weeks after birth, and that the term 'kernicterus' be reserved for the chronic and permanent clinical sequelae of bilirubin-induced neurologic dysfunction (BIND).

Pathogenesis/Pathophysiology

Benign jaundice is observed during the first week of life in ~60% of term infants and 80% of preterm infants. Some infants, however, may experience extreme hyperbilirubinemia, which can result in kernicterus, if not recognized and treated vigorously. Kernicterus is a disease of the infants because of their immature blood–brain barrier, which normally protects older children and adults from the devastating effects of extreme hyperbilirubinemia. The efficacy of the blood–brain barrier may be further diminished by disease, asphyxia, and other factors.

The pathogenesis of kernicterus is multifactorial and involves an interaction between unconjugated bilirubin levels, albumin binding, passage across the blood–brain barrier, pH, and neuronal susceptibility to injury. Laboratory investigations have demonstrated that bilirubin is neurotoxic at a cellular level. The potential mechanisms for bilirubin neurotoxicity are impairment of glucose utilization, oxidative stress, impairment of DNA and protein synthesis, and others. Bilirubin staining can be noted on autopsy in basal ganglia, particularly globus pallidus and subthalamic nucleus, hippocampus, substantia nigra, dentate nuclei, cerebellar vermis, and cranial nerve nuclei (such as the oculomotor, vestibular, and cochlear). Neuronal injury corresponds closely to the distribution of bilirubin staining, but nonpigmented areas may also be damaged, characterized by neuronal loss, reactive gliosis, and atrophy of involved fiber systems. Conversely, bilirubin staining may be present but unrelated to bilirubin toxicity.

Epidemiology/Risk Factors

The exact incidence of kernicterus is not known. A few European population-based studies reported the incidence to be in the range between 1/100 000 and 1.4/100 000.

The exact blood level above which free (not bound to albumin) unconjugated (indirect) bilirubin will be toxic for an individual infant is not known. Approximately 1 in 650–1000 infants, >35 weeks of gestation, develop serum bilirubin values of $\geq$427 μmol l^{-1} ($\geq$25 mg dl^{-1}), and ~1 in 10 000 have levels of $\geq$510 μmol ($\geq$30 mg dl^{-1}). In otherwise healthy infants, extremely high total serum bilirubin levels of more than 30 mg dl^{-1} are known to cause kernicterus, but the risks associated with less extreme elevations of total serum bilirubin levels seem to be minimal.

Race (more in Caucasian) and sex (more in male infants) influence risk of bilirubin encephalopathy. The more immature the infant is, the greater is the susceptibility to bilirubin encephalopathy. The duration of exposure needed to produce toxic effects is unknown.

Table 1 Clinical signs of acute and chronic bilirubin encephalopathy

Presentation	*Timeframe*	*Signs*
Acute	Phase 1 (first 1–2 days)	Hypotonia, poor sucking, stupor, seizures
	Phase 2 (middle of first week)	Hypertonia of extensor muscles, opisthotonos, retrocollis, fever
	Phase 3 (after first week)	Hypertonia, high-pitched cry
Chronic	First year	Hypotonia, active deep tendon reflexes, obligatory tonic neck reflexes, delayed motor skills
	After first year	Movement disorders (athetosis, chorea, ballismus, dystonic posturing, tremor), gaze disturbances, sensorineural hearing loss

Source: Dennery PA, Seidman DS, and Stevenson DK (2001) Neonatal hyperbilirubinemia. *New England Journal of Medicine* 344: 581–590.

Among infants reported in the US kernicterus registry, glucose-6-phosphate dehydrogenase deficiency was diagnosed in 26 of 116 infants (22%); severe hemolytic processes were identified in 22 infants (19%), birth trauma in 17 infants (15%), and other causes such as galactosemia, Crigler–Najjar syndrome, and sepsis were diagnosed in eight infants (7%). In 43 infants (37%), no etiology for the severe hyperbilirubinemia was discovered.

Clinical Features and Diagnostic Criteria

The early signs may be subtle and indistinguishable from those of sepsis, asphyxia, hypoglycemia, intracranial hemorrhage, and other acute systemic illnesses in a neonate. Although the majority of the affected infants exhibit neurological signs, 15% of infants with proven kernicterus will not demonstrate neurological abnormalities in the neonatal period.

The clinical signs (**Table 1**) of acute bilirubin encephalopathy usually occur within the first week of life. Infants present with lethargy, hypotonia, paucity of movement, and poor suck. Subsequently, the infant may appear severely ill and irritable, with increased muscle tone, which can evolve to opisthotonos. The cry is usually high-pitched. In advanced cases, stupor or coma and persistent increased muscle tone occur. The infant with acute bilirubin encephalopathy may also present with seizures. In the first year of life, the survivors of the acute phase of bilirubin encephalopathy exhibit hypotonia (evolving from neonatal hypertonia), pronounced deep tendon reflexes, persistent and obligatory tonic neck reflex, and delayed motor development. The clinical picture of chronic bilirubin encephalopathy may take several years before it becomes fully developed. The major features include extrapyramidal movement abnormalities (athetosis, chorea, ballismus, dystonic posturing, tremor), gaze disturbances (especially of upward gaze), bilateral high-frequency sensorineural hearing loss, and intellectual deficits. Chorea develops earlier in kernicterus than after hypoxic-ischemic encephalopathy.

Table 2 Differential diagnosis of kernicterus

Bacterial meningitis
Cerebral palsy
Fetal alcohol syndrome
Head trauma
Hearing impairment
Herpes simplex virus infection
Hyperammonemia
Hypoglycemia
Hypothyroidism
Hypoxic-ischemic brain injury in the newborn
Intracranial hemorrhage
Periventricular leukomalacia
Sepsis

Differential Diagnosis and Diagnostic Work-up/Tests

Evaluation of the hematologic parameters is the cornerstone of evaluation of an infant with hyperbilirubinemia and identification of infants who are at risk for brain injury due to bilirubin toxicity. Total and direct bilirubin, blood type, complete blood cell count, reticulocyte count, direct Coombs test, and serum electrolytes are recommended. Sepsis can be excluded by evaluating inflammatory parameters such as C-reactive protein or procalcitonin and lumbar puncture. **Table 2** lists differential diagnoses of kernicterus.

The value of ultrasound and computed tomography is limited in evaluation of newborns with bilirubin encephalopathy, but brain MRI is of major value in evaluation of acute and chronic period of bilirubin encephalopathy. The posteromedial aspect of the globus pallidus is bilaterally affected in more than 90% of cases (**Figure 1**), a finding present in both acute and chronic phases. Subthalamic nuclei and hippocampi may be affected as well. MR spectroscopy provides additional data in the acute period.

Brainstem auditory evoked response is of great value for the early detection of hearing loss.

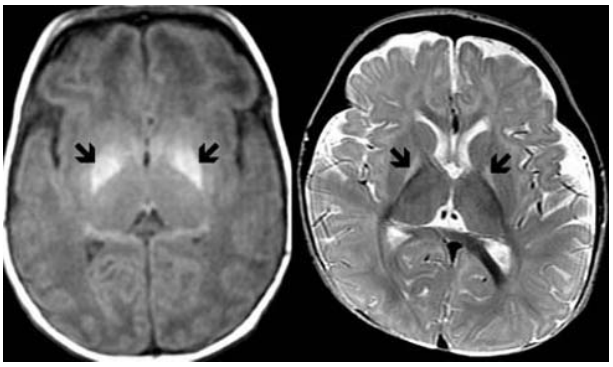

Figure 1 MRI images of a 9-day old infant with acute (left; T1) and an 8-month old infant with chronic (right; T2) bilirubin encephalopathy. The typical findings of bilateral signal change in posteromedial aspect of the globus pallidus (arrows) are present in more than 90% of infants with bilirubin encephalopathy. Courtesy of Dr. A James Barkovich.

Management

The essential aspect of kernicterus management is the prevention and early detection of the infant at risk for brain injury caused by bilirubin. Phototherapy and, if unsuccessful, exchange transfusion remain the primary treatment modalities used to keep the maximal total serum bilirubin below the pathologic levels. The risk of injury to the central nervous system (CNS) from bilirubin must be balanced against the potential risk of treatment. The AAP has published guidelines on the bilirubin level at which phototherapy or exchange transfusion in infants of $\geq$35 weeks of gestation has to be initiated (see Further Reading).

Exchange transfusion is not effective in improving neurological outcome when bilirubin levels are in the region of 35–40 mg dl^{-1}. In fact, neurological signs may become more prominent in these individuals if treated with exchange transfusion. Enhanced deposition of unconjugated bilirubin in the CNS is thought to result from decreases in blood albumin concentration during the exchange transfusion.

Treatment with intravenous immunoglobulin (IVIG) reduces jaundice in many cases of neonatal isoimmunization. The recommended dose of IVIG is 500 mg kg^{-1} infused over a 2-h period.

A potentially important alternative pharmacological therapy is the use of metalloporphyrins (e.g., tin-mesoporphyrin (SnMP)) for hyperbilirubinemia. The use of bilirubin oxidase, an enzyme that degrades bilirubin to biliverdin, dipyroles, and other products is still experimental, but has shown some promise.

The AAP has identified potentially preventable causes of kernicterus: (1) early discharge (<48 h) with no early follow-up (within 48 h of discharge), (2) failure to check the bilirubin level in an infant noted to be jaundiced in the first 24 h, (3) failure to recognize the presence of risk factors for hyperbilirubinemia, (4) underestimation of the severity of jaundice by clinical (visual) assessment, (5) lack of concern regarding the presence of jaundice, (6) delay in measuring the serum bilirubin level despite marked jaundice, or delay in initiating phototherapy in the presence of elevated bilirubin levels, and (7) failure to respond to parental concern regarding jaundice, poor feeding, or lethargy.

Prognosis

In the kernicterus registry mentioned above, 5 of 115 (4.3%) patients died. The number of patients who died from kernicterus without being reported to the registry is unknown, as is the experience in countries other than the United States. Of patients reported to the kernicterus registry, 92 of 110 survivors (84%) had severe sequelae due to BIND; 9 of 110 babies (8%) had no discernible sequelae after the age of 1 year.

See also: Athetosis; Chorea; Dystonia; Tremor.

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Kinesia Paradoxica

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Glossary

Akinesia – Akinesia ('without movement') is the inability to initiate movement often associated with parkinsonism.
Akinesia paradoxica – A temporary increase in akinesia with levodopa therapy.
Kinesia paradoxica – A sudden and temporary disappearance of akinesia in the face of an immediate threat of catastrophe; also may be an improvement in motor performance with increasing motivation.

Definition and History

Kinesia paradoxica is a motor phenomenon, occasionally observed in Parkinson's disease (PD) patients, that is characterized by a sudden and temporary disappearance of akinesia during a threat of catastrophe or sudden shock. It may also be defined as an improvement in motor performance with increasing motivation. It is distinguished from akinesia paradoxica, the latter referring to a temporary increase in akinesia with levodopa therapy.

The phrase was first coined by Bing in 1923 and expanded upon by Kinnier Wilson in 1925. Several vivid examples, such as one patient described by Schwab, demonstrate the sudden ability of a parkinsonian subject to move when faced with a natural disaster:

> A 61-year-old woman with advanced bilateral, totally disabling Parkinson's disease had become restricted to a wheel chair existence, requiring full time attendance of her daughter and nurse in the home where a 1-year-old grand-daughter resided. The patient lived on the second floor of the house. One night while the infant's parents were away briefly, the house caught fire, burning briskly with great columns of smoke. The patient jumped out of her wheel chair, grabbed the baby in her arms and ran down the stairs to the arriving firemen, and then collapsed back to her state of total invalidism.

Pathogenesis

The pathogenesis of kinesia paradoxica is not known. Observations by Kinnier Wilson in PD patients demonstrated a relative preservation of what he called 'movements of reaction and defense.' As such, when severely affected parkinsonian patients were tilted abruptly while seated, they automatically developed extension and abduction of the arms and legs. Other similar observations included the retained ability to blink to loud auditory stimuli in spite of severe facial masking or withdrawal of a body part from an applied noxious stimulus even when the patient could not volitionally move. He recognized that a 'conscious element' played a role in more complex movements such as the removal of a hand from a hot surface or the ability to walk after complex external stimuli were applied, and that these types of responses were retained and highly intact even in the face of severe parkinsonism. He conjectured that apathy and indifference played a role in parkinsonian akinesia, and reasoned that the cortex had to be involved with mediating paradoxical kinesia in patients with striatal disease.

Because dopamine is known to play a critical role in reward pathways, there has been some research into which neurochemical pathways might mediate kinesia paradoxica. Stricker recognized that activating situations could restore motor activity to rodents that were made parkinsonian with intraventricular 6-hydroxydopamine. Subsequent work in this animal model provided evidence that dopamine release is not the mechanism by which activating circumstances resulted in the loss of akinesia. Keefe et al. demonstrated that rats that were given intraventricular 6-hydroxydopamine were able to escape from an ice bath with relatively preserved speed compared to control rats. Haloperidol, a dopamine antagonist, did not block this effect. This observation led them to postulate three possibilities: (1) dopamine is potentially only a modulator of striatal response to sudden, threatening sensory stimuli; (2) norepinephrine or serotonin are critical for motor behavior during times of stress; and (3) spinal cord, brain stem and cerebellar pathways, and limbic/motor integration networks can mediate motor behavior in systems with striatal damage.

The precise manner by which sudden increased motor performance can be elicited under sudden, stressful conditions has been a subject of debate. In humans, response times to externally cued stimuli have been compared in healthy controls and subjects with PD, showing that externally cued stimuli are more effective in generating a faster response compared to a self-initiated cue. Muscles of facial expression and verbal fluency have also been thought to be susceptible to this phenomenon. The types of stimuli that best elicit kinesia paradoxica may be sensory modality-specific, and may serve as clues to defining the anatomic pathways involved in this phenomenon. In studies of a related observation, namely the ability of parkinsonian patients to

overcome gait freezing with visual cues, Glickstein and Stein suggested that having conscious goals or subgoals may enable patients to move in a way that is not normally feasible. They felt that visual stimuli could represent such goals, referring to well-known anecdotes of patients being able to ambulate after placing transversely oriented stripes along the floor. They hypothesized that visual information could be routed to the cerebellum for motor guidance, bypassing the dysfunctional striatum in PD. They cited a body of work indicating that visual information is relayed to cerebellar cortex by way of pontine nuclei. However, impending threat is not always represented in a singularly visual or auditory manner, and it seems likely that multiple modalities and their corresponding pathways may mediate similar sudden changes during an unexpected threat or stressful event.

Epidemiology

Epidemiological studies of the incidence of kinesia paradoxica are lacking. The phenomenon may be observed uncommonly since near-catastrophic or life-threatening events occur very infrequently in disabled patients. One notable study by Schlesinger et al. interviewed 50 PD patients in northern Israel who came under heavy rocket fire during July 2006. Only two patients experienced kinesia paradoxica, one in response to evacuation alarms from an impending rocket attack and the other in response to a cup of hot coffee almost spilling into the patient's lap. The overall phenomenon was thought to be uncommon. The authors concluded that this observation supports the idea that visual stimuli rather than extensive auditory cueing is critical for instigating externally cued rapid motor responses.

Practical Issues

The phenomenon of paroxysmal kinesia can be explained to families and patients who will find comfort in understanding that in dire emergencies, even very impaired PD patients may successfully mobilize themselves to safety.

See also: Bradykinesia; Freezing of Gait; Gait Disturbances in Parkinsonism; Parkinson's Disease: Definition, Diagnosis, and Management; Wilson, Samuel Alexander Kinnier.

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Kuru

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Introduction

Kuru is believed to have developed in the early part of this century in a small isolated Eastern Highlands population of Papua New Guinea, where the people regarded it as a form of sorcery. It was the first noninflammatory degenerative disease of man proved to be caused by a filterable agent, by transmission to chimpanzees and monkeys. Because of its histopathological similarities to kuru, Creutzfeldt–Jakob disease (CJD) was soon demonstrated to be similarly transmissible. Both kuru and CJD are now believed to be caused by strange atypical infectious agents who lack any DNA or RNA and are infectious nucleants made from a normal host precursor protein by a conformational change to its cross β-pleated conformation. In this new conformation the molecules self-assemble and autocatalytically induce a similar change in normal precursor protein molecules, producing further infectious protein nucleants (or prions). These discoveries rapidly led to a demonstration of transmissibility and similar etiology for familial genetically dominant forms of CJD and to the further delineation of its clinical and

pathological variant, Gerstman–Sträussler–Scheinker syndrome. Scrapie in sheep and goats, transmissible mink encephalopathy, chronic wasting disease in Rocky Mountain mule deer and elk, and bovine spongiform encephalopathy (mad cow disease), were all shown to have the same cause. All these diseases share the characteristic vacuolating lesions inside the neurons, as observed by electron microscopy and the resulting status spongiosus of the gray matter, seen by light microscopy.

The word 'kuru,' in the language of the Fore people of the Eastern Highlands of New Guinea means shivering or shaking and refers to one of the several movement disorders seen in this disease. The story, which resulted in the discovery and disappearance of a disease, as well as the Nobel Prize for Dr. Gajdusek in 1976, started in a rather unorthodox and exotic way in 1957. D.C. Gajdusek was a visiting investigator at the Walter and Eliza Hall Institute of Medical Research with Frank McFarlane Burnet in Melbourne, Australia from 1955 to 1957, when a territorial health officer from New Guinea, Dr. V. Zigas, reported to the government Public Health Service a strange fatal neurologic disorder, that was decimating the primitive Fore people in the Eastern Highlands of New Guinea.

The disease was confined to an area east of Mt. Michael (elevation 12 000 ft) inhabited by 35 000 people in 169 villages and hamlets, consisting of 9 linguistic groups afflicted by kuru, living in stone age culture. It was specifically limited to the Fore people and their immediate neighbors, who intermarried with the Fore. The total population affected was 17 000 (Fore plus the neighboring tribes), of which 11 000 were the Fore.

Kuru is believed to have resulted from the contamination of women and their infants and toddlers with highly infectious brain tissue during ritual cannibalism as a rite of mourning and respect for the dead close kinsmen. Women and children crowding about or in the arms of women were more exposed to the kuru infected human tissue than were the men, who left this ritual largely to women. Brain tissue infected with kuru has a high infectivity and is transmissible, using bacteria free infiltrates of brain, even at dilutions as high as 1:1 000 000 and therefore self inoculation through the mouth, eyes, nose, or skin was a certainty whenever a victim was eaten. It has been postulated that the disease had its origin in a case of sporadic CJD, was perpetuated through endocannibalism, and dissipated with cessation of endocannibalism, after this initially Stone Age culture acculturated to Western civilization.

Epidemiology

In 1957, when Gajdusek and Zigas went to the Eastern Highlands of New Guinea, kuru had a yearly incidence and prevalence rate of about 1%. Over 1% of the entire population died annually of kuru. In most affected villages, active cases comprised 5–10% of the inhabitants. In the first decade after the discovery of the disease by western scientists, kuru claimed about one quarter of all deaths, and in the villages with the highest incidence it accounted for over 90% of all deaths. In childhood and adolescence the male female ratio was close to 1:1, but among adults, in whom 60% of the cases occurred, the female–male ratio was over 14:1. Incubation period ranged from 4 to more than 40 years.

The incidence of kuru has declined sharply, falling from 220 registered cases in 1959 to 86 in 1970 and disappearance in people under the age of 35 by 1985 and under 45 by 1995. The incidence has declined more markedly among women than men. It has disappeared from children, adolescents, and young adults. The gradual disappearance of kuru, regularly by age group, resulted from the cessation of the practice of ritual cannibalism among the Fore people after 1957.

Clinical Presentation

Kuru is characterized by predominantly cerebellar symptomatology, which follows a progressive and remarkably uniform course to total incapacitation and death, usually within 3–9 months. Different MDs occur preferentially in different stages of the disease. It starts insidiously without acute antecedent illness, and is divided into three stages: the first or ambulant stage, the second or sedentary, and the third or terminal stage. Some patients report prodromal symptoms of headache and limb pains.

The first stage or ambulant is usually self diagnosed, with ataxic gait and postural instability, truncal tremor and titubation being the first signs. Dysarthria develops early and speech progressively deteriorates as the disease advances. A convergent strabismus often appears early in the disease and persists. For most of the first stage of the disease the patient usually continues to work in the garden and attempts to pursue his normal activities and take full part in village social life, in the latter part of this first stage, he starts utilizing a stick for support.

The second or sedentary stage is reached when the patient can no longer walk without complete support. Tremor becomes progressively more severe and other movement disorders appear. Mental slowing is apparent, but severe dementia is conspicuously absent. Emotional liability, leading to outbursts of pathological laughter, is frequent. Laughter and smile can be persistent with slow relaxation, reminiscent of facial dystonia. This feature has given rise to the unfortunate journalistic synonym of 'laughing death.' Most patients show a resignation to, and a light-hearted attitude toward their disease bordering on true euphoria.

The third or terminal stage is reached when the patient is unable to sit up without support, and ataxia, tremor and dysarthria become progressively more severe and

incapacitating. Some patients show characteristic extrapyramidal defects of posture and movement. A grasp reflex may appear and tendon reflexes become exaggerated. Urinary and fecal incontinence develop, and dysphagia leads to thirst and starvation. Of interest is that even in the advanced stage of incapacitation, the mute patient who occasionally groans may still respond intelligently to requests, with a feeble motor response after much verbal urging.

See also: 6-OH Dopamine Rat Model; Variant Creutzfeldt–Jakob Disease.

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L

Lafora Disease

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Glossary

Autosomal recessive inheritance – Autosomal recessive inheritance means that the gene carrying the mutation is located on one of the autosomes, and that both copies of the gene must have a mutation in order for a person to have the trait. One copy of the mutation is inherited from the mother, and one from the father. A person who has only one recessive gene mutation is said to be a 'carrier' for the trait or disease, but he/she does not have any health problems from carrying this one mutation. Once parents have had a child with a recessive disease, there is a 25% chance, with each subsequent pregnancy, for another child to be born with the same disorder.

Dual-specificity phosphatase – Subclass of the protein tyrosine phosphatase (PTP) gene superfamily, which appears to be selective for dephosphorylating the critical phosphothreonine and phosphotyrosine residues within MAP kinases.

E3 ubiquitin ligase – A ubiquitin ligase is a protein that covalently attaches ubiquitin to a lysine on a target protein via an isopeptide bond. In general, the ubiquitin ligase is involved in polyubiquitination: a second ubiquitin is attached to the first, a third is attached to the second, and so forth. Polyubiquitination marks proteins for degradation by the proteasome.

Lafora bodies – Lafora bodies are composed of starch-like polyglucosans, which are insufficiently branched and hence insoluble glycogen molecules, which accumulate in neurons, skin, muscle, liver, and other tissues.

MAP kinases – Mitogen-activated protein (MAP) kinases are important players in signal transduction pathways activated by a range of stimuli, and mediate a number of physiological and pathological changes in cell function.

Photosensitive epilepsy – Patients are called photosensitive when seizures are triggered by certain frequencies of flashing lights or contrasting light and dark patterns such as stripes or checks.

Definition and History

Lafora's disease is named after Gonzalo Rodriguez Lafora (1887–1971), a Spanish neuropathologist who reported the presence of spherical inclusions in brains of patients with myoclonus epilepsy, which were called Lafora bodies. Lafora bodies would later prove to be the key feature to distinguish Lafora's disease from other epileptic conditions.

The diagnosis of Lafora's disease is suspected in a previously healthy older child or adolescent with fragmentary, symmetric, or generalized myoclonus, and/or generalized tonic–clonic seizures, visual hallucinations (occipital seizures), and progressive neurological deterioration, including cognitive and/or behavioral deterioration, dysarthria, ataxia, and at later stages, spasticity and dementia.

Diagnosis is confirmed by the identification of two mutations in one of the two genes known to be associated with Lafora's disease, *EPM2A* or *NHLRC1*.

Pathogenesis/Pathophysiology

EPM2A is located on chromosome 6q24, and encodes the dual-specificity phosphatase laforin. By differential splicing of its transcripts, *EPM2A* encodes two laforin isoforms having distinct carboxyl termini. *NHLRC1* is located on chromosome 6p22.3, and encodes an E3 ubiquitin ligase called malin.

The mechanisms by which mutations in either *EPM2A* or *NHLRC1* result in Lafora's disease, and the exact role of the Lafora bodies has not been entirely clarified. Laforin

and malin participate in different mechanisms involved in the regulation of glycogen metabolism, including the proteasome-dependent degradation of protein targeting to glycogen (PTG) and muscle glycogen synthase (MSG), suppression of excessive glycogen phosphorylation, and degradation of misfolded proteins.

Epidemiology/Risk Factors

Exact prevalence figures for Lafora's disease are not available. It occurs worldwide, but because of its autosomal recessive inheritance, it is relatively more frequent in ethnic isolates, and other parts of the world with a high rate of consanguinity.

Apart from two mutational hotspots in *NHLRC1* (p.Pro69Ala and p.Gly158fs), mutations are distributed evenly across the *EPM2A* and *NHLRC1* genes. Some mutations occur more frequently in specific populations. Examples include the relatively frequent presence of the p.Arg241X mutation in *EPM2A* in the Spanish population, and the p.Cys26Ser mutation in *NHLRC1* in French Canadian families.

Clinical Features and Diagnostic Criteria

Lafora's disease typically starts between ages 12 and 17 years, after a period of apparently normal development. Many affected individuals experience isolated febrile or nonfebrile convulsions in infancy or earlier in childhood. Intractable seizures rarely begin as early as the age of 6. In families with more than one affected child, clinical signs such as subtle myoclonus, visual hallucinations, or headaches are noted earlier in subsequent affected children than in the proband. Intra- and interfamilial variability in the age of onset is considerable.

The main seizure types in Lafora's disease include myoclonic seizures and occipital seizures, although generalized tonic–clonic seizures, atypical absence seizures, and atonic and complex partial seizures may occur.

Myoclonus can be fragmentary, symmetric, or massive (generalized). It occurs at rest and is exaggerated by action, photic stimulation, or excitement. Both negative (loss of tone) and positive (jerking) myoclonus can occur. Myoclonus usually disappears with sleep. Trains of massive myoclonus with relative preservation of consciousness have been reported. Myoclonus is the primary reason for early wheelchair dependency. In the advanced stages of the disease, affected individuals often have continuous generalized myoclonus.

Occipital seizures present as transient blindness, simple or complex visual hallucinations, photomyoclonic or photoconvulsive seizures, or migraine with scintillating scotomata.

The course of the disease is characterized by increasing frequency and intractability of seizures. Status epilepticus with any of the previously mentioned seizure types is common. Cognitive decline becomes apparent at or soon after the onset of seizures. Dysarthria and ataxia appear early, while spasticity late. Emotional disturbance and confusion are common in the early stages of the disease, and are followed by dementia.

By their mid-twenties, most affected individuals are in a vegetative state with continuous myoclonus. Some maintain minimal interactions, such as a reflex-like smiling, with the family. Affected individuals who are not tube-fed aspirate frequently as a result of seizures; death from aspiration pneumonia is common.

Results of additional investigations and their evolution over time are summarized in **Table 1**.

Differential Diagnosis

Although the occurrence of myoclonus and generalized tonic–clonic seizures in adolescence may raise the possibility of juvenile myoclonic epilepsy, the persistence of EEG background slowing and cognitive deterioration should raise the suspicion of a more severe epilepsy syndrome, such as progressive myoclonus epilepsy.

Later age of onset, more rapid rate of disease progression, and presence of Lafora bodies on skin biopsy differentiates Lafora's disease from Unverricht–Lundborg disease.

Careful ophthalmologic examination, including electroretinography, is useful in addressing the possibilities of neuronal ceroid-lipofuscinoses and sialidosis.

Other conditions to consider are myoclonic epilepsy with ragged red fibers, subacute sclerosing panencephalitis, or schizophrenia.

Diagnostic Work-up/Tests

Molecular Genetic Testing

Diagnosis is confirmed by detection of two mutations in *EPM2A* or *NHLRC1*.

Although some evidence suggests that persons with *NHLRC1*-associated Lafora's disease tend to live longer than those with *EPM2A*-associated Lafora's disease, the clinical manifestations caused by mutations in either gene are so similar that it is not possible to predict which gene will be mutated in any given individual.

Studies of the combined mutation detection frequency by sequence analysis of *EPM2A* and *NHLRC1* reveal that between 88% and 97% of mutations in these two genes can be detected using sequence analysis alone. The proportion of mutations in *EPM2A* and *NHLRC1* not detected

Table 1 Clinical evaluation of Lafora's disease

Evaluation	*At onset*	*Later in disease course*
General physical examination	Normal	Normal
Neurological examination, including fundi and reflexes	Normal	Dysarthria, ataxia, spasticity; fundi remain normal
Mental state examination	Visual hallucinations (epileptic), depressed mood, cognitive deficits	Increased hallucinations, agitation, dementia
EEG	Normal or slow background, loss of α-rhythm and sleep features, photosensitivity is common	Slow background, paroxysms of generalized irregular spike-wave discharges with occipital predominance, and focal, especially occipital, abnormalities
Visual-, somatosensory-, and auditory brainstem-evoked potentials	High-voltage visual and somatosensory evoked potentials	Amplitudes may return to normal size; prolongation of brainstem and central latencies
Nerve conduction studies	Normal	Normal
MRI of the brain	Normal	Normal or atrophy[a]
Proton MR spectroscopy of the brain	Reduced NAA/creatine ratio in frontal and occipital cortex, basal ganglia, and cerebellum[b]	Reduced NAA/creatine ratio in frontal and occipital cortex, basal ganglia, and cerebellum[a]

[a]No significant correlation observed with disease evolution.
[b]At least 2 years after onset of symptoms.

by sequence analysis that are attributable to deletions is unknown. Deletions should be suspected in affected individuals who have a single heterozygous mutation in one of the genes, and in patients who have an apparently homozygous mutation in one of the genes but the mutation is carried by only one parent.

Finally, two independent studies have provided evidence for the existence of a third locus for Lafora disease.

Skin Biopsy

Before the advent of molecular genetic testing, diagnosis was confirmed by the presence of Lafora bodies on skin biopsy. Lafora bodies are present in either eccrine duct cells or in apocrine myoepithelial cells. The interpretation of findings on skin biopsy includes a risk of false negative results, especially in newly symptomatic individuals, and a risk of false positive results because of the difficulty in distinguishing Lafora bodies from normal Periodic Acid-Schiff positive polysaccharides in apocrine glands. It is therefore favored to biopsy the skin outside the axilla and genital regions, as eccrine duct cell Lafora bodies are unmistakable.

Management

To establish the extent of disease in an individual diagnosed with Lafora's disease, a clinical evaluation with special attention to speech, walking, coordination, handwriting, school performance, and emotional status is recommended. Follow-up consists of clinical and psychosocial evaluations at 3–6-month intervals throughout the teenage years.

Antiepileptic drugs have a major effect against generalized seizures, sometimes controlling seizures for many months. Valproic acid is the traditional antiepileptic treatment for Lafora's disease because it is a broad-spectrum drug that controls both the generalized tonic–clonic seizures and myoclonic jerks. Clonazepam can be used as an adjunctive medication for the control of myoclonus. Other possible treatments include zonisamide, piracetam, and levetiracetam.

The use of phenytoin should be avoided. Anecdotal reports describe possible exacerbation of myoclonus with carbamazepine, oxcarbazepine, and lamotrigine.

Myoclonus is often drug-resistant in Lafora's disease, and care should be taken not to overmedicate patients for this reason.

Placement by percutaneous endoscopy of a gastrostomy tube for feeding can be helpful in decreasing the risk of aspiration pneumonia in individuals with advanced disease.

Prognosis

Since there is no curative treatment, and therapy is mainly supportive and symptomatic, most affected individuals die within 10 years of onset, usually from status epilepticus or from complications related to nervous system degeneration.

See also: Ataxia; Dementia, Movement Disorders; Myoclonus; Myoclonus, Epileptic.

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Lance–Adams Syndrome

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Glossary

Action myoclonus – Myoclonus induced by execution of willed movement.
Cortical myoclonus – Myoclonus originating from hyperexcitable motor cortex.
Cortical reflex myoclonus – Myoclonus induced by a transcortical reflex mechanism via the sensorimotor cortex.
Hypoxia – Decreased arterial oxygen causing insufficient oxygen supply to brain.
Intention myoclonus – Myoclonus induced by initiation of willed movement.
Myoclonus – Shock-like involuntary movements.
Negative myoclonus – Myoclonus caused by sudden lapses (silent period) of ongoing muscle contraction.
Positive myoclonus – Myoclonus caused by abrupt muscle contraction.
Postural myoclonus – Myoclonus induced during maintenance of posture (isometric muscle contraction).
Reticular reflex myoclonus – Myoclonus induced by a reflex mechanism via the brainstem reticular nucleus.

Definition and History

Lance–Adams syndrome is characterized by persistent postural or action/intention myoclonus occurring after acute hypoxic insult to brain, and is also called posthypoxic myoclonus.

In 1963, James W. Lance and Raymond D. Adams wrote a famous paper entitled 'The syndrome of intention or action myoclonus as a sequel to hypoxic encephalopathy' in *Brain*. In that paper, they described thoroughly the clinical and electrophysiological features of four cases of this condition. The cause of anoxia was cardiac arrest in two cases and airway obstruction in the other two. They were initially comatose for 2–4 days, and they were followed up by the authors for 1–8 years. Three cases had generalized convulsions while they were unconscious. Soon after recovery from coma, they exhibited multiple, intensive jerks. The jerks were more generalized in the early stage soon after the episode of hypoxia, but after a few days, the jerks became more restricted in site and more irregular. The arms were chiefly affected in two cases and legs in the other two. The jerks were elicited or enhanced by willed movement requiring precision and by emotional arousal. In addition, the jerks were very sensitive to external stimuli such as touch, pin prick, passive movement, and in two cases, to sound as well. They were especially sensitive to unexpected presentation of stimuli, showing a feature of startle myoclonus.

Electrophysiologically, electroencephalogram (EEG) in three cases showed positive–negative biphasic spike discharges at the central electrodes. Electromyogram (EMG), recorded with electrodes placed on the skin over the contracting muscles, showed abrupt muscle discharges in association with myoclonic jerks, which were often associated with the EEG spike activities. The spikes were localized to the midline vertex when the myoclonus involved legs, and to the lateral convexity when the myoclonus involved hands. The initial positive peak of the cortical spike led the myoclonic jerk by 7 ms for occipital muscles, 12 ms for biceps, 16 ms for wrist extensors, and 32 ms for quadriceps, which was compatible with the conduction time of impulses from the motor cortex descending to each muscle via the corticospinal tract and peripheral motor nerves.

Lance and Adams paid special attention to silent periods or lapses of muscle contraction, lasting up to 340 ms, either following myoclonic jerks or in isolation, which explained frequent falling attacks of those cases. The EEG spikes were often followed by slow wave lasting 80–250 ms. Thus, the time course was similar in the two electrophysiological parameters; spike followed by slow wave on EEG and abrupt muscle discharge followed by silent period on EMG. They also found that the EEG response similar to the spike-and-wave complex was elicited by pin prick of hand and it was accompanied by myoclonic EMG burst followed by silent period. The authors postulated a role of the thalamocortical volley relayed down the corticospinal tract as a possible mechanism underlying generation of those jerks.

Halliday in 1967 classified myoclonus into pyramidal, extrapyramidal, and segmental type, and the electrophysiological features of the above posthypoxic myoclonus matched with those of pyramidal myoclonus. Later Young and Shahani coined the term 'negative myoclonus' for the lapses of EMG discharges causing falling of limbs or drop attack.

Pathophysiology

The main feature of myoclonus described by Lance and Adams corresponds to what is now known as cortical myoclonus or cortical reflex myoclonus. In this condition, both the primary somatosensory cortex and the primary motor cortex are pathologically hyperexcitable, which can be demonstrated by electrophysiological studies. Spontaneous myoclonus is preceded by spike discharges arising from the corresponding area of the primary motor cortex which is located in the precentral gyrus. Electrical stimulation of peripheral nerves evokes extremely enhanced cortical responses in the corresponding area of the primary somatosensory cortex which is located in the postcentral gyrus, and this enhanced cortical response is followed by motor evoked potential at the stimulated site via a transcortical reflex mechanism. This long-loop reflex is also present in normal subjects while the corresponding muscle is kept in gentle contraction, but it is extremely enhanced in the patients with cortical reflex myoclonus and called C (named after 'cortical') reflex. The same phenomena can be demonstrated for the negative myoclonus. Namely, the EMG silent period is preceded by spontaneous cortical spikes arising from the corresponding part of the motor cortex, and somatosensory stimuli elicit silent periods via the transcortical reflex mechanism, thus called cortical reflex negative myoclonus. Since the patients with cortical or cortical reflex myoclonus often develop generalized convulsions, this type of myoclonus is also called epileptic myoclonus.

In case 3 and case 4 of the Lance and Adams' series, myoclonic jerks were induced by external stimuli including auditory stimulus especially when the stimuli were presented unexpectedly. As the startle myoclonus is an exaggerated form of physiological startle response and is mediated by brainstem reticular nucleus, it is most likely that those two cases had an additional feature of myoclonus called reticular reflex myoclonus. In this condition, the initial reflex jerk to the stimulus occurs in the muscles innervated by medulla oblongata, such as sternocleidomastoid and trapezius muscles, and then the jerks spread rostrally to involve facial muscles as well as caudally to limb muscles.

Autopsy cases of anoxic encephalopathy show extensive neuronal damage in multiple areas of brain, but neuropathological correlates of posthypoxic myoclonus have not been clearly elucidated. However, based on the common observation of cerebellar ataxia and cerebellar pathology in

these patients, impairment of cerebellar input to the motor cortex is postulated to be an important physiological mechanism underlying the pathogenesis.

Attempts to produce experimental models of posthypoxic myoclonus have been made to induce myoclonus in animals by experimental cardiac arrest or mechanical obstruction of major cardiac vessels. The rats subjected to these experiments, after recovering from acute anoxic state, manifested generalized reflex jerks in response to auditory stimulus. Thus, the clinical pattern in these experimental rats seems to resemble, at least in part, the reticular reflex myoclonus occasionally seen in patients with posthypoxic myoclonus. Pharmacological studies suggested dysfunction of neuronal circuits mediated by serotonin receptors, and valproate, clonazepam, and 5-hydroxytryptophan were found to suppress the jerks in the animals. However, typical positive and negative myoclonus of cortical origin commonly seen in patients with Lance–Adams syndrome have not been successfully produced in animals.

Epidemiology

The incidence and prevalence of posthypoxic myoclonus vary among geographical regions and among clinical institutions. It is the most common cause of postural and action myoclonus in cardiovascular disease centers, but in general neurology centers it is perhaps second to a group of diseases causing progressive myoclonus epilepsy, as listed in the Differential Diagnosis section.

Clinical Features and Diagnostic Criteria

Since postural or action/intention myoclonus is seen in a variety of diseases, the clinical manifestation itself does not make a final diagnosis of this condition. Therefore, the final diagnosis has to be confirmed by the preceding history of coma, often accompanied by generalized convulsions, due to cardiac arrest or airway obstruction. However, certain features are more commonly seen in the posthypoxic myoclonus than in other similar conditions. Abrupt falling of limbs and drop attacks due to negative myoclonus seem to be more commonly seen in patients with posthypoxic myoclonus as compared with other conditions presenting with similar clinical pictures. Further, the negative myoclonus tends to be more severe and even the dominating feature in posthypoxic cases. By contrast, generalized convulsive seizures seem to be less commonly encountered in posthypoxic cases, except for the acute phase of the illness, as compared with various conditions causing progressive myoclonus epilepsy.

In addition to myoclonus, the patients with posthypoxic myoclonus show cognitive and motor disturbances of various kinds and variable degrees depending on the severity of hypoxic insult to the brain.

Differential Diagnosis

A variety of diseases cause cortical or cortical reflex myoclonus. Among them, hypoxic encephalopathy and progressive myoclonus epilepsy are the two most common causes. The latter category is composed of a variety of conditions including Unverricht–Lundborg disease, Lafora disease, lipidosis, dentatorubral–pallidoluysian atrophy (DRPLA), ceroid lipofuscinosis, myoclonic epilepsy associated with ragged red fibers (MERRF) which is a form of mitochondrial disease, and benign adult familial myoclonic epilepsy. These are all hereditary neurodegenerative diseases. In addition, similar kinds of myoclonus are seen in patients with renal failure or uremic encephalopathy, and 'transient myoclonic state with asterixis in the elderly.'

The diagnosis of posthypoxic myoclonus is made without difficulty if the preceding history of hypoxic episode is known. However, when the precise history is not available, the clinical manifestation itself does not help distinguishing from other similar conditions. If there is similar condition in the patient's family, it suggests other conditions such as a group of neurodegenerative diseases comprising progressive myoclonus epilepsy. Metabolic encephalopathy, especially uremic encephalopathy, can cause positive and negative myoclonus of cortical origin, and its diagnosis depends on the results of laboratory test suggestive of renal failure. 'Transient myoclonic state with asterixis in elderly patients' was reported by Hashimoto et al. in 1992 and is characterized by negative myoclonus involving upper limbs seen only in the elderly people and lasting for 1–2 weeks. It is benign although the episode may recur.

Clinical symptoms and signs other than myoclonus are not helpful in the differential diagnosis, because other conditions, especially a variety of diseases causing progressive myoclonus epilepsy, show other associated clinical features such as motor and cognitive disturbances. In posthypoxic myoclonus, however, these symptoms and signs are usually not progressive whereas, in progressive myoclonus epilepsy, other symptoms and signs are slowly progressive.

Psychogenic myoclonus is commonly seen, and its diagnosis is sometimes established with difficulty. In psychogenic disorders, the jerks are often incongruous or difficult to be explained on the basis of recognized organic diseases. The jerks change from time to time in terms of their pattern, distribution, and frequency and tend to be suppressed by drawing the patient's attention to other

subjects; the effect of distraction. Furthermore, the patients often show other behavioral abnormalities or have psychogenic factors in the background.

Diagnostic Tests

Polygraphic recording of EMG and EEG is useful for confirming the nature of the jerks and for elucidating the underlying pathophysiology. In cortical myoclonus, EMG shows abrupt discharges of short duration (usually less than 50 ms) involving agonist and antagonist muscles synchronously. Silent periods are often recognized in the records, and they also involve agonist and antagonist muscles simultaneously. Simultaneous recording of EMG from multiple muscles is especially useful to see the distribution and spread of myoclonic jerks. The EMG polygraph also helps to detect the reticular reflex myoclonus which starts from the muscles innervated by medulla oblongata and spreading rostrally as well as caudally.

EEG shows spike-and-wave or multiple spikes-and-wave discharges at the central region. However, absence of spikes on EEG does not exclude the diagnosis of Lance–Adams syndrome. If the EEG discharges are associated with the EMG discharges, it strongly suggests the cortical origin of the myoclonus. Application of jerk-locked back averaging technique may disclose EEG spikes which are not otherwise detected on the conventional EEG records and will help investigating the precise time and spatial relationship between the cortical activities and myoclonus. Somatosensory evoked potentials might be pathologically enlarged. However, absence of giant somatosensory evoked potentials does not exclude the diagnosis of cortical myoclonus. Imaging study of brain may show some cortical and cerebellar atrophy, but no specific abnormality for this condition is known.

Management

Antimyoclonus agents such as clonazepam and sodium valproate are used, but myoclonus in this condition often tends to be resistant to the conventional anticonvulsants. Recently, levetiracetam was reported to be effective in some cases of posthypoxic myoclonus. Furthermore, in some patients whose myoclonus responds to ethanol like essential tremor, γ-hydroxybutyric acid, which is prescribed as sodium oxybate for treating cataplexy accompanying narcolepsy in the United States, was shown to be effective. A serotonin precursor, L,5-hydroxytryptophan, has been reported to be effective in some cases of posthypoxic myoclonus.

Prognosis

Posthypoxic myoclonus is usually persistent, causing severe disability for daily life, and resistant to various anticonvulsant treatment. Development of more effective antimyoclonus agents is expected to improve the prognosis.

See also: Brainstem Reticular Myoclonus; Cortical Myoclonus; Myoclonus; Myoclonus, Animal Models; Myoclonus, Epileptic; Myoclonus-Dystonia/Essential Myoclonus; Propriospinal Myoclonus; Spinal Segmental Myoclonus.

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Relevant Websites

www.movementdisorders.org – Movement Disorder Society.
www.ninds.nih.gov/disorders/myoclonus/detail_myoclonus.htm – National Institutes of Health.

Latah

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Glossary

Coprolalia – Pathological use of foul language.
Culture-specific syndrome – Forms of abnormal behavior restricted in distribution to defined racial or social groups, discrete areas of the world, or particular historical periods.
Echolalia – Pathological repetition of words just spoken.
Echopraxia – Pathological repetition of the acts of other people.

Definition and History

Latah is originally a Malay term for a broad category of strange behavior. Literally it means 'Tiklish,' 'Jumpy' or 'Love-madness.' It was suggested by Yap that references to Latah in Malay literature date to the fourteenth century. In 1849, Logan was the first to write in English about Latah behavior and to describe it as an uncontrollable startle reaction. There are only a few recent descriptions. Remarkably, the characteristics of Latah described over 100 years ago and those who were described recently are quite similar. However, the equal sex distribution described by O'Brien in 1884 has changed; Latah is nowadays a predominantly female disorder. The nature of the European presence in the Malayan World during colonial times has probably influenced the occurrence and/or the older reports on the Latah phenomenon.

Clinically, Latah is a *culture-specific syndrome* consisting of complex of behaviors occurring in Malayan or Indonesian patients. It includes nonhabituating hyperstartling and various other stereotypic behavioral responses like *coprolalia, echolalia, echopraxia*, 'forced obedience' (involuntary, immediate obedience to commands), and hyper suggestibility. It was described to occur in Indonesia and Malaysia but was also reported in certain regions of Africa and Arabia (this separate form differs slightly from the Malay/Indonesian form; e.g., it does not include *coprolalia*). As the features of the matching behavior are prominent and highly exploited by others, culture-specific startle syndromes like Latah are also referred to as startle-matching syndromes. There are several other similar syndromes (Jumping Frenchmen of Maine and Myriachit in Siberia), but the most extensive descriptions concern Latah. Latah is most often classified as a neuropsychiatric startle syndrome but to some extent may be seen as behavior and part of the Malay/Indonesian culture.

In 1968, Geertz described some Latah women at a party:

> "The first latah exclaimed in a loud voice to the second latah, 'Dag!', the Dutch greeting, 'Good-day!'. The latah, immediately responded, 'Dag!' several times, raising her hand automatically each time. When she paused, the first latah woman started her up again. Then, tired of this game, the first latah cried out, 'Merdeka!', the Indonesian slogan 'Freedom!' and the second latah imitated her, and again repeated it over and over. The first latah then left us to take care of her guests, and the second Latah quieted down. She was a very tense-looking woman, with large nervous eyes, of about sixty. She said nothing unless spoken to. It is the custom in Java at one of these feasts, for all of the guests to urge each other politely to eat, saying over and over again, 'Mangga!', 'Please eat!' The second latah had been sitting at the side for some time when she suddenly burst out – this time without being teased – with 'Manga, manga, manga!', compulsively repeating the polite word and its accompanying gesture, over and over. People then began to tease her and she grew more rattled, and in this upset condition began mixing obscene words in her speech. At one point she offered a cup of tea to someone, with the words 'please have some vagina'. The word for tea has something of the same sound as the word for vagina."

Pathophysiology

See Jumping Frenchmen of Maine. Malay/Indonesian cultural beliefs and habits play a role specifically in the etiology of Latah. Geertz mentioned the importance of elegant and polite speech, the concern over status, sexual prudery, and the dread of being startled as four cultural themes which are possibly related to Latah. It has been suggested by several authors that social repression of the women with often a low social status is an important etiological factor. The Indonesian neurologist Syahrir states that Latah patients demonstrate regression both as a form of protest and to evoke sympathy, acceptance, and pity for the person. He argues that rebellion (do prohibited things), dread or fear (for an authorial figure), and conditioning by the environment (attention) may play a part in the development of the symptoms.

Epidemiology

According to a study of Chiu published in 1972, the prevalence of Latah is well under the 1% (of 13.219 Malays, 69 Latah patients were identified). However, the same author estimated that Latah occurred in 15% of Malay females. In an earlier report of 1924, a number of 300 patients in total were described as seen by Dutch physicians working in Indonesia; about 80% of all the Dutch physicians who were interviewed indicated to have come across a Latah patient.

Clinical Features and Diagnostic Criteria

As the responses of the patients were never recorded, there are no clear diagnostic criteria other than that the responses are stimulus induced. Clinical features are *coprolalia* (more specifically, involuntary blurting of sexually charged words like genitalia), saying idiosyncratically stereotyped things or calling out the name of the thing that excited them (e.g.,'tiger!') *echolalia*, *echopraxia*, and compulsive unquestioning obedience when ordered to perform actions which may be ridiculous, improper, or even dangerous ('forced obedience'). Usually, the patients are prone to constant teasing by others. Latah is typically evoked by being poked forcefully in the side, loud noises, unexpected, or phobic objects (snakes, spiders, etc.) and possibly merely the presence of Westerners. The individuals are conscious while being Latah and able to recollect their behavior afterwards, but claim to not be able to constrain their actions. Latahs are typically middle-aged women of low social–economical status. However, Latah is also prevalent among homosexual transvestite males. In contrast to the Jumping Frenchmen of Maine, there is an absence of Latah among preadolescent children. Geertz described that the persons severely afflicted with Latah give an appearance of being under extreme tension. Those only mildly afflicted seem no different from the other people around them. The patients described in early recordings are typically servants of European employers, but this may be caused by an author's bias. Onset, often sudden and specific, tends to occur during periods of anxiety, depression, or worry, or in a situation in which the person finds himself (herself) wary. Intense life events (e.g., the death of a loved one), being intensely startled by others and a 'preonset' dream (of a sexual or a frightful nature) have been described as occurring shortly before onset of the symptoms. There may be different types of Latah, including at least a mild form, in which the response is associated with hyperstartling itself, and a more extreme form. One classification consists of the immediate-response Latah (episodes of hyperstartling with or without throwing, dropping, striking out, or cursing), attention-capture Latah (episodes in which matching or obedience may occur) and enacted Latah (a long sequence of absurd-appearing behavior, even in the absence of adequately startling stimuli). Concerning the latter, several authors wrote that Latah patients have to be separated into genuine cases and those which are basically histrionic and exhibitionistic in nature. Latah has a social function in the Malay/Indonesian society. Virtually everyone in the Malay community participates in the complex of behaviors concerning Latah, either as a Latah, or as an elicitor of Latah episodes, or as a spectator. Simons concluded: "to a great extent, it is the behavior of others towards potential Latah that results in developing Latah, and it is the behavior of others towards Latah that largely determines the behaviors that Latah perform." The other way round, Latah patients have a license to mock those about them regardless of relative social status and show conduct considered improper for Malay women. Lower-status persons are more likely to receive startle teasing than those of higher status. Although they are often embarrassed, Latahs are not considered either morally or legally responsible for what they do after being startled.

Prognosis

The condition is usually described as chronic. In Chiu's study of 37 Latah patients, 23 claimed that their symptoms were static, 8 improved, and 6 worsened.

Differential Diagnosis and Diagnostic Work-Up Tests

See 'Jumping Frenchmen of Maine'.

Management

See 'Jumping Frenchmen of Maine'.

See also: Hyperekplexia; Jumping Frenchmen of Maine; Myriachit; Startle reflex.

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Leaner Mouse

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Glossary

Ataxia – An inability to coordinate voluntary muscular movements, which is symptomatic of some nervous disorders.
Channel open probability – This is the probability that at any given point in time, a specific ion channel is likely to be open and to allow ions to pass through the channel instead of being closed and impermeable to ions.
Cortical spreading depression – Cortical spreading depression is a short-lasting depolarization wave that moves across the cortex at a rate of 3–5 mm min^{-1} and is associated with sensory disturbances during migraine auras.
Gangliosides – Gangliosides are unique acidic glycolipids that are selectively concentrated in the plasma membrane of cells. Gangliosides are found in highest concentration in cells of the nervous system, where they can constitute as much as 5% of the lipid.
n-NOS – Nitric oxide synthase (NOS) catalyzes the conversion of L-arginine to NO and L-citrulline. NOS exists in three major isoforms: (1) neuronal NOS (n-NOS); (2) endothelial NOS (e-NOS); and (3) inducible NOS (i-NOS). n-NOS is constitutively expressed and dependent on calcium ions and calmodulin to function.
Paroxysmal dyskinesia – These disorders are neurologic conditions that exhibit sudden episodes of abnormal involuntary movements. These may include combinations of involuntary, rapid, irregular movements (chorea), and slow, writhing motions (athetosis) as well as other types of involuntary movements. The term paroxysmal indicates that the abnormal movements are episodic and the individual will eventually return to normal motor function and/or behavior.
Phospholipids – These can be any of a variety of phosphorus-containing lipids that are composed mainly of fatty acids, a phosphate group, and a simple organic molecule such as glycerol. Phospholipids are the main lipids found in cell membranes.
SGGLs (sulfoglucuronyl glycolipids) – SGGLs are a type of ganglioside. Gangliosides are a type of glycosphingolipid. Gangliosides are expressed in the surface membranes of vertebrate nerve cells. SGGLs are temporally and spatially regulated during the development of the nervous system.
Spike-and-wave discharges – These are abnormal discharges that are observed in an electroencephalogram (EEG) and typically observed during epileptic seizures. The absence seizure (also called 'petit mal' epilepsy) displays a very distinctive oscillation consisting of generalized and bilaterally synchronous spike-and-wave EEG patterns recurring at a frequency of about 3 Hz in humans.

History

In 1960, an AKR/J mouse displayed a prominent movement disorder phenotype, which was due to a spontaneous, autosomal recessive mutation, but this mutation had not received the name, 'leaner,' until 1963. In 1971, this mutation was identified as an allele at the tottering locus and also discovered to be closely linked to serum esterase, *Es-1* and oligosyndactyly, *Os*. Crossing over events are exceedingly rare between the tottering locus and *Os*, making *Os* an extremely useful marker to visually distinguish between heterozygous and homozygous leaner (and tottering) mice. Currently, the leaner mutation resides on the C57BL/6 background. It is important to note that when the leaner mutation was transferred to an inbred Swiss White Webster background, no significant alteration in phenotypic expression was observed.

Description of the Mutation

The leaner mutation maps to the *Cacna1a* gene, which codes for the α_{1A} calcium channel pore-forming subunit of Cav2.1 (P/Q-type) voltage-gated calcium ion (Ca^{2+}) channels. Several different mutant mouse alleles also exist at this same locus, including tottering, rolling Nagoya, and rocker. The leaner mutation is designated as *Cacana1a*$^{tg\text{-}la}$. The resulting defect is a splice donor mutation that causes truncation of the open reading frame and deletion of the C-terminus of the α_{1A} protein. There appear to be few differences in *Cacna1a* mRNA or protein expression levels in the leaner cerebellum compared with age-matched wild-type mouse cerebella. Three human neurological diseases are attributed to CACNA1A mutations: episodic ataxia type 2 (EA-2), familial hemiplegic migraine (FMA), and spinocerebellar ataxia type 6 (SCA6).

Clinical and Morphological Features

Clinical and morphological features of leaner mice were first described in the Catalog of the Neurological Mutants of the Mouse and are summarized in **Table 1**. Homozygous leaner male and female mouse pups exhibit major locomotor abnormalities as early as postnatal days 8–10, and include ataxia, stiffness, and reduced motor activity. Motor impairments increase during the second and third postnatal weeks with juvenile homozygous leaner mice demonstrating increased periods of brief immobility as well as periodic rigid hypertonia of trunk and limb muscles, but curiously, leaner mice do not exhibit tremor, which is typically associated with cerebellar defects. Leaner mice are among the most severely affected cerebellar mutant mice with respect to ataxia and typically exhibit a wide-based hind limb stance when standing or attempting to walk. Leaner mice typically repeatedly fall to their side after only one or two steps and they cannot swim.

Leaner mice also exhibit nonconvulsive, generalized spike-and-wave discharges (SWDs) that are quite similar to human absence epilepsy. SWDs display an average of 6–7 spikes per second with typical durations of one to several seconds. Numerous SWDs can occur when mice are awake and SWDs are accompanied by absence seizures, which are characterized as a behavioral arrest with a fixed staring posture, twitching of vibrissae, and sometimes

Table 1 Summary of leaner mouse characteristics

Neurological disorders	*Morphological characteristics*	*Biochemical characteristics*	*Electrophysiological characteristics*
Severe cerebellar ataxia without tremor	Purkinje cell, granule cell, golgi cell loss postnatally	Reduced calretinin mRNA and protein expression in cerebellar granule cells	60% reduction in P-type Ca^{2+} current
		Reduced calbindin and parvalbumin mRNA expression in Purkinje cells	
6–7 Hz spike and wave epileptiform discharges that are accompanied by absence seizures	Reduced cerebellar volume and weight	Decreased nNOS mRNA in cerebellar granule cells at postnatal day 20; n-NOS mRNA and NADPH-d staining decreased in adult cerebella	Threefold reduction in the open-probability of Cav2.1 channels and no difference in single-channel conductance
	Atrophic dendritic branches and reduced Purkinje cell area	Aberrant TH and zebrin II (aldolase C) protein expression in surviving Purkinje cells	Decreased α_{1G} (T channel) mRNA expression in cerebellar granule cells and increased α_{1G} expression in Purkinje cells
	Ectopic spines on Purkinje cell dendrites	Significantly reduced serum and cerebellar IGF-I protein concentrations at postnatal day 30	
Paroxysmal dyskinesia expressed in juvenile and young adult leaner mice and decreasing after postnatal days 50–60	Minor atrophy in leaner inferior olive	Elevated phospholipids and decreased gangliosides in leaner cerebellum at postnatal day 21	10x resistance to cortical spreading depression and slower transcortical propagation speeds
	Moderate proliferation of glia in sites of Purkinje cell loss	Sulfoglucuronyl glycolipids (SGGLs) decreased in surviving Purkinje cells	Purkinje cells exhibit lower current threshold for Na^{+} spike firing, larger subthreshold membrane depolarizations and do not generate Ca^{2+}–Na^{+} spike bursts
	Moderate loss of myelinated fibers in cerebellar white matter	Calcium buffering values (ratio of bound/free calcium ions) significantly reduced	

myoclonic jerks of the head or jaw. A third neurologic disorder, previously described in various ways but currently thought to be paroxysmal dyskinesia, has been reported to be present in homozygous leaner mice. Paroxysmal dyskinesia episodes decrease significantly after postnatal days 40–50 in leaner mice, which is the age of peak Purkinje cell loss in the leaner cerebellum (see the following paragraph), suggesting that dysfunctional Purkinje cells in the anterior cerebellum are important for the expression of paroxysmal dyskinesia and loss of Purkinje cells decreases the expression of this phenomenon in adult leaner mice. This observation is supported by lesioning the anterior cerebellum in homozygous tottering mice, which also reduces the incidence of paroxysmal dyskinesia, indicating that the anterior cerebellum is important for maintaining the expression of this specific neurological disorder.

Adult leaner mice exhibit severe cerebellar atrophy (see **Figure 1**; arrows indicate cerebellum), resulting from a gradual degeneration of cerebellar granule, Purkinje, and Golgi cells. Peak cerebellar granule cell death occurs at P20, while Purkinje cell death peaks at P40–50. Cerebellar Purkinje cell loss is restricted to alternating sagittal compartments of the leaner cerebellar cortex. There is significantly more Purkinje cell loss in the anterior cerebellar lobe than in the posterior lobe, which is accompanied by aberrant expression of tyrosine hydroxylase (TH) expression in surviving adult Purkinje cells. The expression of TH is normal in the major catecholaminergic nuclei in homozygous leaner mice, but the normally transient developmental expression of TH in a parasagittal 'striped' pattern remains in surviving cerebellar Purkinje cells in adult leaner mice and not in wild-type mice. Purkinje cells primarily use GABA as a neurotransmitter and TH expression in noncatecholaminergic neurons may have an important but transient role in neuronal development that is not suppressed in leaner mice. The leaner Purkinje cells expressing TH also express zebrin II. The major clinical features correlate well with localization of major Purkinje cell loss in the anterior cerebellar lobe. Additional changes in cellular physiology and protein expression in leaner mice are summarized in **Table 1**. Leaner cerebella exhibit enlarged parallel fiber varicosities synapsing on two or more Purkinje cell dendritic spines along with the typical one-to-one spine to varicosity contacts. Leaner Purkinje cells commonly present atrophic dendritic branches with ectopic spines, and Purkinje cell axons display numerous swellings called 'torpedos.' Minor atrophy also has been observed in leaner inferior olive nuclei. Changes in IGF-1 and n-NOS expression has been observed in specific cerebellar neurons and at specific ages in leaner mice (see **Table 1**).

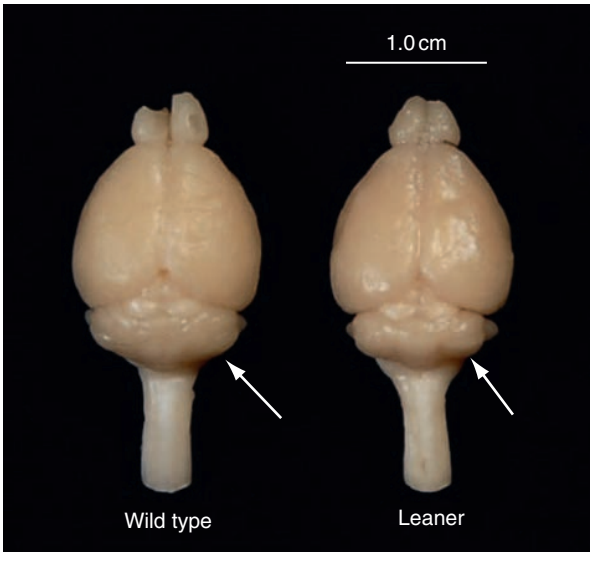

Figure 1 Photomicrograph comparing the dorsal view of an adult wild-type mouse brain to an age-matched homozygous leaner mouse brain. The arrows point to the cerebellum. Note the much smaller leaner cerebellum compared to the wild-type cerebellum.

Homozygous leaner mice are reported to exhibit reduced viability and often die in the third or fourth postnatal week. However, leaner mice die due to hypothermia, dehydration, and/or starvation brought on by their locomotor deficits. If homozygous leaner pups are fostered to lactating foster dams and their diet is supplemented with moistened rodent chow that is easily accessible, both male and female leaner mice actually have a longer life span than wild-type C57BL/6 mice. The critical time period for survival of homozygous leaner mice appears to be postnatal weeks 3–8, which is the time frame during which the majority of cerebellar neuronal cell death takes place.

Channel Characteristics

Leaner Purkinje cells show a 60% decrease in Ca^{2+} current density with little to no alteration in the voltage dependence of channel gating. Leaner Purkinje cells also show a threefold reduction in the open-probability of channels relative to wild-type Purkinje cells, which may account for the observed reduced whole-cell current. Calcium buffering values (ratio of bound/free ions) were significantly reduced in leaner Purkinje cells relative to wild-type cells and calbindin D28k and parvalbumin mRNA levels also were reduced in leaner Purkinje cells, while calretinin expression was decreased in cerebellar granule cells. Altered T channel expression, cortical spreading depression, and transcortical propagation speeds have been noted for the leaner mouse (see **Table 1**).

Characteristics of Heterozygous Leaner Mice

Early reports suggested that heterozygous leaner mice were behaviorally and morphologically indistinguishable from wild-type mice, but we now know that this is not the case. Functional studies showed a reduction of ~30% in Ca^{2+} conductance in heterozygous leaner Purkinje cells. Heterozygous leaner mice show age-dependent impairment on the rotarod and hanging wire test and spatial learning and memory impairments in the Morris water maze. Progressive dysfunction in escape reflexes also are observed in heterozygous leaner mice and they exhibit impaired motor learning in the vestibulo-ocular reflex, suggesting that subtle disruption of Cav2.1 Ca^{2+} currents is sufficient to disrupt motor function.

See also: Ataxia; SCA6; Tottering Mouse - a Definition.

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Leigh Syndrome

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Glossary

ATP synthase – Complex V of the mitochondrial pathway that generates ATP by oxidative phosphorylation.
Cytochrome *c* oxidase (COX) – Complex IV of the mitochondrial respiratory chain.
Heteroplasmy – A mixture of different forms of multicopy DNA molecules (e.g., mtDNA).
Homoplasmy – A uniform population of multicopy DNA molecules.
Maternal inheritance – Vertical transmission of DNA from mother to progeny.
Mitochondrial DNA – A small (16 569 base-pair) circular DNA molecule within mitochondria and encoding 37 genes. Abbreviated to mtDNA.
Oxidative phosphorylation – The mitochondrial metabolic pathway that utilizes energy released by the oxidation of nutrients (mainly carbohydrates and fatty acids) to generate adenosine triphosphate.
Ragged-red fibers – Abnormal muscle fibers with subsarcolemmal reddish appearance by modified Gomori trichrome stain.
Respiratory chain – A set of four multisubunit enzymes (complexes I–IV) embedded in the mitochondrial inner membrane that transfer reducing

equivalents (electrons) to generate a transmembrane proton gradient.
Succinate dehydrogenase – Complex II of the mitochondrial respiratory chain, abbreviated to SDH, and a component of the tricarboxylic acid cycle.
Transfer RNA – A small RNA molecule that transfers an amino acid to a growing polypeptide.

Definition and History

Leigh syndrome (LS or subacute necrotizing encephalomyelopathy) was originally described in 1951 by Dr. Denis Leigh, a British neurologist, who reported a 6.5-month-old infant boy presenting with developmental regression that progressed quickly and led to death 6 weeks later. At autopsy, Dr. Leigh observed multiple symmetric foci of spongy degeneration with microvascular proliferation in the brainstem tegmentum, thalami, cerebellum, posterior columns of the spinal cord, and optic nerves. He astutely noted that the neuropathological alterations resembled those of Wernicke syndrome but spared the mamillary bodies: a consistent feature that distinguishes the two disorders. Subsequently, hundreds of patients with 'Leigh disease' were reported and the condition was renamed LS in recognition of the diverse biochemical and genetic etiologies. The term Leigh-like syndrome has been used to describe patients with clinical and other manifestations of LS, but have uncharacteristic features such as atypical neuropathology or unusual or normal brain MRI scans.

Pathogenesis and Pathophysiology

Deficiency of pyruvate carboxylase was the first biochemical defect linked pathogenically to LS. We now know that the biochemical causes of LS are heterogeneous and include defects of pyruvate dehydrogenase complex (PDHC) and mitochondrial respiratory chain complexes I, II, IV, and V. The inheritance pattern depends on the specific defective gene, but may be autosomal recessive, X-linked recessive, or maternal. Although the specific causes of LS are biochemically and genetically diverse, the unifying metabolic defect in all patients is impaired adenosine triphosphate (ATP) synthesis.

Among the mitochondrial DNA (mtDNA) defects that cause LS, the m.8993T→G and m.8993T→C point mutations in the ATP synthase gene are particularly common (**Table 1**). Both mutations were originally described in patients with neuropathy, ataxia, and retinitis pigmentosa

Table 1 Molecular genetic causes of Leigh or Leigh-like syndrome

Biochemical or genetic defect	*Transmission*	*Approximate frequency*
Pyruvate dehydrogenase complex (PDHC) deficiency		
PDHC E1-alpha subunit	XR	20%
Complex I defects		
NDUFS1, NDUFS2, *NDUSF4*, *NDUFS6, NDUFS7*, *NDUFS8*, *NDUFV1,* and *NDUFV2*	AR	20%
NADH dehydrogenase (ND) subunits	Maternal	<10%
ND6: m.14487T→C, m.14459G→A, m.14484T→C		
ND5: m.13513G→A, m.13514A→G, m.12706T→C		
ND4: m.11777C→A m.10197G→A		
ND3: m.10158T→C, m.10191T→C		
Complex II defects	AR	Rare
SDHA		
Complex IV	AR	25%
SURF1, COX10, COX15, SCO2, LRPPRC		
COXIII	Maternal	
Complex V defects		
ATP synthase subunit 6	Maternal	15–20%
m.8993T→G, m.8993T→C, m.9176T→C, m.9176T→G, m.9191T→C, m.8851T→C, m.9185T→C		
Multiple respiratory chain complex defects		< 5%
mtDNA tRNA genes		
m.3243A→G, m.1624C→T m.1644G→t, m.8363G→A, m.5537insT	Maternal	
mtDNA single deletion	Sporadic	
mtDNA depletion	AR	
SUCLA2		
mitochondrial protein synthesis defects	AR	
EFG1		
Biotinidase deficiency	AR	Rare
Pyruvate carboxylate deficiency	AR	Rare

(NARP), but later found to also cause maternally inherited LS (MILS). In addition, mtDNA mutations in complex I (NADH dehydrogenase (ND)) subunit genes are common causes of LS; the ND5 and ND3 genes are hotspots for LS mutations. The disorder is often caused by autosomal recessive mutations affecting structural subunits or ancillary factors required for the synthesis of mitochondrial respiratory chain complexes I, II, IV, or V. Nuclear genes for complex I structural subunits and complex IV ancillary factors (e.g., *SURF1*) are especially common causes of autosomal recessive LS. Primary CoQ_{10} deficiency can also cause LS.

Epidemiology/Risk Factors

In southeastern Australia, the prevalence of LS or Leigh-like syndrome was estimated to be 1:40 000 live births and in western Sweden, the prevalence of LS in preschool children was 1:34 000 live births. The major risk factor is the presence of a LS-associated mtDNA mutation in the maternal lineage or LS-associated nuclear mutations in relatives.

Clinical Features and Diagnostic Criteria

The diagnosis of LS is based upon the clinical features of motor and intellectual regression with dysfunction of the basal ganglia, brainstem, or both along with either neuroradiological or neuropathological evidence of symmetric lesions in the basal ganglia, thalamus, and brainstem.

The clinical presentations of LS are heterogeneous, due to variations in age-of-onset, rates of progression, frequency of epilepsy, and presence or absence of pigmentary retinopathy. The onset is often acute and may coincide with a febrile illness or may follow a seizure. Most LS patients present in infancy with psychomotor regression, while some present in childhood or adolescence. Adult-onset LS is uncommon. In infants with LS, besides developmental regression, generalized hypotonia, feeding problems, progressive vision loss due to optic neuropathy or pigmentary retinopathy, progressive external ophthalmoplegia, hearing loss, nystagmus, ataxia, and seizures are typical manifestations. In addition, failure to thrive, dysarthria, vomiting, and diarrhea are common manifestations. Respiratory dysfunction is often prominent and often causes death. In older infants or young children, LS may begin with ataxia, dystonia, or intellectual decline. Typically, patients show episodic deterioration with periods of clinical stability.

Genotype–phenotype correlations in patients with LS show that patients with T8993G NARP mutation often (40%) have retinitis pigmentosa, which is a clue to the molecular diagnosis, because retinitis pigmentosa is rarely – if ever – seen in other forms of LS. In addition, seizures are more common in patients with the NARP mutation or PDHC deficiency compared with children with LS due to COX deficiency.

Differential Diagnosis

Psychomotor regression, the major clinical manifestation of LS, is also a common presentation in other inborn errors of metabolism, including white matter diseases (e.g., vanishing whiter matter disease), congenital disorders of glycosylation, defects of amino acid metabolism, and disorders of carbohydrate metabolism.

Diagnostic Workup/Tests

The clinical diagnosis of LS is usually confirmed by brain magnetic resonance imaging (MRI) scans, which reveal increased signals in the basal ganglia and brainstem on T2-weighted or FLAIR images. The lesions are typically symmetric and commonly affect the putamen, globus pallidus, caudate, thalami, substantia nigra, inferior olivary nuclei, periaqueductal gray matter, and brainstem tegmentum. Magnetic resonance spectroscopy (MRS) scans reveal decreased *N*-acetylaspartate and increased lactate in the affected brain regions.

Urine organic acid and amino acid analyses are useful to exclude other inborn errors of metabolism and may reveal elevated urine lactate in patients with LS due to a respiratory chain defect. An increased urine excretion of methylmalonic acid has been reported in patients with LS due to mutations in *SUCLA2*.

To identify the molecular genetic cause of LS in patients, blood lactate and pyruvate may provide helpful preliminary clues. Defects of the mitochondrial respiratory chain and oxidative phosphorylation typically elevate lactate out of proportion to pyruvate (lactate:pyruvate ratio > 20:1). By contrast, a defect of PDHC may be suspected when pyruvate and lactate are similarly increased. PDHC deficiency can be determined in cultured fibroblasts. Defects of the mitochondrial respiratory chain are better identified by biochemical analyses of skeletal muscle biopsies, but can also be detected in cultured fibroblasts. In patients suspected of having MILS, based on family history, blood DNA can be screened for point mutations in the *ATPase 6* gene.

In patients with mitochondrial respiratory chain defects, screening for cardiac, hepatic, and renal involvement is important.

Management

Treatment of LS is mainly symptomatic, but important and includes the management of seizures with anticonvulsants (avoiding valproic acid and barbiturates if

possible), the treatment of dystonia (e.g., benzhexol, baclofen, tetrabenazine, and gabapentin), and standard therapies for cardiomyopathy and renal disease if present. CoQ_{10} supplementation is often given to LS patients with respiratory chain defects, but is particularly crucial for patients with CoQ_{10} deficiencies at high doses (up to 30 mg kg^{-1} day^{-1}). Thiamin (vitamin B1) is a cofactor for PDHC and can be beneficial in PDHC defiency. Riboflavin (vitamin B2) may have modest therapeutic value in deficiencies of complex I or II. Antioxidants (e.g., vitamin C, alpha lipoic acid, and idebenone) are often administered, but have not been proved to be efficacious through placebo-controlled clinical trials. Dichloroacetate (DCA) reduces lactic acid by activating PDHC and has been used to acutely lower lactate in LS, but long-term DCA use in patients with MELAS caused peripheral neuropathy, indicating that chronic use may be more harmful than beneficial.

In families with an identified molecular genetic defect, prenatal diagnosis is often feasible, particularly with autosomal recessive mutations or with mtDNA mutations in the *ATP6* gene (see NARP section).

Prognosis

The clinical course of LS is variable and characterized by episodic deterioration with periods of clinical stability. Most infantile-onset LS patients die before the age of 2 years of respiratory or cardiac failure.

See also: Ataxia (Familial Cerebellar) with Muscle CoQ_{10} Deficiency; Myoclonic Epilepsy with Ragged Red Fibers (MERRF); Neurogenic Muscle Weakness, Ataxia, and Retinitis Pigmentosa (NARP).

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Lesch–Nyhan Disease

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Glossary

Dystonia – Involuntary movements characterized by twisting and unnatural posturing.
Gout – A form of arthritis caused by precipitation of uric acid in the joints.
Hyperuricemia – Elevated serum uric acid.
Nephrolithiasis – Kidney stones.
Purines – A class of small organic molecules required by all living cells for many basic biochemical processes, examples include ATP, adenosine, and uric acid.
Tophi – Plural form of tophus, which is a solid subcutaneous deposit of uric acid.
Uric acid – A naturally occurring end-product of purine metabolism that may serve as an antioxidant.

Definition and History

Lesch–Nyhan disease (LND) is an inherited metabolic disorder that was described by William Nyhan and his

student Michael Lesch in 1964. The clinical features of the classical phenotype include a characteristic neurobehavioral developmental syndrome along with signs of overproduction of uric acid.

Clinical Features

The neurobehavioral syndrome includes severe generalized dystonia, sometimes with spasticity and chorea. The majority of patients also have mild or moderate cognitive disability, with the most prominent difficulties with attention and executive functions. They also exhibit stereotypical self-injurious behavior, a telltale feature characteristic of the classical phenotype (**Figure 1**). Signs indicative of overproduction of uric acid include hyperuricemia, gouty arthropathy, uric acid kidney stones, or subcutaneous tophi (**Figure 1**).

In addition to the classical phenotype, there has been increasing recognition of variant forms of the disease where some clinical features are attenuated or absent. The LND variants all suffer overproduction of uric acid, but they lack the telltale feature of self-injurious behavior. Some have normal cognition, and motor disability varies greatly. Some have severe generalized dystonia with spasticity and chorea similar to the classic phenotype. Others have milder generalized dystonia, focal patterns of dystonia, or minor clumsiness. The most mildly affected cases overproduce uric acid but have no apparent neurobehavioral abnormalities.

Epidemiology

LND and its variants are considered 'ultra-rare' diseases, occurring worldwide with no significant regional variations. Incidence estimates range from 1 per 235 000–380 000 births and prevalence estimates range from 1 per 2.3–3.5 million persons. Since LND is inherited as an X-linked recessive disorder, virtually all cases are male.

Pathogenesis

LND and its variants are caused by mutations in the gene that encode an enzyme, hypoxanthine–guanine phosphoribosyltransferase (HPRT). The mutations are heterogeneous, with more than 300 distinct gene defects reported.

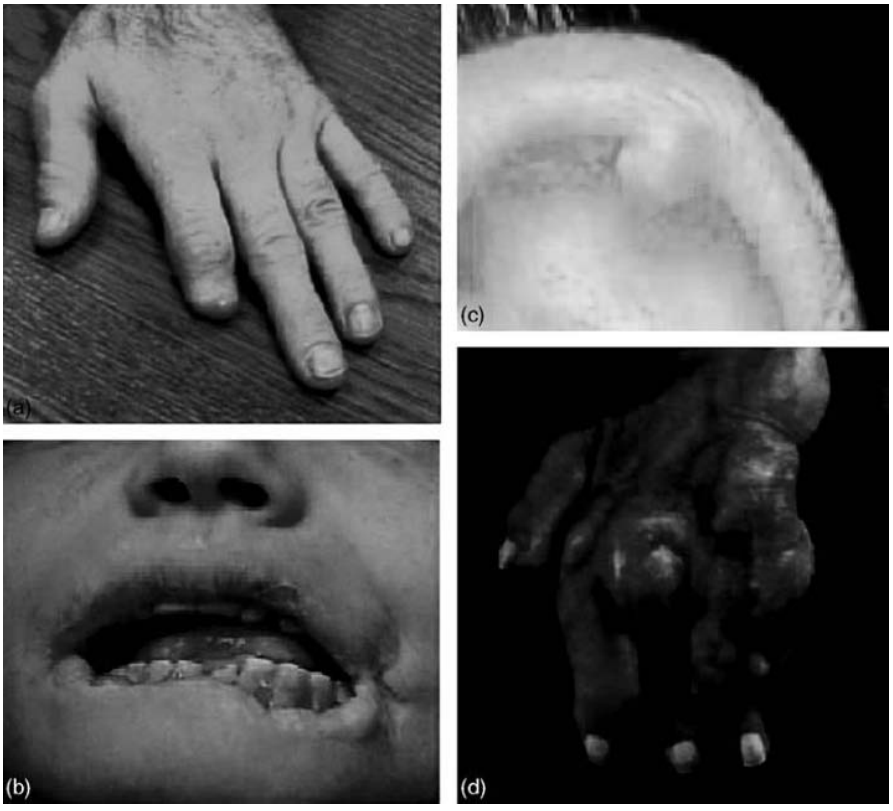

Figure 1

Mutations that result in dysfunctional proteins with less than 1.5% of normal HPRT enzyme activity cause the classical phenotype of LND. Mutations that result in enzymes with more than 2% of residual function result in the milder phenotypes. There is a good correlation between residual enzyme function and clinical severity.

The HPRT enzyme plays a central role in the recycling pathway for purines, small organic molecules that play an essential role in many cellular processes (**Figure 2**). Without HPRT, the bases hypoxanthine and guanine cannot be recycled. Instead, they are excreted or degraded to uric acid. Since uric acid is close to its limit of solubility in the body, increased levels cause it to precipitate in certain areas of the body. Precipitation in the joints causes gouty arthritis, and precipitation in the subcutaneous tissues results in solid masses known as tophi. Uric acid is excreted by the kidneys, where high levels result in kidney stones. Thus, many of the clinical manifestations of the disorder result from the poor solubility of uric acid.

The pathogenesis of the neurobehavioral disturbances is less well understood. Neuroimaging with CT or MRI does not reveal any dramatic structural anomalies. Neurochemical studies of brain tissue reveal 60–90% reductions of dopamine in the basal ganglia. These results led to speculation that nigrostriatal dopamine axonal projections fail to develop properly, or that they undergo early degenerative changes. However, studies in animals and tissue culture models suggest that the loss of dopamine is due to metabolic processes instead. In keeping with this concept, human autopsy studies fail to reveal any consistent histopathology among dopamine neurons.

It is likely that early developmental failure of the dopamine pathways contributes to the neurobehavioral phenotype. Early loss of dopamine is known to cause dystonia in other metabolic disorders, such as dopa-responsive dystonia. The pattern of cognitive dysfunction is also consistent with a loss of dopamine. Finally, animal studies show that early brain dopamine loss sensitizes to the development of self-injurious behavior. Thus, dysfunction of basal ganglia dopamine pathways during early development may be a central process underlying much of the neurobehavioral phenotype in LND.

Diagnosis

Preliminary suspicion for LND arises when all of the clinical features are apparent. The diagnosis is more challenging during early development, when all of the features are not yet apparent. The diagnosis is particularly challenging in the LND variants, because they do not exhibit certain telltale features of the disease.

Laboratory confirmation is essential, because of the implications for treatment and genetic counseling. Serum uric acid can be obtained by most clinical laboratories, and hyperuricemia provides a useful early clue to the diagnosis. Hyperuricemia is found in most cases, but its magnitude may be minor and easily overlooked, and some patients have normal serum levels (**Figure 3**). Serum uric acid is sometimes elevated in disorders other than LND. Thus, hyperuricemia is neither sufficiently sensitive nor specific to serve as a definitive test.

Genetic testing can identify mutation in the HPRT gene. Since mutations are heterogeneous, the entire coding region is usually sequenced. Genetic testing provides the most convenient means for screening potential female carriers. Its main limitation is that it does not always

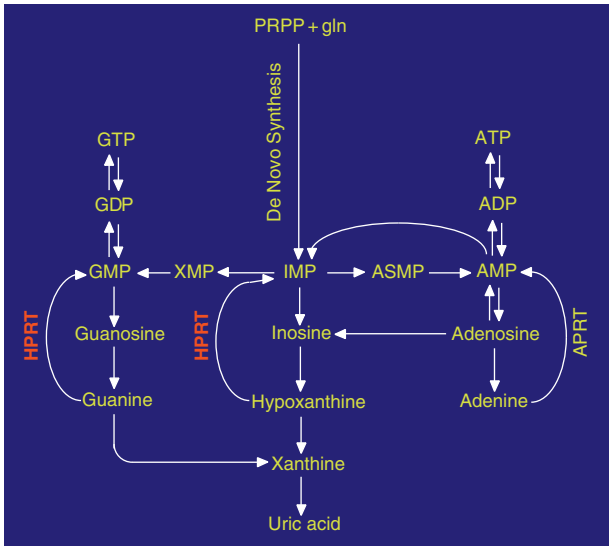

Figure 2

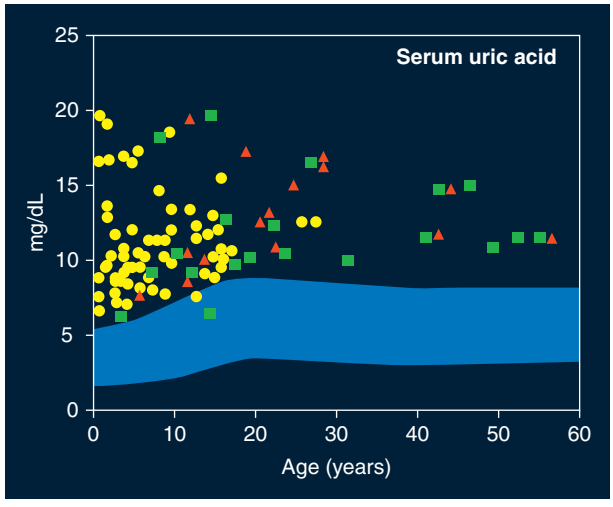

Figure 3

provide prognostic value for distinguishing classic LND from the less severely affected variants.

Biochemical testing of HPRT enzyme activity is not standardized, and many different assays are in use. Assays based on live cells (e.g., whole erythrocytes in suspension or cultured fibroblasts) are considered superior to extract-based assays for predicting disease severity. Its main limitation is that it is technically more demanding and less suitable for carrier detection. A combination of biochemical and genetic tests is performed for most cases.

Management

Uric Acid Overproduction

Controlling overproduction of uric acid is essential for preventing kidney stones and gout. Proper treatment requires two interventions. One is allopurinol, which inhibits the production of uric acid by the enzyme xanthine oxidase. The other is generous hydration to maintain high urine volumes. Despite best medical therapy, regular renal ultrasounds are sometimes needed, because some patients will continue to develop kidney stones. Lithotripsy or surgical extraction is sometimes needed in refractory cases.

Motor Disorder

Like most other generalized dystonias, medical treatments are limited. Anticholinergics and levodopa do not appear to have a major impact, but may be useful in some patients. Muscle relaxants such as baclofen or benzodiazepines can help reduce muscle tone. Severely affected patients remain wheelchair-bound and need assistance for basic activities such as feeding and hygiene. A custom wheelchair, with all dangerous parts covered with padding to prevent self-injury, is an important part of good supportive care.

Aberrant Behaviors

Self-injurious behaviors are the most challenging to control. These behaviors are exacerbated by physical or psychological stressors. The most effective approach involves a combination of behavioral therapy to extinguish problem behaviors, protective devices to prevent self-injury, and ancillary medications when required. Protective devices include arm splints or straps to prevent the hand from reaching dangerous places. Many patients require tooth extraction for definitive control of self-biting. Useful medications include benzodiazepines, gabapentin, and neuroleptics. Enthusiasm for chronic use of neuroleptics is limited by known side effects, but occasional use can be helpful during difficult periods.

Prognosis

Although many texts and reviews list LND among the hereditary degenerative syndromes, there is no evidence for a degenerative process. The clinical features evolve in a manner suggestive of a developmental disorder analogous to cerebral palsy, with evolution during the first few years of life, followed by a static level of disability.

With good supportive care, patients with LND live to their fourth or fifth decades. Typical causes of death include aspiration pneumonia or renal failure from recurrent nephrolithiasis. Some suffer sudden and unexpected death of unknown cause.

See also: Basal Ganglia; Basal Ganglia, Functional Organization; Dopamine; Dystonia; Dystonia, Secondary.

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Levodopa

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Glossary

Decarboxylation – The metabolism of L-DOPA into the neurotransmitter dopamine.
Large neutral amino acid transporter – Transporter found in bowel and blood–brain barrier that is specific to large and branched chain amino acids.
Long-duration response – Clinical effect of levodopa seen early with treatment with levodopa that builds up after several days of drug administration and declines several days or longer after drug withdrawal.
Short-duration response – Clinical effect of levodopa seen when motor fluctuations occur. This may reflect plasma levodopa concentration.

Biochemistry of Levodopa

Levodopa or dihydroxyphenylalanine (DOPA) is a large neutral amino acid (LNAA) that is the precursor for catecholamines: dopamine, norepinephrine, and epinephrine. Levodopa is not normally found in the diet of humans and must be synthesized from the dietary LNAAs, phenylalanine, and tyrosine. Tyrosine is taken into neurons and hydroxylated to DOPA by the enzyme tyrosine hydroxylase, which is the rate-limiting step in catecholamine synthesis. The concentration of tyrosine in the brain depends on plasma levels of tyrosine and other LNAAs competing for transport into the brain by the LNAA transporter.

The discovery by Hornykiewcz that dopamine concentrations were extremely low in the striatia of humans with PD suggested that replacement of dopamine in the striata would reduce the signs of the disease. Dopamine, however, would not cross the blood–brain barrier and therefore would not raise striatal levels of dopamine. However, the work of Carlsson had shown that DOPA could be administered to rats that had the brain catecholamines depleted by reserpine and reverse the catatonia induced by reserpine. The DOPA required only decarboxylation by the enzyme aromatic amino acid decarboxylase (AAAD) to be converted into dopamine. Hornykiewcz and Birkmayer were stimulated by Carlsson's observations to try administering DOPA intravenously to patients with PD. They reported brief resolution of parkinsonism. Their observations were difficult to reproduce and intravenous administration of DOPA was clearly impractical. In 1967, Cotzias reported that L-DOPA administered in large oral doses would markedly improve parkinsonism and thereby changed the treatment of PD. Soon thereafter, the biologically active form of DOPA, the levo isomer, L-DOPA or levodopa, which is the mainstay of PD treatment today, became available.

Absorption and Distribution of Levodopa

Unlike most centrally active drugs that diffuse across membranes, levodopa is actively transported by the LNAA transporter that carries all the dietary LNAAs across cellular membranes. This transporter may be saturated by high concentrations of dietary LNAAs and limit the amount of levodopa absorbed. After oral administration, levodopa is absorbed in the small bowel where LNAA transporters are located. The stomach and large bowel do not have the LNAA transporters and therefore are not absorptive sites for levodopa. Thus, the absorption of levodopa is limited to the time for which levodopa is in the small bowel, a fairly constant, 2–3 h in most people. This point is particularly important to understanding the variable relationship between oral levodopa administration and the plasma levodopa concentrations. Thus, factors that alter delivery of levodopa to small bowel or passage through the small bowel will affect when and to what extent levodopa will appear in plasma.

Gastric emptying greatly influences the timing of levodopa absorption. The administration of levodopa in the morning before breakfast generally results in a rapid absorption, plasma levodopa peaking within 1 h. Delayed gastric emptying caused by meals with high fat and protein content or by medications that slow gastric motility may result in a delayed passage of levodopa to the small bowel and thus entry into blood. As gastric acidity increases, the time to peak plasma concentration of levodopa increases, presumably due to delayed gastric emptying. A small study has implicated *Heliobacter pylori*-induced alteration in gastrointestinal function, which may impair levodopa handling and result in poor response to oral therapy.

The absorption of levodopa in the small bowel is influenced by two factors. First, competition for transport between levodopa and other LNAAs may occur during absorption in the gut. However, the LNAA system has a large capacity in the gut so that the competitive inhibition of levodopa at this location is probably not an important issue.

The second is an enzymatic barrier to entry. The bowel has high concentrations of AAAD and decarboxylation of levodopa will make it unavailable as a precursor to dopamine synthesis in the brain. Inhibitors of AAAD, such as carbidopa or benserazide, reduce this first pass metabolism of levodopa by the gut and the liver.

After oral dosing levodopa appears rapidly in the plasma and is rapidly distributed from plasma into tissue. The distribution half-life is about 15 min. This means that after stopping an intravenous infusion of levodopa, the plasma concentration is halved in 15–30 min and represents the passage of levodopa from plasma into other body tissues. This rapid distribution and rapid metabolism result in a plasma half-life of <2 h.

Levodopa, as a member of the essential LNAA class of amino acids, enters all tissues and there are large amounts in liver and muscle. Distribution of levodopa to brain is the essential step for the therapeutic efficacy of levodopa. The transport of levodopa through the blood–brain barrier is proportional to the ratio of plasma concentration of levodopa and the concentrations of other LNAAs competing for the limited capacity LNAA transporter. This LNAA transporter is saturated at normal plasma concentrations of LNAAs so that changes in the ratio may make big changes in the entry of levodopa into the brain. A large meal may double or triple the dietary LNAAs in plasma and thus reduce levodopa transport by one half or more. Experiments in parkinsonian patients have demonstrated that aromatic or branched chain amino acid administration will reduce the clinical effectiveness of levodopa. Phenylalanine or leucine orally administered at 100 mg kg^{-1} during levodopa infusion reversed the antiparkinsonian actions of the intravenous levodopa without reducing plasma levodopa concentration. A 100 mg kg^{-1} dose of an amino acid from another class of amino acids had no effect on the infused levodopa effects. This suggests that competition between levodopa and other dietary LNAAs at the blood–brain barrier is a critical step for the therapeutic effect of levodopa. Conversely, a carbohydrate meal may enhance the effectiveness of levodopa. A glucose load has been shown to lower the concentration of branched chain amino acids, one component of the LNAAs. By decreasing the branched chain amino acids, aromatic amino acid transport, including levodopa, may be enhanced. Occasionally, PD patients report this effect but it is not as prominent as the problems encountered after high-protein meals. To enhance the effects of levodopa, some patients severely limit protein intake until the end of the day.

Experiments in dogs suggest that there is a gradient to the absorption of levodopa in the small bowel with more absorbed proximally in the duodenum and less in the ileum. Direct administration of levodopa into the duodenum results in rapid appearance of levodopa in the plasma. This notion is behind the intestinal infusion methods to be discussed shortly.

Metabolic Pathways of Levodopa and Dopamine

Metabolism of levodopa and dopamine may proceed by four pathways: decarboxylation, *O*-methylation, transamination, and oxidation.

Levodopa is decarboxylated to dopamine by the enzyme AAAD. This enzyme is ubiquitously distributed in the gut, liver, and kidney. The gastric and intestinal wall contains AAAD that significantly metabolizes levodopa. At least half of an oral levodopa dose is decarboxylated during absorption and first pass hepatic metabolism. Further decarboxylation may occur by AAADC during successive circulation through these tissues. Approximately 70% of the levodopa metabolites appear as dopamine and its degradation products, indicating that decarboxylation is the major route of metabolism. The portion of the orally administered levodopa that is decarboxylated to dopamine in peripheral tissues will not enter the brain, and therefore is lost for the intended therapeutic purpose, elevation of dopamine in the brain.

Decarboxylation of levodopa in the brain is essential to its antiparkinsonian actions. AAAD is present in dopamine nerve terminals in the striatum but is also in serotonergic nerve terminals, and perhaps other cellular elements of brain, as well as in the endothelial cells of the brain capillaries. AAAD is reduced in the brain of PD patients as well as in laboratory animals with toxin-induced parkinsonism. However, the AAAD appears to be in adequate concentration to convert levodopa into dopamine and produce a pharmacological effect. Drugs that block the AAAD in the brain will also block the central pharmacologic actions on the motor system in laboratory animals.

Since extensive decarboxylation of levodopa may occur in peripheral tissues, the inhibition of AAAD was an important development in the therapy of PD. Carbidopa and benserazide are inhibitors of the AAAD enzyme. One or the other of these drugs is typically given in combination with levodopa to inhibit AAAD in peripheral tissues and to augment the effect of levodopa while reducing the peripheral adverse effects of dopamine, namely anorexia, nausea, and vomiting. The addition of an inhibitor of AAAD to levodopa reduced the dose of levodopa required by $\sim$75%. Carbidopa and benserazide given in low doses do not penetrate the blood–brain barrier. Thus, levodopa transported into the brain is assumed to be largely converted into dopamine by central AAAD unaffected by carbidopa or benserazide and utilized in dopaminergic neurotransmission.

Conversion of levodopa to 3-*O*-methyldopa and dopamine to 3-*O*-methyldopamine by catechol-*O*-methyltransferase (COMT) is an important metabolic pathway, especially when decarboxylation is inhibited. *O*-Methylation of levodopa produces a metabolite that cannot be converted into dopamine in the brain. *O*-Methylation of

dopamine is one manner in which to deactivate the neurotransmitter. COMT is present in many peripheral tissues as well as in brain. This pathway is probably responsible for metabolizing about 10% of levodopa when levodopa is administered without an inhibitor of AAAD, and may be more significant when coadministered with AAAD inhibitors that increase levodopa concentration. Tolcapone and entacapone are two competitive COMT inhibitors used in the treatment of parkinsonism. Entacapone acts peripherally to inhibit COMT and thereby to increase the portion of a levodopa dose that enters the brain as levodopa. Tolcapone inhibits the enzyme both centrally and peripherally; whether the central inhibition of COMT is clinically important is not known. A Cochrane review of these drugs found both reduced 'off' time and increased 'on' time. Diarrhea and discoloration of the urine are the most common specific side effects reported with the use of these drugs. Additional side effects associated with increased concentration of levodopa may occur, and usually responds to the decreasing of either the dose or frequency of levodopa administration. Three cases of fatal liver toxicity have occurred in association with use of tolcapone. Although this occurred out of 40 000 patient years of use, strict monitoring of liver function is required during the first 6 months of tolcapone therapy.

Monoamine oxidase (MAO) metabolizes dopamine and 3-*O*-methyldopamine. It exists in two isoforms: MAO-A and MAO-B. MAO-B is the predominant form found in the human brain. MAO-A is primarily found in the gut and is responsible for deactivating catecholamines and vasoactive substances in the periphery. The role of MAO-A in central nervous system metabolism is believed to be minor. The historical role of nonselective MAO inhibition has been in the treatment of psychiatric disorders. Nonselective inhibition of MAO may result in the 'cheese effect' with tachycardia and hypertension. Patients ingesting cheese containing high amounts of tyramine have made this a well-known syndrome. Selective inhibition of MAO-B has a role in the treatment of parkinsonism, presumably because it slows the metabolism of dopamine in the brain and thereby prolongs its actions. Since the MAO-A is not inhibited, the inhibition of MAO-B does not produce the adverse effects of nonselective MAO inhibition. Selegiline was the first MAO-B to have widespread use in the treatment of PD. Given in oral tablet form, it undergoes extensive first pass metabolism and has a relatively low bioavailability. At low doses, selegiline selectively inhibits MAO-B, but at higher doses it loses its selectivity and has been associated with a 'cheese effect.' Selegiline has an amphetamine metabolite although it is the less active isomer and of uncertain significance. An orally disintegrating form may largely avoid the first pass metabolism of standard formulations. Rasagaline is a newly introduced MAO-B inhibitor that does not result in amphetamine metabolites. Overall, the bioavailability of rasagiline may be slightly higher than that of selegiline, and animal studies suggest that it may be a better inhibitor of brain MAO-B. Like selegiline, rasagiline may be more specific to MAO-B at lower doses and lose this specificity at higher doses. Both selegiline and rasagiline have shown mild but significant symptomatic benefits in reducing off time in PD. The excitement about selective MAO-B inhibitors is their putative neuroprotective effects, which remain to be proved.

Clinical Effects of Levodopa

The short-duration response is an antiparkinsonian response to a dose of levodopa that parallels the plasma concentrations of the drug. As the plasma concentrations rise the clinical effects appear and as the plasma levels drop the clinical response wanes. There is a lag between the clinical response and the plasma levodopa levels so that the clinical state at any point in time is not directly related to the concurrent plasma levels. It is the short-duration response that is responsible for motor fluctuations. The key point for clinicians to know is that the short-duration response is not very dose responsive; once a dose exceeds a threshold level, the full response is achieved and higher levels do not influence the maximum response. However, the duration of the response is dose responsive; larger doses produce longer effects.

The long-duration response is a response that builds up over days and also declines over days. Thus, when patients have been on levodopa for weeks or more, stopping the drug will produce an immediate loss of motor function as the short-duration response disappears, but then there is a slow, gradual decline in motor function over days to weeks and the long-duration response decays. Thus, the 'practical off' after overnight without antiparkinsonian medications is not a reflection of a person's untreated disease severity.

Dyskinesia is an unwanted response to levodopa that emerges during chronic therapy in most patients that receive benefit from levodopa. Dyskinesia is linked to the short-duration response with very similar time course and threshold. Although other antiparkinsonian medications occasionally cause dyskinesia, levodopa is the drug that is primarily responsible for dyskinesia.

Formulations of Levodopa

The most common medication used to treat PD is the combination drug carbidopa/levodopa. Different strengths and ratios (1:10 and 1:4) of carbidopa and levodopa are commercially available. Carbidopa is also available in stand-alone form. Extra carbidopa is sometimes used to reduce gastrointestinal side effects that are present despite

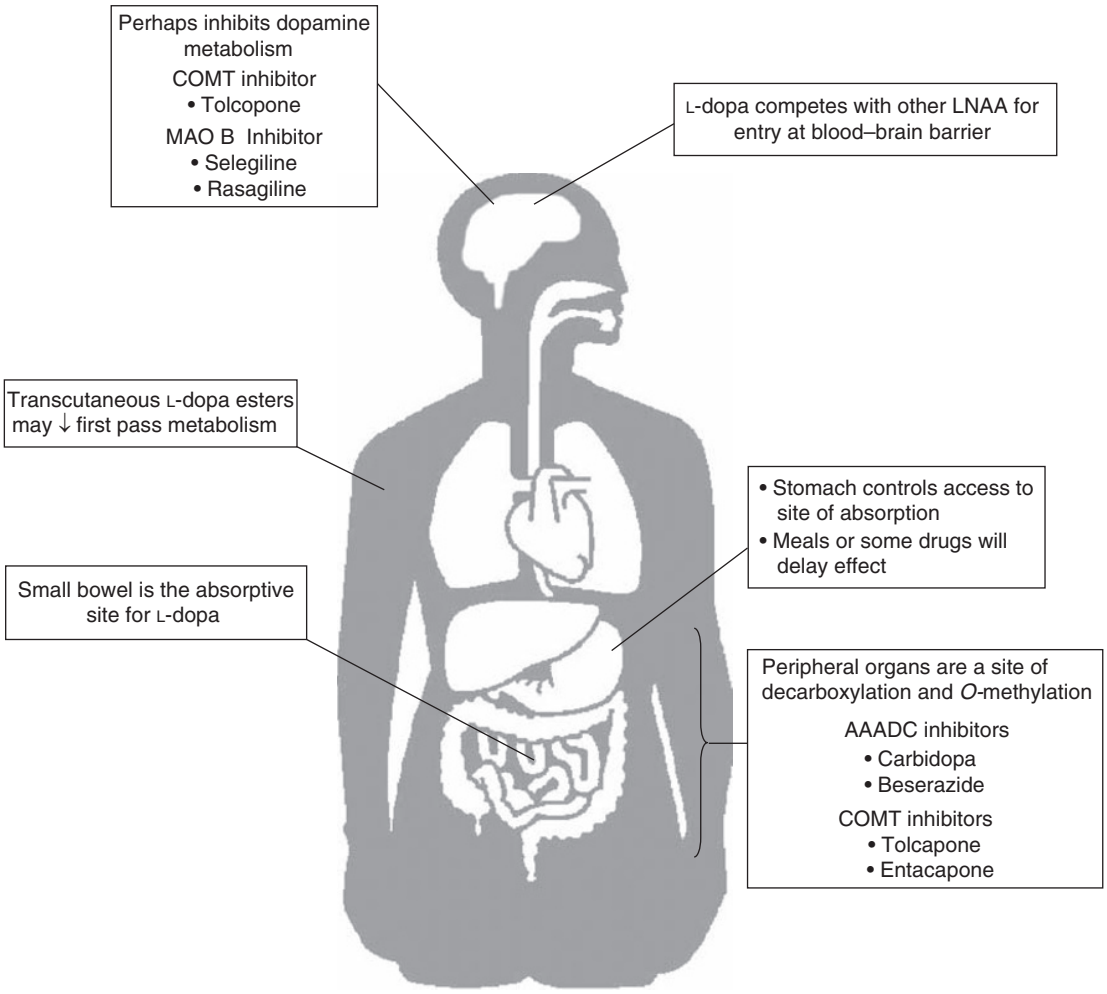

Figure 1 Possible sites for levodopa modulation.

using the usual carbidopa/levodopa combination. It is generally believed that at least 75 mg of carbidopa should be administered to fully inhibit peripheral AAAD. Thus, when initiating levodopa, it is preferable to give it as a 25/100 carbidopa/levodopa combination to get full inhibition of AAAD with the usual daily dose of one tablet 3 times per day. On the other hand, when patients get on very large doses of levodopa, it may be better to use the carbidopa/levodopa preparations with a 1:10 ratio to limit the total amount of carbidopa administered, although no clinical effects of very high doses of carbidopa are recognized. Levodopa without carbidopa is sometimes used in patients who are very sensitive to the medication. Levodopa is available commercially but must be prepared by a compounding pharmacy for oral use. An alternative is to dissolve a 25/100 carbidopa/levodopa tablet in water and take aliquots of the well mixed solution to get small doses.

Levodopa has a very short plasma half-life and is metabolized quickly in both peripheral compartments, necessitating multiple doss throughout the day. Further dose escalation is very typical as parkinsonism progresses and may require dosing every few hours to maintain the optimum clinical effect. The rapid metabolism of levodopa means that there are peaks and troughs of plasma levodopa throughout the day. A common misperception is that this variability in plasma levodopa concentrations can be reduced by giving smaller doses more frequently. The consequence is that the response often becomes more variable, because the peak concentrations are closer to the threshold concentrations and variability in absorption will result in doses that do not exceed threshold so that no clinical effect is obtained. Further, the duration of response to a dose is related to the size of the dose. Small doses will give briefer clinical responses.

Controlled release carbidopa/levodopa was developed in the hope that gradual and sustained release of levodopa in the gut would result in more stable plasma concentrations of levodopa. The problem, however, is that absorption takes place in only the small bowel, a section of the gut where gut contents move along quickly with an average transit time of 2–3 h. The bioavailability of controlled release preparations are reduced by 25% and the peak

concentrations are at hour 2 rather than at hour 1. Clinically, controlled release preparations tend to be absorbed more erratically. Early in PD, the controlled release preparation is effective in reducing symptoms, but as the disease progresses, the therapeutic response becomes less predictable with each dose of sustained release carbidopa/levodopa. If unpredictability of response to each dose of carbidopa/levodopa is an issue, at this point predictability may be improved by switching back to regular or immediate release carbidopa/levodopa. The slower rise of plasma levodopa after controlled release carbidopa/levodopa causes a longer latency to the onset of antiparkinsonian actions. This delay in clinical effects may be counteracted by giving a small dose of immediate release carbidopa/levodopa with the controlled release preparation. Efforts to produce preparations with a more rapid onset of action combined with a more sustained delivery over many hours are underway.

Orally disintegrating cardidopa/levodopa is an immediate release preparation available in a 1:4 or 1:10 ration of carbidopa to levodopa. Limited clinical data on this drug is available. Since it may be given without water, it may be useful in patients experiencing delayed on from gastric emptying problems or in those undergoing surgery who cannot take other oral forms of carbidopa/levodopa.

The three-drug combination of carbidopa/levodopa/entacapone has come into clinical use in recent years and takes advantage of peripheral decarboxylase and COMT inhibitors to improve the clinical effect of levodopa. Although this combination appears similar in benefits and side effects to carbidopa/levodopa given separately with entacapone, ease of dosing and patient preference make this drug a useful alternative. Plasma levodopa levels with this three-dose preparation are more similar to controlled release preparations than to immediate release carbidopa/levodopa preparations.

Due to the inherent problems with the oral administration of levodopa, other means of drug delivery have been investigated. The intravenous infusion of levodopa along with orally administered decarboxylase inhibitor has resulted in a therapeutic benefit for parkinsonian patients. This type of infusion reduces motor fluctuations seen in parkinsonian patients. The requirement of a pump, poor solubility of levodopa necessitating large volumes of levodopa solution, and complexity of drug administration by an intravenous route have made this approach suitable for short times in experimental settings. Also, in the United States of America this can only be done under an investigational drug license.

Enteral infusions of levodopa began in the 1980s. Initial results were promising and the clinical benefit appeared similar to studies of intravenous levodopa infusion. Problems with this method of delivery included relatively large volumes of infusate because of levodopa's low solubility and problems with keeping the tube tip positioned in the duodenum. A more stable suspension of levodopa and carbidopa in a methycellulose gel has led to lower volumes of infusate that can be delivered by an ambulatory pump into tubes placed into the stomach or directly into the duodenum. The improvement in pump technology and drug formulation has led to chronic use of this type of therapy in a small subset of patients with motor fluctuations.

Transcutaneous delivery of levodopa is under investigation. In animals, the transcutaneous administration of an esterified form of levodopa can produce plasma levels that begin to approximate those that would be necessary in humans. Bypassing intestinal and first pass metabolism has been shown to result in stable levels of levodopa in plasma even in animals not given carbidopa. A very recent small study on humans suggests that the transcutaneous administration of levodopa results in stable plasma levels of levodopa and its metabolites.

The bean *Mucuna pruriens* is the only recognized food source of levodopa. Mucuna has been used for over two thousand years as part of Ayurvedic medicine and is being used in the United States as a 'natural levodopa.' To be successful, it generally requires the coadministration of carbidopa. The benefits of mucuna relative to commercially manufactured levodopa are unknown.

Side Effects of Levodopa

The most prominent peripheral adverse effects of levodopa are gastrointestinal anorexia, nausea, and vomiting. Tolerance to these effects generally develops over days to weeks. These effects are thought to arise from peripheral dopamine affecting the area postrema, which lies outside the blood–brain barrier. Increasing the carbidopa dose will reduce this effect, or the use of a dopamine D_2 receptor antagonist that does not enter the brain, such as domperidone, will counteract these adverse events.

Visual hallucinations become more common in PD as the condition progresses and cognitive impairment emerges. Earlier in PD, patients may experience hallucinations related to the use of levodopa. It is not unusual for these patients to describe nonthreatening visual hallucinations of animals or people. Typically, the hallucinations remit when the dose of levodopa and other antiparkinsonian medications are adjusted. More complex hallucinations may occur in advanced stages and are likely related to several factors, including polypharmacy with centrally acting medications used to treat PD as well as to underlying dementia. These types of hallucinations may not remit with the lowering of the dose of levodopa and require other interventions such as cholinesterase inhibitors or antipsychotics such as quetiapine or clozapine.

An increased prevalence of melanoma has been described in parkinsonian patients. Levodopa may be

metabolized into melanin in dopaminergic neurons, and this has raised the notion that levodopa use predisposes to the development of melanoma. Based on several studies, levodopa has not been demonstrated to have a causal association with melanoma, but further investigation may reveal the dynamics of this association.

See also: Dysarthria; Dysphagia; Parkinson's Disease: Genetics.

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Lick-force Rhythm Test

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Glossary

Central pattern generators – A group of interconnected neurons that provide for the timing and organization of rhythmic behavior patterns. A key feature of CPG's is that the behavior pattern does not rely on sensory feedback to trigger or elicit the next step in the response sequence.
Dopamine – A monoamine neurotransmitter involved in Parkinson's disease, schizophrenia, reward-related behavior, and drug abuse.
Dysarthria – Disturbance in the musculature used for speech.
Dysphagia – Difficulty in swallowing.
Fourier analysis – A set of operations for mathematically decomposing a time series of complex waveforms into combinations of separate, simple periodic components. In doing so, Fourier analysis extracts frequency (rhythmic) information from the data.
Hypoglossal nucleus – A group of motor neurons and interneurons in the brain stem that gives rise to the twelfth cranial nerve, which innervates the tongue muscles enabling the tongue to be quickly protruded and retracted.
Inferior olive – A dense collection of neuronal cell bodies that give rise to axons (the climbing fibers) that contact Purkinje cells in the cerebellum; involved in motor control and some types of learning.

Introduction

Rodents, like most mammals, have muscular tongues that bring food or water into the oral cavity for ingestion. Rhythmic repetitions of such tongue movements are usually referred to as licking. Although rodent licking is often

measured with the purpose of making inferences about motivation or hedonic qualities of ingestants, our development of the lick-force-rhythm methods arose from the interest in pharmacological and nervous systems variables that affect motor behavior.

It has been long noted that rodent ingestive licking has a 'stereotyped' quality in that the alternating protrusions and retractions of the tongue are quite regular. The well-regulated rhythmicity is thought to be due to central pattern generators (CPGs) in the brainstem that control the tongue's motor neurons located in the hypoglossal nucleus. Accumulating evidence shows that licking is not only controlled by brainstem structures, but is also modulated by cortical, subcortical, and cerebellar influences. Tongue sensory fibers, moreover, relay data on the properties of foods or liquids to both cortical and subcortical loci in the brain, thereby providing information that can influence the force, shape, orientation, and rhythm of the tongue as it extends from and returns to the oral cavity. It is also important to recognize that tongue control must be effectively coordinated with mastication, swallowing, and respiration. Rodent licking is the product of coordinated, parallel operations of many different brain structures. Thus, the measurement of rodent ingestive licking can be used to address a wide variety of biobehavioral questions.

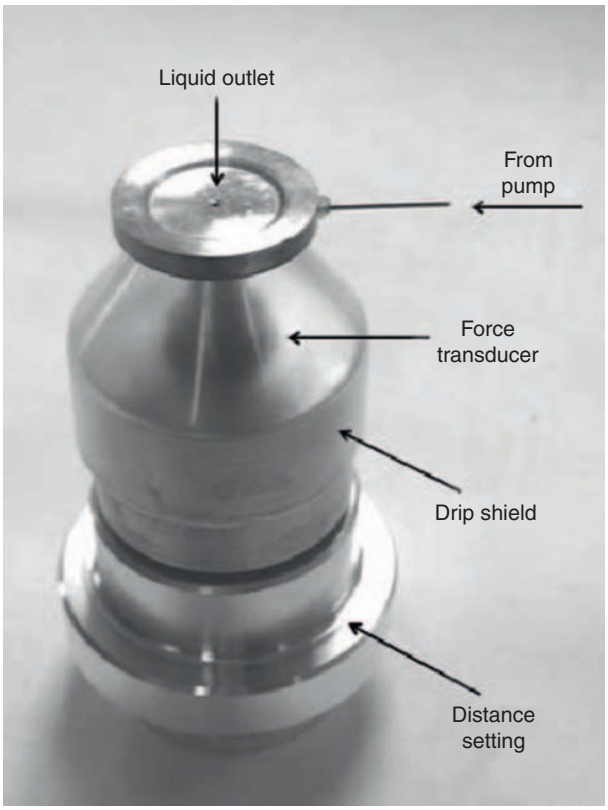

Figure 1 Photograph of a hardware ensemble for measuring tongue force during licking of liquids by rats or mice. Liquids to be ingested are carried to the lick disk by a computer-controlled peristaltic pump. The lick disk through which the liquid emerges for consumption is 18 mm in diameter. Rats or mice access the disk by protruding their tongues through a 12-mm-diameter hole.

Lick-Force-Rhythm Method

The lick-force-rhythm task for rodents was developed as an improved alternative to the more commonly used contact circuit method for quantifying licking. With the contact circuit, a very low voltage is arranged between a drinking spout and the floor of the chamber. When the rodent licks the spout, its body completes the circuit and an imperceptible, nondamaging electric current flows through the animal. The occurrence and duration of the contact can then be recorded. With the force method, an appropriately sensitive force transducer (see **Figure 1**) is used to measure the force of tongue contacts during licking. The force method eliminates the flow of current through the rats tongue and body and provides information about the tongue force which is not available with the contact circuit method. In addition, the force method requires interfacing and appropriate software for sampling and recording the force signal and parsing the analog signal into tongue-strike events and the time between these events (see **Figure 2**). Data analysis software provides measures of lick number, peak force, duration, interlick interval, and lick rhythm.

A lick begins when force rises above a force threshold (see **Figure 2**) and ends when the force drops below threshold. We usually select a threshold of 2 g-force for rats and 1 g-force for mice. The threshold is selected so that

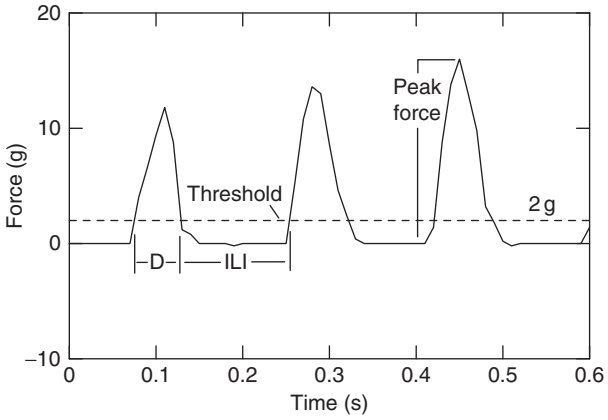

Figure 2 Illustration of dependent measures derived from the force–time output of the force-transducer detector shown in **Figure 1**. The force (expressed in gram-equivalent forces) of a rat's licking is plotted on the *y*-axis as a function of time on the *x*-axis. Three consecutive licks are shown. D = Duration of the lick; ILI = Interlick interval.

neither extraneous environmental vibrations nor vibrissae contacts will be mistakenly recorded as licks. Thus, the force-based method effectively eliminates artifacts that

often arise with contact circuit methods where, for example, water bridging via wet snout hair or wet vibrissae can cause the recording of impossibly short-duration events or mask lick detection. As shown in **Figure 3**, peak force, rhythm and number of licks recorded are all significantly affected by the distance between the rodent's muzzle and the location of the liquid to be ingested. For this reason, specifying and calibrating this distance is critical to obtaining reliable measurements of tongue motility during licking.

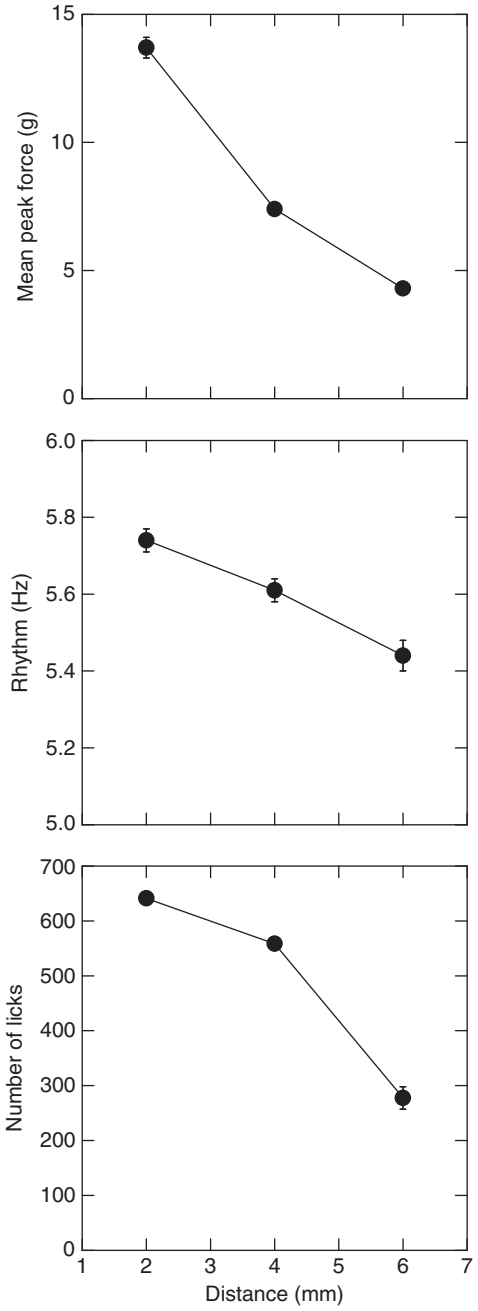

Figure 3 Effects on lick measures as a function of distance between the muzzle and the liquid orifice. Mean peak force (expressed in gram-equivalent forces), lick rhythm (Hz), and number of licks each significantly decreased as a function distance. Data were taken from Table 2 in Fowler SC, McKerchar TL, Zarcone TJ (2005) Response dynamics: Measurement of the force and rhythm of motor responses in laboratory animals. In LeDoux, M (ed.) *Animal Models of Movement Disorders*, pp. 73–100. San Diego, CA: Academic Press.

Experimental control of the 'lick-distance' is facilitated by mounting the transducer on a positioning device such as a micrometer. Our experience suggests that distance specification is facilitated by locating the liquid source below the horizontal floor that supports the rodent as it licks. The arrangement is more 'natural' than the sipper tube located above the animal, because licking of liquid ingestants, such as water, from horizontal surfaces (i.e., water puddles) evolved long before sipper tubes were invented. By careful specification of the distances and force variables, one can probe for deficits in orolingual motor behavior by posing distance or force challenges. In regard to quantifying the lick rhythm (i.e., frequency of nearly periodic repetitions of licks expressed in cycles per second or Hz), we prefer the Fourier analysis approach because it is the method of choice for detecting periodic repetitions in time series of analog data.

Research Applications

The lick-force-rhythm method has been used in research involving the motor effects of drugs, neurotoxic brain lesions, genetic variables, aging, and neurodegenerative diseases. We will now provide a brief synopsis of findings across several studies these domains.

Drug Effects

In the case of drug effects, the atypical antipsychotic drug, clozapine was shown to reduce lick rhythm and peak force in male Sprague–Dawley rats (see **Figure 4**). In addition, clozapine caused irregularly shaped force-time waveforms compared with saline control conditions (note ellipse marking a 'notched' waveform in **Figure 4**). The notched waveforms likely reflect poor tongue control arising from the strong sedative effect of this drug upon acute administration.

Neurotoxic Lesions

Other research has assessed linguomotor function in a rat model of Parkinson's disease caused by unilateral dopamine depletion of the striatum produced by 6-hydroxydopamine (6-OHDA). Dopamine depletion significantly reduced all of the dependent measures discussed: peak force, number of licks, and lick rhythm. Such results suggest that the lick-force-rhythm method may be a useful procedure for evaluating experimental therapies in Parkinson's disease models. In a different study examining the role of the

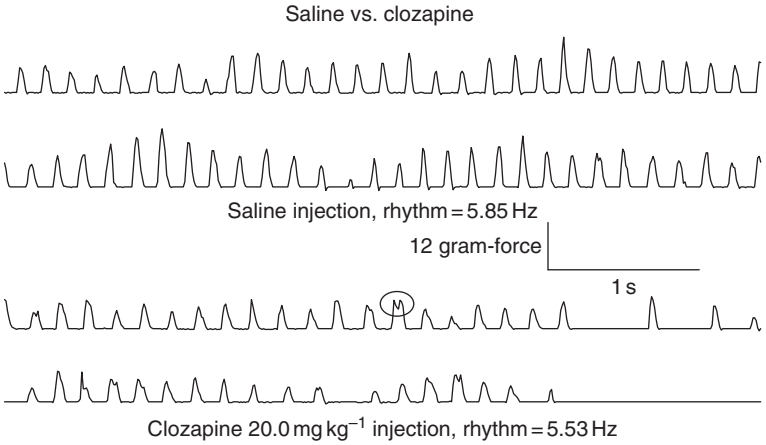

Figure 4 Effects of saline (top two rows) and the atypical antipsychotic drug, clozapine (bottom two rows), on lick-force-time waveforms generated by a rat licking water from the disk shown in **Figure 1**. Note the diminution in peak force in the lower set of graphs, as well as the appearance of long inter-lick intervals. An illustrative example of a 'notched' lick waveform induced by 20 mg kg^{-1} clozapine is indicated by the ellipse.

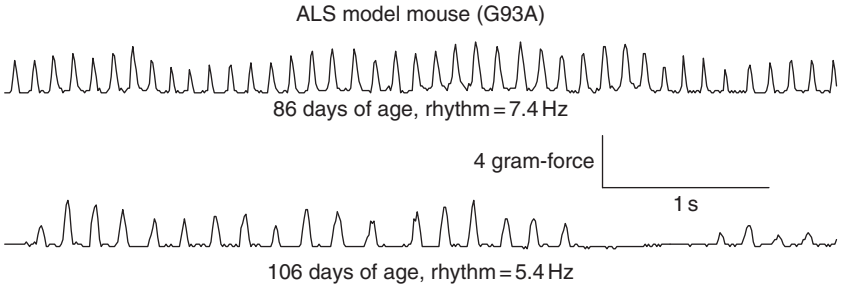

Figure 5 Change in licking rhythm as a function of disease progression in an ALS model mouse (G93A).

olivocerebellar system in licking patterns, rats were exposed to 3-acetylpyridine (a neurotoxin that preferentially kills inferior olive neurons) prior to testing on the lick-force task. Compared with baseline measures, near-total destruction of the inferior olive neurons reduced lick peak force and number of licks. Interestingly, lick rhythm was preserved, showing the independent nature of the lick measures we have described. Additionally, the lack of effect on lick rhythm suggests that the inferior olive is not a major CPG for ingestive licking.

Inbred Mice

In the context of genetic influences on lick rhythm, recent results suggest that differences in lick rhythm among inbred strains are potentially traceable to genomic differences. For example, the inbred strains of mice 129Sv/J, C3H/J, DBA/2J, and BALB/cJ exhibit similar lick rhythms around 8.2 Hz, whereas C57BL/6J mice consistently have rhythms near 7 Hz. Mice that peripherally (i.e., outside the brain and spinal cord) overexpress neurotrophic peptide 3 exhibit a significantly decreased lick peak force, but do not have altered lick rhythm or number of licks.

Rodent Aging Models

In human aging, diminished tongue motility and oromotor force generation can contribute to dysarthria and dysphagia. The F344 and F344/BN rat models of aging exhibit significant decreases in licking rhythm beginning in middle age (18 months for these rats). The decline in tongue motility may be related to changes that have been reported not only in neuromuscular function, but also in brain regions associated with the coordination of licking, swallowing, and respiration (e.g., the basal ganglia, cerebellum and medial bulbar reticular formation). Although these rats did not exhibit age-related tongue force deficits, they have not been challenged with increased tongue force requirements in a manner analogous to human clinical tests.

Neurodegenerative Models

Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS) are neurodegenerative diseases with prominent oromotor impairments. As rodent models continue to develop, the lick-force-rhythm task should be a valuable tool in charting the course of motor

function loss as well as providing a set of measures for evaluating experimental therapies. An illustrative example of the rapid decline in orolingual motor function in the SOD1-G93A mouse model of ALS is shown in **Figure 5**. The prominent decline in lick rhythm suggests the existence of neuromuscular deficits associated with hypoglossal motor neuronal degeneration in this model of ALS.

Summary

Although licking may seem like a simple response, appreciation of the various brain regions involved in licking control and its synchronization with other biological functions, such as swallowing and respiration, reveals a highly modulated, adaptable behavior. Such appreciation has led us to suggest that licking may be used to investigate a wide range of questions. Our methods of addressing those questions rely on force-based measurement of licking. Not only does the method provide for a more naturalistic posture while licking, but also the additional force and rhythm-related information may be recorded. We have reviewed several domains of investigation spanning pharmacological work, murine genetics, and neurodegenerative disease where our methods have been applied. We hope that our descriptions demonstrate the utility of force-based methods for a wide variety of research questions.

See also: 6-OH Dopamine Rat Model; Bradykinesia; Dopamine Depletors and Movement Disorders; Dysarthria; Dystonia, Drug-induced (Acute); Huntington's Disease; Neuroleptic-induced Nonhuman Primate Models of EPS and TD; Neuroleptics and Movement Disorders; Oral Dyskinesia; Parkinson's Disease: Definition, Diagnosis, and Management; Press-while-licking Task.

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Locus Coeruleus and Norepinephrine

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Glossary

Alzheimer's disease (AD) – The most common form of dementia, afflicting up to 40% of individuals over 80 years of age. AD is a multisystem neurological disease with alterations in the hippocampus, cortex, and basal forebrain cholinergic neurons. Some of the most common pathological signs of AD are intracellular neurofibrillary tangles and extracellular amyloid plaques.

Dyskinesia – Abnormal involuntary movements occurring as a complication during the course of DA-replacement therapy in PD patients.

Locus coeruleus (LC) – A nucleus in the pontine region of the brain chiefly consisting of noradrenergic (NE) neurons, which regulate sleep/wakefulness, memory, and attention among other things. NE neurons send their axons to the spinal cord and most regions of the brain, most likely playing a regulatory role in many brain regions.

Microglial cells – These cells play a major role in the innate immune system of the central nervous system. Microglial cells can exist in a resting state, and when triggered by an external or internal trigger, they will become activated and release proinflammatory cytokines, such as IL-1 and TNF-α.

Norepinephrine – One of the monoamine neurotransmitters, which is found in both central neurons of the locus coeruleus and peripheral neurons (sympathetic ganglion cells).

Oxidative stress – This cellular condition is common and thought to play a major role in cell damage occurring in many types of disorders, such as neurodegenerative diseases, cardiovascular disease, and stroke, as well as in the normal aging process. It is caused by an imbalance between production and scavenging of free radicals, which are normally broken down by endogenous enzymes in the cell, including glutathione and super oxide dismutase.

Parkinson's disease (PD) – A motor disorder characterized by muscle rigidity, tremor, bradykinesia (slowness of movement), akinesia (lack of movement), and in some cases, cognitive impairment. PD is a neurodegenerative disorder affecting dopaminergic neurons of the substantia nigra, noradrenergic neurons (NE) of the locus coeruleus, olfactory system, motor neurons, and other nerve cells in the brain; it is thought to be caused by an interplay of genetic and environmental factors.

Introduction

Due to the 'baby boomer' generation, the rate of senior citizens in the western world will increase dramatically in the next 2–3 decades. For example, the number of individuals over the age of 65 is expected to double by the year 2030 in the United States. With this increase in aged individuals, we will see a specialized set of health issues that may become a major public health problem. In particular, movement dysfunction and cognitive decline become progressively worse as the individual ages, so that up to 50% of individuals over the age of 85 have one or both of these conditions. This article provides an interesting correlation between two degenerative disorders that are known to increase with age: Parkinson's disease (PD) and Alzheimer's disease (AD). Interestingly, a significant portion of individuals who have been diagnosed with idiopathic PD develop cognitive impairment with time, and conversely, individuals with AD are known to exhibit a progressive decline on Parkinson's rating scales. Noradrenergic neurons (norepinephrine, NE) of the pontine nucleus locus coeruleus (LC) have been noted to deteriorate in both number and function in AD and PD patients. Recent data even suggest that LC-NE neuronal loss occurs relatively early in the disease process for both conditions, before a significant loss of nigra dopamine neurons (PD) or basal forebrain cholinergic neurons (AD) has occurred. In addition, animal studies using neurotoxins targeting LC-NE neurons demonstrate that both cholinergic and dopaminergic central neurons are negatively affected by noradrenergic degeneration. The data therefore suggest a causative role for LC-NE neurons in the progressive degeneration of both cholinergic and dopaminergic central neurons, and also that the loss of function of this particular cell group in the brainstem is a common denominator for these two diseases.

Functional Roles of the Central NE Transmitter System

There is clear evidence for a strong influence of the LC-NE system on learning and memory. NE, released at nerve terminals in target areas of the limbic system, facilitates shifts in attention, information processing, and memory through its well-documented gating and tuning effects, and its permissive role in hippocampal long-term potentiation (LTP). Specifically, it has been shown in both humans and animal models that LC-NE neurons play a crucial role in

- Inhibitory avoidance
- Delayed matching-to-sample tasks
- Spatial reference and spatial working memory
- Novelty seeking behavior
- Visual discrimination
- Motor coordination
- Motor-related memory
- Rapid eye movement (REM) sleep
- Attention and anxiety

Compton and collaborators found that unilateral or bilateral destruction of the LC-NE nucleus in rodents leads to moderate versus severe deficiencies in spatial memory tests such as the Morris water maze and the Greek cross task. Collier and collaborators have shown that transplantation of fetal LC-NE neurons to the brain of aged rats can restore spatial memory function similar to that found in young rats. Activation of the LC-NE neurons by electrical stimulation results in an increased NE release in areas of the limbic system such as the amygdala and the hippocampus, and enhances both spatial and emotional memory task performance. Thus, encoding and storage of memory for both emotional and spatial events seem to be dependent upon LC-NE stimulation, at least in animal models. In humans, it has been shown that genetic variants of NE receptors correlate with performance in both memory and irritability tasks, further substantiating the importance of the NE neurons in memory-related processing. There are several other higher brain functions influenced by LC-NE neurons, such as REM sleep, attention, depression, and motor coordination; therefore, it may not be a coincidence that one of the earliest signs of PD is related to disruption of attention, endogenous depression, and development of sleep problems (see below).

Altered Noradrenergic Neurotransmission During 'Normal' Aging

It has been documented that aging may alter endogenous neurotransmitters, especially acetylcholine, NE, and dopamine. Numerous studies of brains from aged humans and other mammals have demonstrated a significant loss of NE phenotype in the LC nucleus during aging, although others have found less marked effects of aging on LC-NE cell number. A summary of previous findings in humans, in terms of 'normal' aging, age-related disease, and LC-NE cell loss, is shown in **Table 1**. In experimental animal models, significant reductions in NE activity have been reported throughout the aged brain, as well as a loss of NE synapses in the frontal cortex. Furthermore, a number of other indices of NE function have been found to be altered in the aged rat, such as loss of postsynaptic-α and β-adrenergic receptor sensitivity, increased sensitivity to the noradrenergic toxin *N*-(2-chloroethyl)-*N*-ethy-2-bromobenzylamine (DSP-4), and decreased behavioral response to NE agonists in the aged rat. A positive correlation has been shown between the loss of LC-NE neurons and the level of cognitive impairment in aged mice. In addition, as mentioned earlier, transplantation studies have demonstrated that cell replacement with fetal LC-including transplants to the hippocampal formation can alleviate age-related memory loss in the rodent. These studies suggest that there are functional alterations in the NE transmitter system that have consequences for behavioral components regulated by this pathway.

Table 1 LC-NE loss in aging and age-related neurodegenerative disease

Condition	*Direction of LC-NE alteration*	*References*
Normal human aging	Loss of NE phenotype in LC	Vijayashankar and Brody and Chan-Palay and Asan
Aged mouse brain	↓ NE activity in aged mouse brain	Qi and Nomura
	↓ NE synapses in cortex	Ishida et al.
Aged rat	Increased sensitivity to NE neurotoxins	Riekkinen et al.
PD	Early loss of LC-NE neurons	Braak and Del Tredici
AD	Early loss of LC-NE neurons	Weinshenker
AD	Density of LC-NE neurons ↓50%	Strong et al.
AD	↓ NE concentrations in limbic structures	Matthews et al.
PD animal model	Loss of NE lead to increased severity and earlier onset of L-DOPA-related dyskinesias	Fulceri et al.
PD mouse model	Previous LC lesion increased SN DA sensitivity to MPTP lesions	Fornai et al.

Loss of LC-NE Neurons is an Early Event in PD

Recent data by Braak and other investigators have clearly demonstrated that LC-NE cell loss or phenotypic loss occurs early in PD. It is important to note that actual cell death versus phenotypic loss of this neuronal population can only be assessed by using a specific marker for LC-NE neurons (most commonly used marker for this population is dopamine-β-hydroxylase (DBH), antibodies) in combination with a more common neuronal marker such as neurofilament or cresyl violet. These authors found that in a number of patients, the disease process starts in lower brainstem regions, including motor neurons and LC-NE neurons, and only later extends progressively to include substantia nigra dopamine (SN DA) neurons. Thus, the recently described Braak neuropathological staging of PD includes loss of brainstem motor neurons, olfactory neurons, and LC-NE neurons, in addition to the classical progressive SN DA cell loss. This progression had already been mimicked in animal models, since several investigators demonstrated prolonged and increased effects of DA neurotoxins, such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 6-hydroxydopamine (6-OHDA), after lesioning the LC, using a selective NE neurotoxin, DSP-4. These studies further pointed to a causative effect of LC-NE degeneration upon SN DA neurons, and further basic science work was initiated as described in the following section regarding the biological mechanisms involved. There is also behavioral evidence that alterations to the LC-NE system underly the earlier events in PD patients, such as sleeping disturbances and depression, which are noted years before the onset of the classical signs of the disease (tremor, bradykinesia, and rigidity). It is also possible that LC-NE degeneration directly contributes to the motor impairment that develops over time in PD patients, since studies performed by Paula Bickford and her collaborators, as well as others, have shown that noradrenergic innervation of the cerebellum is deficient in aging and results in hampered motor coordination and motor-related memory performance.

A commonality between NE and DA neurons in the brain is the dependency on similar growth factors. In recent work, we performed studies of mice, genetically engineered to be deficient in the glial cell line-derived neurotrophic factor ($GDNF^{+/-}$ mice), a DA-trophic factor. As shown in our previous work by Boger et al., 2006 and in **Figure 1(a)** and **1(b)**, $GDNF^{+/-}$ mice exhibited loss of both SN DA and LC-NE neurons. However, the LC-NE loss was evident already at birth, while SN DA loss occurred later in life. These studies suggest that even though SN and LC-NE neurons are both dependent on GDNF for their maintenance, the NE population appears more vulnerable,

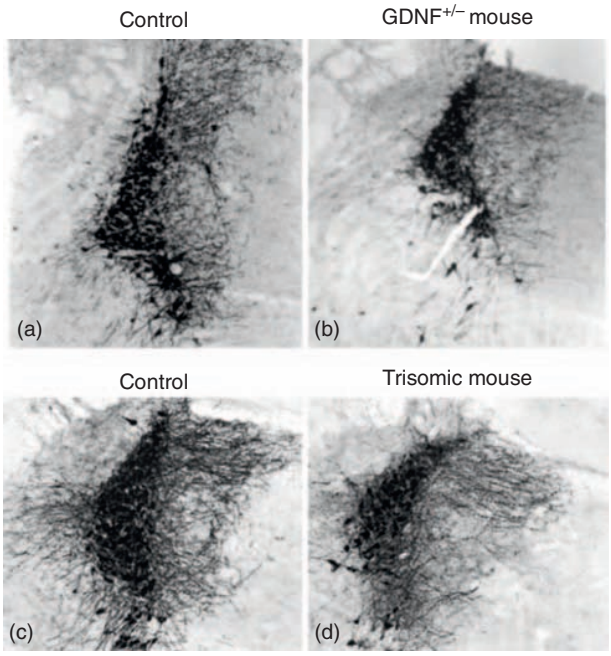

Figure 1 Loss of LC-NE neurons in mice with a partial genetic loss of GDNF (GDNF ± mice) and in a mouse model for DS and AD, the Ts65Dn mice. These data show that the LC-NE neurons are sensitive to different types of genetic alterations such as lack of growth factors (B), or chronic increase in oxidative stress which occurs in Ts65Dn mice (D), suggesting a selective vulnerability of these particular neurons.

at least to the loss of GDNF, and deteriorates at an earlier age in $GDNF^{+/-}$ mice. Interestingly, GDNF is reduced in the SN of PD patients; therefore, clinical trials are being conducted using GDNF supplementation, either by viral delivery techniques or by the direct infusion of GDNF into the brain.

The influence of NE neurons upon progression of PD is not limited to loss of the SN DA neurons; studies both in humans and in animal models have recently suggested that the integrity of the LC-NE neurons is related to the onset of L-DOPA-induced dyskinesia. Animal studies by Angela Cenci and others, using selective NE neurotoxins, demonstrated that the loss of NE innervation accelerates the onset and increases the severity of L-DOPA-induced dyskinesias.

Loss of LC-NE Neurons in AD

AD is characterized neuropathologically by β-amyloid-containing plaques, tau-containing neurofibrillary tangles, and progressive loss of basal forebrain (BF) cholinergic neurons. In addition to the hallmark cognitive impairment, the disease is associated with other neuropsychiatric abnormalities, including sleep problems, aggression, and depression. Some, if not all, of these additional neuropsychiatric symptoms can be attributed, at least in part, to an early loss of NE innervation of cortical areas. Indeed, it has been shown that patients with AD have a significant reduction in NE concentration in limbic structures, and this NE reduction correlates with the level of dementia. Interestingly, it appears that LC-NE neurons may degenerate before the significant loss of cholinergic neurons has occurred.

In our laboratory, we are studying a trisomic mouse model for Down syndrome (DS), the Ts65Dn mouse. More than 90% of individuals with DS develop pathological hallmarks of AD, and more than half also develop cognitive impairment consistent with the findings in AD patients. Ts65Dn mice exhibit progressive deficiencies in working memory, cholinergic cell loss, and altered nerve growth factor (NGF) transport to the BF, all similar to the findings in AD patients. Our recent data show that Ts65Dn mice exhibit an early loss of LC-NE neurons (see **Figure 1(c)** and **1(d)**) and that LC-NE alterations occur prior to cholinergic cell loss, making this animal model an interesting target for mechanistic studies of the relationship between LC-NE denervation and cholinergic neuron vulnerability. In addition, Ts65Dn mice show early signs of mitochondrial dysfunction, with increased oxidative stress occurring in hippocampal, cortical, and subcortical regions, thus recapitulating cellular alterations observed in individuals with AD and DS. We found that the LC-NE degeneration in Ts65Dn mice correlates with elevated oxidative stress markers, and that vitamin E treatment reduced oxidative stress markers as well as reduced degeneration of LC-NE neurons in Ts65Dn mice, suggesting that oxidative stress aggravates loss of LC-NE neurons in our animal model. These data suggest a possible preventive antioxidant treatment in DS individuals, to prevent LC-NE cell loss, that may directly or indirectly protect against the cholinergic loss occurring later in the disease process.

Why Do LC-NE Neurons Die with Aging and in Neurodegenerative Diseases?

Central monoamine neurons such as LC-NE and SN DA neurons are especially sensitive to neurotoxin exposure. It has been shown that LC-NE neurons are selectively sensitive to the toxin DSP-4. Grzanna and investigators found that NE axons originating in non-LC-NE neurons were largely resistant to the neurotoxic action of DSP-4. This neurotoxin reduces the NE levels in cerebral cortex, cerebellum, and hippocampal formation, but has no effect on hypothalamic NE levels, further supporting its LC-NE specificity. The biological mechanism for DSP-4 actions on LC-NE neurons is largely unknown, although previous studies suggested a role for monoamine oxidase-B (MAO-B) in DSP-4 activity. The damage induced by DSP-4 has been related to the formation of a cyclic compound (azyridinium ion) that in turn would be metabolized by MAO-B and taken up by LC-NE terminals. The selective and irreversible MAO-B inhibitor L-deprenyl

prevents chronic loss of LC-NE neurons induced by DSP-4. However, another selective MAO-B inhibitor (MDL72974) failed to protect these neurons against DSP-4. In addition, recent studies with MAO-B knockout mice indicated that this enzyme is not essential for DSP-4 activity. While these knockout mice were protected from the dopamine and serotonin neurotoxin 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy'), they were as sensitive to DSP-4 as the wild-type littermates. Recently, it has been shown that L-deprenyl and its metabolites were also able to block DSP-4 uptake, suggesting that L-deprenyl's neuroprotective efficacy may instead rely on preventing DSP-4 uptake via the NE transporter (NET), although this mechanism of action still requires study. DSP-4 effects are more severe in aged than in young rats, suggesting perhaps altered responsiveness to this neurotoxin in aged rats and providing a potential explanation for the vulnerability of LC neurons to toxic events with aging.

Another explanation as to why LC-NE neurons often succumb to endogenous and exogenous irritants is related to their spontaneous activity, and hence, to high energy demand and high production of reactive oxygen species. Recent work has shown that aberrant oxidation of NE via *o*-quinone may be involved in the pathogenetic mechanisms underlying the degeneration of LC-NE cell bodies in PD, AD and loss of these neurons during the normal aging process, providing further evidence for NE neurons' vulnerability during these conditions.

A Reciprocal Dependency of Cholinergic, Noradrenergic, and Dopaminergic Transmitter Systems in the Brain

An interesting correlation between LC-NE loss and ChAT activity in the LC region was presented by Strong and collaborators, who found that both the density of LC-NE neurons and presynaptic ChAT activity in the same region were reduced by an average of 50% in patients diagnosed with AD compared with age-matched control subjects. It is possible that a 'downwards' spiraling effect may occur in this disease, since ChAT activity has been shown to affect the physiology of LC-NE neurons, which in turn affects many parameters of hippocampal and forebrain activity, such as expression of neurotrophic factors and immediate early genes (cAMP response element binding (CREB) and c-fos). As demonstrated in **Figure 2**, LC-NE neurons innervate and influence both BF and substantia nigra, providing a powerful 'triangle' of action between the limbic system, midbrain, and pontine systems influencing movement and cognition. It is easy to imagine that an imbalance in this system can have significant results on higher brain functions such as movement and cognitive performance, especially when considering the powerful behavioral effects that are achieved by pharmacological agents targeting cholinergic, dopaminergic, or noradrenergic neurotransmission.

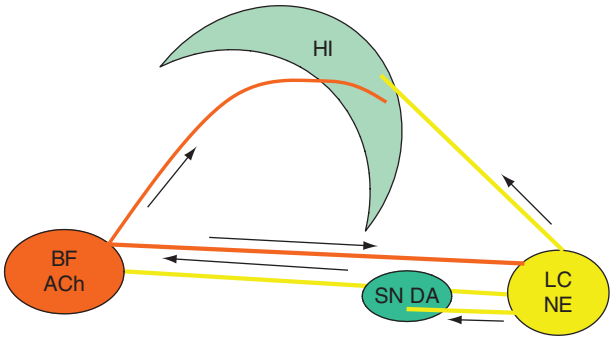

Figure 2 The cholinergic basal forebrain neurons (BF) innervate the hippocampus (HI), substantia nigra (SN), and locus coeruleus (LC), and the LC-NE neurites innervate all the other brain regions involved. The innervation patterns indicate a reciprocal dependency of intact transmission for the three transmitter systems, and it is likely that LC-NE neurons are the first to upset this balance between the BF, hippocampus, and midbrain/pontine regions during either AD or PD, since they appear to be more sensitive to endogenous and exogenous irritants than other neuronal populations.

Neuroprotective Role for LC-NE Neurons

Although it has not been completely determined yet, studies suggest that noradrenergic innervation of target areas, including the SN, BF, and hippocampus, has multiple neuroprotective functions. Studies have shown that LC-NE neurons are dependent on two growth factors: GDNF (glial cell line-derived neurotrophic factor) and BDNF (brain-derived neurotrophic factor). BDNF is also a strong neuroprotective agent for BF cholinergic neurons, and both BDNF and GDNF are neuroprotective for SN DA neurons. In addition, it was shown that LC-NE activity regulates BDNF expression in the hippocampus; lower spontaneous firing rates of LC-NE neurons occurring during, for example, sleep give rise to a significant reduction in BDNF mRNA expression in target areas. This member of the neurotrophin family has been implicated in both AD and PD, with lower levels of BDNF found in the hippocampus and the SN, respectively. It is likely that the loss of LC-NE neurons early in the disease process, coinciding with a degeneration of noradrenergic innervation in these target regions, would result in a loss of target growth factor support that would in turn jeopardize BF cholinergic, hippocampal, and SN DA neuron function and survival.

A second prominent theory for the LC-NE dependency of BF cholinergic and SN DA neurons is the rich microglial environment, which is found intermingled with both of these neuronal populations. Microglia contain functional NE receptors, and culture studies indicate that NE attenuates the inflammatory response of these cells. A DSP-4 lesion of NE innervation in rodent models results in the activation of microglial cells in the BF and SN, suggesting a potential role for NE in suppressing

inflammation in these regions. Neuroinflammation and secretion of proinflammatory cytokines from microglial cells have been demonstrated in both AD and PD; BF cholinergic and SN DA neurons are extremely sensitive to microglial activation, and in vitro studies demonstrate a direct connection between proinflammatory cytokines and disease progression in both AD and PD patients and animal models for these two neurodegenerative diseases. Third, it is also possible that these neuronal populations innervated by LC-NE neurons may be damaged by increased reactive oxygen species production during altered LC-NE neurotransmission, especially if free radical scavenging enzymes are deficient with aging. NE neurons are known to respond to damaged processes by producing more NE in remaining neurons, leading to increased toxicity by increased NE metabolism. Therefore, increased cellular energy metabolism and oxidative stress should be considered in LC-NE influence on both DA and cholinergic neurons.

Conclusions

The data discussed here collectively demonstrate a prominent and often neglected role for LC-NE neurons in protecting both SN DA and BF cholinergic neurons from degeneration with normal aging and age-related neurodegenerative disease. These data provide evidence that PD and AD share common elements, including profound LC cell loss, and may in fact be different manifestations of a common pathophysiological process. Specifically, it is thought that LC-NE neurons regulate expression of growth factors (GDNF and BDNF) and reduce microglial activation, thereby eliminating dangerous proinflammatory cytokines in these brain areas. Therefore, targeting LC-NE neuroprotection may function indirectly to alleviate problems associated with both cognitive impairment and movement disorders of aging.

Acknowledgments

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See also: Braak Classification; Parkinson's Disease: Definition, Diagnosis, and Management.

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Lupus Chorea

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Glossary

Antiphospholipid antibodies – A class of autoantibodies that includes anticardiolipin antibodies and the lupus anticoagulant. Antiphospholipid antibodies have been associated with clotting disorders and fetal loss. Circulating antiphospholipid may be seen in the normal population. Illnesses associated with antiphospholipid antibodies include primary antiphospholipid antibody syndrome and antiphospholipid antibody associated with another autoimmune disorder, such as systemic lupus erythematosus (secondary antiphospholipid antibody syndrome).
Autoimmunity – The failure of the immune system to adequately differentiate the organism's own tissue (self) from foreign tissues, resulting in the activation of immune mechanisms against self antigens.
Chorea – Involuntary movements that are rapid, purposeless, and flowing.
Choreoathetosis – Involuntary movements that combine the rapid, purposeless, and flowing movements of chorea with the slower more sinuous movements of athetosis.
Systemic lupus erythematosus – A systemic autoimmune disease characterized by variable involvement of the skin, muscles, joints, heart, liver, kidney, lungs, and central nervous system and the presence of certain antibodies against self antigens, including anti-DNA antibodies.

Definition and History

The involvement of the central nervous system (CNS) in systemic lupus erythematosus (SLE) was first noted by Hebra and Kaposi in 1875. Chorea is a known manifestation of SLE and is one of the 19 neuropsychiatric syndromes identified in an American College of Rheumatology consensus document. While neuropsychiatric involvement in SLE is common, occurring in up to 90% of cases, chorea is a rare manifestation. Studies suggest movement disorders, especially chorea, occur in 1–4% of SLE cases.

Pathogenesis/Pathophysiology

Autopsy studies have not established a clear localization or specific pathology for lupus chorea. Most studies have shown multiple small infarctions in gray and white matter with cerebral atrophy and granular cortical atrophy. Although some cases have shown damage (neuronal loss and gliosis) to striatal structures, there are clear cases in which striatal damage did not cause chorea. Lupus chorea has an immune-mediated substrate. Three possible mechanisms have been proposed: (1) inflammatory vasculopathy with ischemic basal ganglia injury, (2) immune complex-mediated neuronal dysfunction, and (3) immune and nonimmune effects of infection or toxins. The relationship with antiphospholipid antibodies and lupus anticoagulant suggests that antibody-mediated CNS dysfunction is important in the production of the disorder.

Epidemiology/Risk Factors

SLE has a prevalence of 6–50 per 100 000. Women are more susceptible to SLE as are persons of African Caribbean and Asian racial origin. Neuropsychiatric involvement in SLE is common, affecting up to 90% of patients. Chorea is a well-recognized, although a rare manifestation of neuropsychiatric SLE, affecting 1–4% of patients. Parkinsonism and myoclonus are also seen. In series of SLE cases with neuropsychiatric involvement, the prevalence of antiphospholipid (anticardiolipin) antibodies and lupus anticoagulant was higher than in cases without neuropsychiatric involvement.

Clinical Features and Diagnostic Criteria

A review of 51 cases of SLE chorea found that the gender ratio of 9:1 favors women, similar to the ratio in SLE itself. The mean age at the onset of chorea in SLE is 19 years, and children seem more likely to have choreic manifestations. Since the age range is similar, lupus chorea is often confused with Sydenham's chorea. In about 25% of lupus chorea cases, chorea is the presenting symptom of the lupus. In some cases, the chorea is precipitated by pregnancy or oral contraceptive use. The duration of chorea ranges from days to a few years, and some patients have recurrent bouts of chorea. Chorea is most often generalized, but may have a hemibody distribution. Common comorbid symptoms

include dysarthria, hypotonia, confusion, psychosis, seizures, hemiplegia, and mental deterioration.

An ad hoc committee of the American College of Rheumatology lists two diagnostic criteria: (1) observed abnormal movements and (2) random, unpredictable sequence of movements. The criteria exclude Wilson's and Huntington's disease, and licit and illicit medication-induced movements and list associations with stroke/vascular malformation/hypoxia, tumor, chorea gravidarum, Sydenham's chorea, and antiphospholipid antibody.

Differential Diagnosis

Choreic movements must be differentiated from dystonia, myoclonus, and tics. The differential diagnosis of choreic movements includes degenerative diseases (Huntington's disease, dentatorubropallidoluysiian atrophy), Sydenham's chorea, chorea gravidarum, chorea associated with drugs or metabolic derangements, chorea-acanthocytosis, and benign hereditary chorea.

Diagnostic Workup/Tests

Using clinical criteria, the diagnosis of SLE can be made with 75% sensitivity and 95% specificity. The diagnosis requires the presence of four or more of the following criteria: malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis, renal disorder, neurologic disorder (seizures or psychosis), hematologic disorder, immunologic disorder (anti-double-stranded DNA, anti-Smith or antiphospholipid antibodies), or antinuclear antibodies. There is a relationship between the presence of antiphospholipid antibodies and chorea. Chorea is one manifestation of primary antiphospholipid antibody syndrome and there is a correlation between the presence of chorea and the presence of antiphospholipid antibodies in primary antiphospholipid antibody syndrome.

In children and adolescents, it is most important to exclude Sydenham's chorea in the context of acute rheumatic fever (ARF). The diagnosis of ARF is made by Jones criteria. ARF is characterized by the presence of two major or one major and two minor Jones criteria with evidence of recent group A β-hemolytic strep infection. Major criteria include migratory polyarthritis, carditis, erythema marginatum, subcutaneous nodules, and chorea. Minor criteria include fever, arthralgia, elevated sedimentation rate, elevated C-reactive protein, and P–R interval prolongation on electrocardiogram. Streptococcal infection can be documented by elevated antistreptolysin O titers or throat culture. The presence of carditis should be assessed using echocardiogram. Isolated cases have shown increased T1 signal intensity in the basal ganglia in patients with lupus chorea.

Management

Appropriate treatment for active SLE is the most important approach to lupus chorea. A treatment guideline published in 2007 suggested that treatment of SLE should be individualized and the most important drugs were nonsteroidal antiinflammatory agents, hydroxychloroquine, corticosteroids, and immunosuppressive drugs (azathioprine, cyclosphosphamide, methotrexate, and mycophenolate). Antiinflammatory agents and hydroxychloroquine are useful for milder symptoms, but more aggressive management is generally required for C lupus. In these cases, corticosteroids and immunosuppressive drugs are recommended. Chorea generally improves with adequate treatment of the disease. In a single case, chorea responded dramatically to intravenous immune globulin when corticosteroid treatment was not tolerated.

Should chorea remain a problem in appropriately treated patients, additional symptomatic therapy for the movements themselves should be considered. There is limited evidence on which to base recommendations, but positive responses to valproic acid and to dopamine receptor blocking drugs such as haloperidol have been reported. Agents that effectively treat chorea in other disorders, such as tetrabenazine and amantadine, can also be considered. It is important to initiate symptomatic treatments at a low dose and to titrate the drugs as tolerated. Since lupus chorea tends to be self-limited, frequent reassessments for the need for continued treatment are essential.

Prognosis

With appropriate treatment of the SLE, chorea is generally self-limited. However, chorea in SLE may be recurrent. The overall prognosis for SLE depends on the aggressive nature of the disease itself and on the progressive accumulation of end-organ damage produced by the underlying disease process.

See also: Chorea; Chorea–acanthocytosis; Chorea Gravidarum; Choreiform Disorders; Postpump Chorea; Senile Chorea; Sydenham's Chorea.

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Relevant Websites

www.lupus.org
www.guideline.com

M

Magnetoencephalography (MEG)

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Glossary

Dewar – Special container used in MEG systems to hold liquid helium and protect the subjects from the cold liquid.
Event-related fields – Neuromagnetic time series that were averaged time-locked to a stimulus. Event-related fields represent the time-locked responses of brain areas to a sensory, motor, or cognitive event.
Local field potential (LFP) – LFPs represent extracellularly recorded voltage fluctuations of a local neuronal population.
Postsynaptic potential – Membrane depolarization (hyperpolarization) of the postsynaptic neuron following excitatory (inhibitory) input.
Superconducting quantum interference devices (SQUIDS) – Highly sensitive sensors used in MEG systems for the measurement of tiny magnetic fields originating in the brain. SQUIDS operate at a very low temperature (−269 C) and require liquid helium for cooling.
Superconductivity – The absence of electrical resistance in certain materials at very low temperatures.
Tesla – Physical unit of magnetic flux named after Nikola Tesla.

Magnetoencephalography (MEG) is a noninvasive brain imaging technique that records the small magnetic fields associated with the electrical activity in the brain. The same electrical brain activity leads to fluctuations of electrical potentials that can be recorded at the scalp with the related measurement technique Electroencephalography (EEG).

MEG provides noninvasive recordings of brain activity with good spatial resolution and a very high temporal resolution (about 1 ms). Measurements are challenged by the small amplitude of the neuromagnetic field, which is typically below 10^{-12} Tesla. The earth's magnetic field for comparison is several orders of magnitude larger (about 10^{-4} Tesla). Consequently, MEG recordings require highly sensitive detectors and efficient attenuation of environmental magnetic background activity. State-of-the-art MEG systems are equipped with about 300 highly sensitive superconducting quantum interference devices (SQUIDS). These sensors have to be cooled with liquid helium and operate at a very low temperature of about −269 °C in the state of superconductivity. The sensors are arranged in a helmet-shaped dewar and cover most of the head at a typical scalp distance of about 2 cm. The many sensors allow precise measurements of brain activity in all cortical areas.

The environmental noise is suppressed in three ways. First, a MEG system is typically installed in a magnetically shielded room that consists of several layers of metal. These layers achieve a strong attenuation of magnetic disturbances that may be caused by cars, undergrounds, elevators, etc. Second, most MEG systems allow the measurement of the spatial gradient of the magnetic field. Magnetic fields originating in the brain are close to the MEG sensors and show a strong spatial gradient, whereas distant magnetic (noise) sources show a small spatial gradient. Subtracting signals from additional reference sensors (that are further away from the brain) from the MEG sensors effectively reduces background environmental magnetic noise. Third, noise reduction can be performed offline by removing components that most likely were caused by strong magnetic sources outside the brain.

In a typical experiment, 3–5 small coils are attached to the participants head. The location of these coils with respect to anatomical landmarks is recorded. Then the participant is seated in the MEG system below the helmet-shaped dewar. The small coils are activated with

small electric currents. The corresponding magnetic fields are recorded by the MEG system and the generators (the coils and thereby the participants head) can be accurately localized with respect to the MEG sensors.

During a typical experiment, sensory stimuli may be presented and the participant is asked to perform a specific task. Stimuli and participant's response are repeated many times (about 100 repetitions are common). Information processing in the brain is associated with the activation of neurons that is characterized by changes in their membrane potentials. The MEG signal is caused by magnetic fields that are associated with postsynaptic potentials and thus reflects fluctuations in local field potentials. Prerequisites for a measurable MEG signal are the simultaneous activation of several thousand neurons and a preferred spatial orientation of these neurons (such that the summation of the tiny individual magnetic fields increases the total magnetic field measured outside the head).

The traditional analysis of MEG recordings is based on averaging the measured signals time-locked to the presentation of the stimuli. This reduces components in the data that are not precisely time-locked to the stimulus (such as artifacts, environmental noise, etc.). The resulting event-related fields (ERFs) usually show a number of maxima and minima that can be further analyzed. In the simplest case, the latency and amplitude of these maxima and minima are noted and their modulation by the different experimental conditions can be investigated. For a given time after the stimulus onset, the different measurement values for each sensor can be spatially interpolated, taking into account the location of each sensor. The spatial configuration of magnetic field amplitudes (topography) may show a pattern that is characteristic of a small activated brain region (dipolar field pattern). These topographies contain information about the location of the activated brain areas.

Since magnetic fields (in contrast to electric potentials measured with EEG) are not much distorted by the different conductivities of the brain, cerebrospinal fluid, skull, and scalp, MEG researchers have worked extensively on the problem of estimating the activated brain areas from the neuromagnetic recordings – the so-called inverse problem. Unfortunately, it was already shown in 1853 by Helmholtz that this problem has no unique solution. Further constraints have to be formulated to yield a unique solution. A number of techniques that are based on different models of the underlying activated brain areas have been suggested and are available in commercial or public domain software. Although these algorithms cannot circumvent the nonuniqueness of the inverse problem, they can still provide useful information about the location of activated brain areas and the time course of their activation.

Recently, two new analysis methods have been introduced to the field of MEG research: time–frequency analysis and connectivity analysis. Time–frequency analysis accounts for the fact that oscillatory fluctuations are a prominent feature of brain activity. The result of this type of analysis is an image that displays the temporal changes of brain activity at different frequencies that are induced by a stimulus.

Connectivity analysis allows the identification of networks of interacting brain areas. This type of analysis is motivated by the observation that even simple tasks require a well-coordinated interplay between many specialized brain areas. New developments aim at a characterization of causality and the direction of information transfer between brain areas.

The applications of MEG are manifold.

MEG has been used in cognitive neuroscience to study language, neural plasticity, attention, memory, consciousness, motor control, etc. In addition, detailed studies of sensory processing in primary sensory areas have been conducted using the excellent temporal resolution of MEG.

A large number of studies have used MEG to investigate pathological mechanisms in many diseases.

Several clinical sites use MEG to measure and localize epileptic activity as a diagnostic tool for surgery or they use MEG for the presurgical mapping of eloquent brain areas (such as motor cortex and speech related brain areas). In recent years, MEG has been used to identify and analyze pathological oscillatory processes in the brain of patients suffering from movement disorders such as essential tremor, Parkinson's disease, dystonia, and Wilson's disease, as well as neuropsychiatric diseases such as hepatic encephalopathy and psychiatric disorders such as schizophrenia, obsessive compulsive disorder, and depression. Here, MEG has made important contributions toward a better understanding of the mechanisms leading to the various disorders.

In general, MEG is ideal for applications that require a high temporal and good spatial resolution. Although the spatial accuracy is better for functional magnetic resonance imaging (fMRI), no other noninvasive imaging technique offers a better temporal resolution with coverage of the entire brain combined with a good spatial resolution. These properties are particularly relevant to studying brain dynamics and oscillatory connectivity in healthy subjects and in patients with neurological and psychiatric diseases.

See also: Alzheimer's Disease and Parkinsonism; Dementia with Lewy Bodies; Dementia, Movement Disorders; Dystonia; Parkinson's Disease: Definition, Diagnosis, and Management; Wilson's Disease.

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Malingering

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Glossary

Abasia – Inability to walk.
Atasia – Inability to stand.
Factitious – Fabricated.
Hemiparesis – Weakness on one side of the body.
Hemiplegia – Paralysis on one side of the body.
Malingering – Intentional falsification for specific gain.
Monoplegia – Paralysis of a single limb.
Obsessional – Involving intrusive, unwanted thoughts.
Quadraplegia – Paralysis affecting all four limbs.

Definition

Malingering in a medical setting involves the intentional falsification of a medical or psychiatric condition for a recognizable motive that generates tangible benefits to the presenting patient. Typically, motives are to evade social or personal obligations such as avoiding or shortening a jail sentence, avoiding work, avoiding military service, or avoiding financial obligations such as alimony or child support. Tangible benefits may include obtaining disability or workman's compensation or other financial benefits, or obtaining controlled substances for control of reported symptoms. These motives are distinguished from maladaptive and often self-harming psychological motives, of which an individual may or may not be consciously aware, that underlie factitious disorders and somatoform disorders. Malingering is not considered to be a psychiatric disorder, but rather involves the 'intentional production of false or grossly exaggerated physical or psychological symptoms' for pragmatic gain.

The investigation of the presence and causes of malingering can be influenced by the emphasis of the evaluator on either the legal or psychological aspects of the presenting clinical issue. In general, a balanced perspective is helpful. From the medico/legal standpoint, maintaining awareness of possible malingering in differential diagnosis is of value to prevent individuals from cheating society out of goods, services, or obligations. From a psychiatric standpoint, the psychosocial profile of the malingerer can help to identify the motivations of the malingerer and the reasons for success or failure in achieving his or her aims.

The mental health professions have historically evolved to evaluate, support, and provide care for patients. This predisposes to a clinical bias toward assuming truthfulness of the patient and minimizing ulterior motives for reported symptoms. A better understanding of malingering is, therefore, a helpful antidote to the clinician's becoming inadvertently complicit in authenticating a fabricated illness with potential untoward social consequences for all concerned.

Epidemiology

The incidence of malingering has been estimated to be twice as high in forensic (15.7%) as in psychiatric settings (7.4%). A large survey was conducted by the American Board of Clinical Neuropsychology (more than 33 000 subjects) in settings where some tangible benefit could potentially ensue to individuals from medical, personal injury, disability, or criminal referrals. Assessments of probable malingering were reported in 39% of those with mild head injury, 35% of those with fibromyalgia/chronic fatigue, 31% of those with chronic pain, 21% of those

with 'neurotoxic symptoms,' and 22% of those with electrical injury claims. Clearly, the clinician's level of sensitivity to the possibility of malingering needs to be influenced by the setting and context of the clinical assessment.

Clinical Features

The malingering patient fabricates a medical condition, claiming to have symptoms that are not supported by clinical examination and associated studies, or for which the patient has reportedly sought or received treatment with no reported clinical benefit. The severity of symptoms is often exaggerated in an effort to achieve the desired tangible benefit. The patient may either report a nonexistent accident or may stage a pseudoaccident and then refuse diagnostic evaluation or treatment. Malingerers often resist physicians' efforts to fully evaluate and treat the reported symptoms.

In the domain of movement disorders, common presenting symptoms may include tremors, spasms, weakness, and disturbances of ability to stand (astasia) or to walk (abasia).

Variations on the theme of weakness may include hemiparesis, hemiplegia, monoplegia, paraplegia, or quadraplegia. Other manifestations of somatic malingering may include occulomotor signs, dysfunctions of voice, swallowing and breathing, disorders of vision, disorders of sensation, vomiting, seizures, pain and falsified fever, or other falsified symptoms (e.g., hematuria). In addition, malingering can occur in domains affecting cognitive function and the genesis of pseudopsychiatric symptoms (e.g., posttraumatic stress disorder).

Differential Diagnosis

Malingering needs to be distinguished from factitious disorders and somatoform disorders, as well as from undiagnosed medical illness and psychological factors affecting a physical condition. Factitious symptoms are intentionally reported because of a psychological need to assume the sick-role, for example, to engender sympathy and to receive attention from care givers, as the primary definable goal. When a care giver fabricates or causes symptoms in (usually) a child in order to fulfill his or her own psychological needs, Munchausen by Proxy is diagnosed as a factitious illness variant. Somatoform disorders similarly involve the presentation of physical symptoms which, after adequate medical investigation, cannot be explained to have arisen from an organic cause. Yet, the genesis of these symptoms in somatoform disorders has a psychological basis derived from emotional causes, of which the patient is unaware. A variation on this theme is hypochondriasis, which involves an intrusive obsessional concern regarding postulated illness, with accompanying excessive attention to physical complaints. In both somatoform and factitious disorders, there may be some secondary pragmatic benefits to the patient ('secondary gain'), which should not be construed as an absolute indication that the entire clinical syndrome is simply malingering.

The most crucial category to consider in differential diagnosis is the possibility of an undiagnosed physical disorder. A premature rush to append a psychiatric etiology or to impute malingering because of presenting psychopathology or other atypical features on initial physical assessment runs the risk of destroying the therapeutic rapport that is essential for effective diagnosis and treatment.

Standardized psychological evaluation instruments such as those derived from Minnesota Multiphasic Personality Inventory (MMPI) subscales were designed to identify patient tendencies to falsify answers to diagnostic questions. These instruments have been employed to help to identify individuals attempting to receive fraudulent health benefits from government agencies. It should be noted, however, that such findings are relative, rather than absolute, diagnostic indicators. Furthermore, malingering can coexist with somatoform or factitious disorders, as well as with primary medical or psychiatric illness.

According to Rogers, malingering can be best understood as

1. a symptom of underlying mental illness (e.g., anxiety or depression, which the patient feels unable to express directly),
2. clinical evidence for an antisocial personality disorder, or
3. an adaptive (albeit devious) response to a threat or challenge in one's environment that the subject feels unable to confront directly.

The presence of an underlying medical illness neither excludes nor supports a diagnosis of malingering, which can coexist with documented medical illness. Similarly, the attribution of malingering to antisocial behavior merely describes, but fails to explain the use of falsification or deception to achieve instrumental gain. The adaptational model of Rogers provides a common sense explanation that encompasses most clinical presentations, and avoids the pitfall of pushing the clinician to unnecessarily confront the patient with moral disparagement. The model predicts that a patient may exaggerate and/or deceive more in settings where monetary and physical safety and security are at stake. This would include evaluations for fitness for military duty or forensic examinations for criminal or civil legal cases.

Management

To maintain the integrity of the doctor–patient relationship, it is inadvisable to directly confront the patient prematurely with suspicions of malingering, as this will harm any clinical alliance that has been formed. In a

hospital setting, observations of nursing and other support staff are valuable in delineating features of inconsistency of symptom state and aspects of the patient's interpersonal style that are relevant. It is reasonable to supportively apprise the patient of inconsistencies found between physical complaints and clinical findings, which point to the possibility that psychological factors play a role in symptom formation, although physical components may also pertain. Although a thorough medical evaluation of presenting symptoms is, of course, requisite, excessive ordering of nonrelevant tests is to be avoided. Proposing a psychiatric or psychological consultation with supportive clarification of the role played by stress in many illnesses can be a way of introducing this concept without rupturing the therapeutic alliance. The patient's response to this suggestion may be informative. A patient with somatoform disorder may be appreciative, whereas a malingering patient may become hostile and defensive. At the conclusion of one's evaluation, a supportive explanation to the patient that delineates the relative roles of physical versus psychological factors in symptom formation may be judicious, but use of the term malingering is best avoided, as it can often be difficult to establish with certainty and is likely to be inflammatory. Reports to the referring institution or clinical entity that are specifically authorized by the patient may reasonably allude to evidence of malingering as part of the differential diagnosis, but one wants to be cautious in delineating the conclusion of malingering in the absence of certainty because of the potential adverse effects for the patient, and, by extension, for a misdiagnosing clinician.

Prognosis

By definition, the prognosis for the persistence of a malingering symptom will be directly related to the duration of time that the tangible benefits associated with it persist. The termination of benefits or prospect thereof, such as the conclusion of a civil court case or criminal prosecution may, in that sense, be quite 'therapeutic.' It should be recalled, however, that malingering may coexist with both medical illness and psychiatric illness that may continue to be legitimate domains for clinical attention.

See also: Malingering; Psychogenic Movement Disorders; Somatoform Disorders.

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Manganese

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Glossary

Acquired hepatocerebral degeneration – A neurologic disorder secondary to chronic hepatobiliary diseases or portosystemic shunt, with presentations including parkinsonism, various hyperkinetic movements, ataxia, neuropsychiatric abnormalities, and altered mentation.

Chelator – A molecule that forms a complex structure with a metal ion. Chelation renders the bound metal no longer toxic, and facilitates its elimination.

Manganese – A heavy metal, the twelfth most abundant element in the earth's crust, and an essential trace mineral in organisms.
Manganism – The clinical manifestation of chronic manganese intoxication; it is called neuromanganism when referring specifically to the neurologic manifestation.

Introduction

Used for millennia, manganese (Mn) enters the scene of toxicology far behind lead and mercury, two metals known to be poisonous since antiquity. Not until 1837 was a syndrome including tremor, weakness, and a whispering voice first reported in workers at a Mn ore-crushing site. Since then, knowledge of manganism has advanced through studies of human cases and in animal models. It is now realized that excess Mn targets specific cerebral structures and produces distinctive symptoms. As a result, the epidemiology of manganism has extended beyond the realm of occupational medicine. What remains inconclusive is the role of Mn exposure as a risk factor for certain disorders generally considered to be due to other causes than metal intoxication.

Types of Manganism

Abundant in the environment, Mn enters the human body from air, water, and mostly from food, at a rate of 2–8 mg day^{-1}. Once absorbed, Mn is under homeostatic regulation, and is cleared by the liver into bile and then feces. A small fraction of Mn is also renally excreted. Physiologically, Mn is a trace element essential for multiple metabolic and cellular functions. However, when the amount of Mn exposure exceeds the capacity of clearance, Mn starts to accumulate and intoxication ensues. Mn can exist in an elementary form and in organic and inorganic compounds. Different forms of Mn vary with the mode of exposure, metabolism, and toxic effects.

Occupational exposure is the leading cause of manganism. With over eight million tons extracted annually, Mn finds plentiful uses in industries like iron- and steel-making, battery manufacture, and in products like gasoline, welding rods, and pesticides. Workers in these occupations are, therefore, at the risk of manganism when hazard-preventing measures in the work place are inadequate. From inhalation of Mn dust or fume, Mn miners and millers, smelters, welders, and workers in battery factories constitute the majority of cases of occupational manganism. Methylcyclopentadieny manganese tricarbonyl (MMT) is an Mn-containing additive in gasoline. Workers in gasoline industries and related occupations are susceptible to manganism when exposed to high ambient levels of Mn released from MMT. In farmers, gardeners, and other agricultural workers, manganism has been reported to occur from inhalation and dermal exposure to maneb and mancozeb, two Mn-containing pesticides.

Nonoccupational environmental exposure is a less frequent and less certain cause of manganism, but poses public health concerns. Of primary significance is the risk of manganism from drinking water with excess Mn. Few outbreaks of manganism have been attributed to drinking groundwater that is contaminated by Mn-containing waste, but in areas where drinking water has a high Mn level, surveys of local populations often disclose higher Mn burden in the body, and an association with neuropsychologic abnormalities. Inhalation of excess Mn emitted from MMT-supplemented gasoline has increasingly been scrutinized as a source of manganism in nonoccupational settings. Equally concerning is whether an Mn-rich diet increases the risk of manganism. While there have been no verified human cases of manganism from dietary sources, in animal models, ingestion of excess Mn can lead to intoxication.

An unusual category of manganism derives from nonenvironmental exposure, exemplified by manganism in patients who receive total parental nutrition with high levels of Mn. This iatrogenic type of manganism sometimes becomes reversible after reducing the concentration of infused Mn. Manganism has been observed in a child with pica who ingested Mn-laden soil. Furthermore, Mn plays a possible pathogenic role in a parkinsonian syndrome among users of an illicit substance methcathinone, which is often contaminated with potassium permanganate during its synthesis.

Manganism can conceivably result from inadequate hepatobiliary clearance of Mn. A candidate for this possibility is acquired hepatocerebral degeneration, a neurological syndrome seen in patients with hepatobiliary dysfunction. It shares clinical features with manganism, and Mn accumulation in the basal ganglia has been documented in acquired hepatocerebral degeneration. Acquired hepatocerebral degeneration has increasingly been considered a forme fruste of manganism.

Toxicopathology

Chronic Mn exposure exerts toxicity overwhelmingly to the brain. Other organ systems are less affected in chronic Mn poisoning; for instance, chronic Mn exposure sometimes leads to impotence, dermatitis, and pneumonitis. Acute Mn poisoning is rare, and has a more systemic involvement.

Mn reaches the brain across the blood–brain barrier via a number of mechanisms, including facilitated diffusion, transferrin-dependent transport, and divalent metal transport 1-mediated transport. At elevated Mn concentrations, the choroid plexus becomes the major route of Mn transport into the brain. Mn has high binding affinity for transferrin, and this binding may underlie the predilection of excess Mn to accumulate in the pallidum and

striatum, both with high expression of transferrin. At the cellular level, oxidative stress, mitochondrial dysfunction, excitotoxicity, and interaction with other metals have all been implicated as the mechanisms of Mn toxicity.

Neuropathology of manganism stems from a few autopsies of human cases, and mostly from studies in animal models. Pathologic findings of manganism center on the globus pallidus, especially the pars interna, which exhibits extensive neuronal loss and gliosis. The pars externa of the globus pallidus, striatum, subthalamus, and substantia nigra pars reticularis show less severe changes, sometimes observed in animal models only. The rest of the brain, specifically the substantia nigra pars compacta, which is the primary site of degeneration in Parkinson's disease (PD), is unaffected, and neither the Lewy body nor abnormal α-synuclein staining that typifies PD is present in manganism. These neuropathologic features underscore that manganism is distinct from PD.

Clinical Features and Diagnosis

Parkinsonism is the hallmark of manganism and can have a symmetric or asymmetric distribution. Every cardinal feature of parkinsonism – tremor, rigidity, bradykinesia, abnormal posture, and gait – has been observed in manganism. The tremor in manganism tends to occur in the upper extremity, lower face, and tongue, and often a postural tremor predominates rather than a rest tremor that typifies classic PD. Rigidity in manganism can be detected in the limb and trunk, and sometimes has a cogwheel property. Bradykinesia in manganism commonly manifests as masked faces, monotonous speech, impaired dexterity and slowness of limb motions, and paucity of overall movements. Postural and gait abnormalities in manganism include anteropulsion, retropulsion, and a peculiar gait aptly named 'cock-walk.' The cock-walk gait is a dystonic toe-gait with the trunk extended and arms flexed. Dystonia may occur at other sites, and is another prominant feature of manganism. None of these motor phenomena is specific to manganism, as they also occur to other parkinsonian disorders including PD. Nevertheless, compared with PD, in manganism, dystonia, antero- and retropulsion, and the cock-walk gait are more common, whereas tremor is less common, and if present, it is typically postural, of higher frequency, and in smaller amplitude.

Neuropsychiatric disturbances frequently accompany parkinsonism in manganism. There is a spectrum of affective and behavioral symptoms associated with manganism, from apathy, anxiety, compulsions to depression, and hallucinations. A psychotic state with aggression and emotional lability was formerly known as 'manganese madness' (locura manganica). Cognitive impairment is also common in manganism. Subtle changes in neuropsychological functions may be the earliest manifestation of manganism and can be the only manifestation in mild cases of manganism.

In addition to a history of exposure and neurologic findings, the definite diagnosis of manganism hinges on laboratory evidence of chronic Mn exposure, which can be provided by measurements of Mn and by magnetic resonance imaging (MRI). The likelihood of obtaining such evidence is determined in part by the factor of time. Due to continuous clearance of Mn, its accumulation starts to dissipate once the exposure has ceased, or in acquired hepatocerebral degeneration, once biliary excretion of Mn returns. After a period as short as several months, previously accumulated Mn may leave no trace on measurements of Mn or MRI. Under these circumstances, the diagnosis of manganism is primarily based on clinical grounds.

Mn levels can be measured in various body fluids and tissues such as blood, urine, feces, and hair. Certain measurements of Mn are reliable biomarkers of chronic Mn exposure only on a group basis, but not on an individual basis. Blood Mn reflects mixed cumulative and current exposure, and the levels often fluctuate. Therefore, levels of blood Mn and amounts of accumulated Mn do not always correlate. Nevertheless, hypermanganesemia that is repeatedly measured above a locally calibrated range is suggestive of chronic Mn exposure. Mn excretion in either urine or feces is not an accurate marker of Mn exposure. Hair Mn has been shown to be an accurate marker of Mn exposure, but this finding needs further validation. Currently, all measurements of Mn are considered approximate but not accurate biomarkers of Mn accumulation in the body.

A paramagnetic metal, accumulation of Mn generates signals of a characteristic pattern on MRI, which are hyperintense on T1-weighted images, but are normointense on T2-weighted and other images, a pattern seldom encountered in other pathological processes. On brain MRI of patients with manganism, T1 hyperintensity is often present in the pallidum, striatum, and midbrain tegmentum in a bilateral, symmetric distribution (**Figure 1**). Bilateral pallidal T1 hyperintensity has been documented in most types of manganism and is considered diagnostic of manganism.

Functional imaging modalities, including positron emission tomography (PET) and single photon emission computed tomography (SPECT) are instrumental in investigating the pathophysiology of manganism. The nigrastriatal pathway has been the focus of investigation in the light of presence of parkinsonism, and is assessed with tracers for the presynaptic and postsynaptic functions of dopaminergic transmission such as fluorodopa, 2β-carbomethoxy-3β-4-iodophenyltropane (β-CIT) for the former, and raclopride for the latter. These studies consistently demonstrate normal nigral functions but abnormal striatal functions in manganism. While they are useful research tools, functional imaging studies do not give a specific diagnosis of manganism. Functional imaging studies on other pathways or neurotransmissions have not been systemically performed.

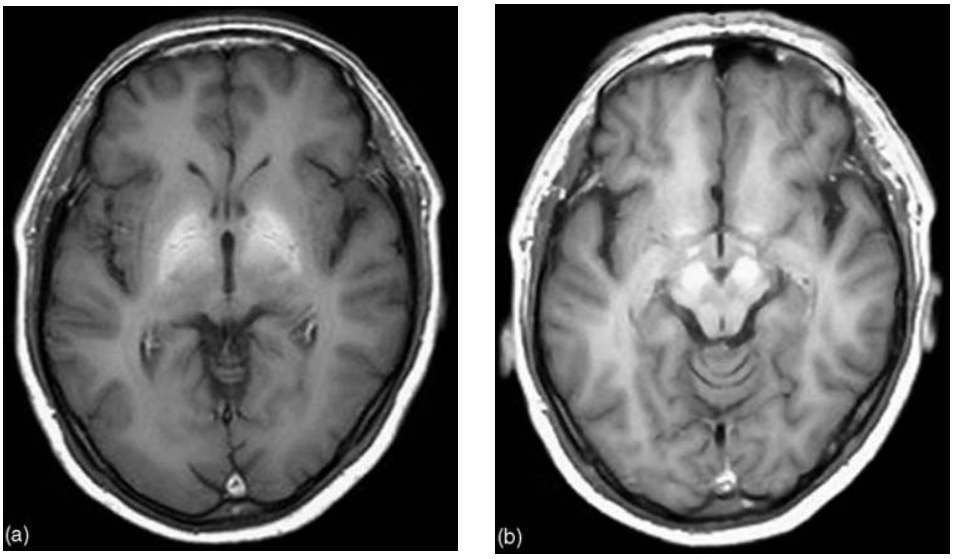

Figure 1 MRI findings in manganism. The brain MRI from a patient with welding-related manganism demonstrates bilateral, symmetric hyperintensity in the globus pallidus on the T-1 weighted images (a). Similar signal abnormalities are also present in the midbrain (b). Pictures provided here courtesy of Dr. Chin-Chang Huang of Chang Gung Memorial Hospital, Taipei, Taiwan.

The onset of manganism is insidious, and progression is gradual. Three clinical stages have been delineated in the progression of manganism, from behavioral symptoms to parkinsonism, and then to superimposed dystonia. Deterioration is typically more precipitous in the first several years after onset of the symptoms than later in the course. With continuing Mn exposure, manganism progresses relentlessly over a decade, but may eventually reach a plateau afterwards, likely representing a burnt-out state. If Mn exposure is finally removed after the diagnosis, manganism may improve but is not expected to resolve completely. Signs may persist at the same severity, or may even continue to progress for a period up to 10 years. The limited recovery or no recovery in absence of ongoing Mn exposure indicates that the damage in manganism is largely functionally irreversible.

Treatment

Treatment of manganism includes symptomatic and chelation therapy. In symptomatic treatment of manganism, symptoms of parkinsonism have been the focus, and levodopa is the most frequently used medication. As expected for secondary parkinsonism, in manganism the results of treatment with levodopa have been unsatisfactory; it is either ineffective, or only has partial, temporary benefit. In a 5-year follow-up study of patients with manganism, the response to levodopa declines quickly after 2–3 years. Other medications are less explored as symptomatic treatment for manganism.

Chelation therapy aims at reducing the toxicity and accumulation of Mn. Ethylenediaminetetraacetic acid (EDTA) is a chelator of lead and zinc, and its effectiveness in treating manganism has been evaluated in several case series. In EDTA-treated patients, their blood Mn levels decreased, and Mn excretion in urine increased, indicating EDTA has chelated and removed Mn, but their neurologic symptoms failed to improve accordingly. The discordance between efficacy of chelation and neurological outcome may be due to poor penetration of EDTA across the blood–brain barrier, or due to irreversible nature of Mn-induced cerebral damage.

Chelators with structures related to EDTA, such as cyclohexylene–aminotetraacetic acid (CDTA) and dimercaptol-1-propanesulphonic acid (DTPA), reduce Mn burden in animal models, but have not been tested for human manganism. Triethylenetetraamine (trientene), a copper chelator, has been used successfully to treat manganism in a case of acquired hepatocerebral degeneration. *para*-Aminosalicylic acid (PAS), first developed as an antituberculosis drug, has cast promise in treatment of manganism. In the experience garnered mainly in China, PAS not only eliminated Mn but also significantly alleviated neurological symptoms. PAS has been postulated as a Mn chelator or as an antiinflammatory neuroprotective agent, but its exact mechanism in treating manganism is still uncertain. The therapeutic potential of these chelators for manganism warrants further investigation.

Summary and Future Perspectives

Manganism is a disease with well-defined etiology, pathology, clinical manifestations, and paraclinical findings. Due to phenomenological similarity between manganism and PD, Mn toxicity has been speculated to be the mechanism of neurodegeneration in PD. Differences between manganism and PD in many aspects argue against a causative role of excess Mn in PD (**Table 1**).

Table 1 Comparison between manganism and Parkinson's disease in clinical, paraclinical, and pathological features

	Manganism	*Parkinson's disease*
Clinical manifestation	Tremor is postural and less common; dystonia, anteropulsion, and retropulsion are more frequent; Cock-walk gait is characteristic	Tremor is usually resting and more common; anteropulsion is rare and retropulsion occurs in advanced stage; festinating gait is typical
Response to levodopa	No response, or partial, temporary response	Significant, long-lasting response
Brain MRI	T1 hyperintensity in pallidum, striatum, and midbrain	Unremarkable
Functional imaging studies	Postsynaptic dopaminergic dysfunction	Presynaptic dopaminergic dysfunction
Pathology	Degeneration of pallidum and striatum, without Lewy body or synucleinopathy	Degeneration of substantia nigra, with Lewy body and synucleinopathy

However, a few epidemiologic studies, especially those in welders, have noted an increased incidence of PD in people exposed to excess Mn. A hypothesis has been raised that Mn exposure is, instead of a cause, a risk factor of PD which precipitates or accelerates its pathogenesis. This hypothesis awaits further testing.

For an illness that is mostly irreversible, has limited treatment options, but is preventable, prevention is critical. Regulatory agencies – for example, the Environmental Protection Agency (EPA), Food and Drug Administration (FDA) and Occupational Safety and Health Administration (OSHA) in the United States, and the World Health Organization (WHO) have set limits on Mn levels in air, drinking water, and diet. In an ever-industrialized world, new Mn-containing chemicals will continue to be synthesized, and their new applications to be found. Manganism in multiple environmental settings will therefore likely continue to emerge, necessitating vigilance for early recognition and prevention.

See also: Cock-walk; Parkinson's Disease: Definition, Diagnosis, and Management; Wilson's Disease.

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Marinesco-Sjogren's Syndrome

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Glossary

ATPase – Adenosine triphosphatase, an enzyme that hydrolyzes ATP into ADP and phosphate.
Chaperone – A protein required for the proper folding and/or assembly of another protein or protein complex.
Frameshift mutation – A mutation that alters the reading frame of a coding sequence.
Heat-shock protein 70 family – A class of molecular chaperones found in several compartments of cells. These proteins can interact with polypeptides during a variety of assembly

processes in such a way as to prevent the formation of nonfunctional structures.
MIM – Mendelian Inheritance in Man, its online version OMIM contains referenced overviews on all known Mendelian disorders and over 12 000 genes.
Missense mutation – A mutation that replaces one amino acid with another in the gene product.
Nonsense mutation – A mutation that converts a codon for an amino acid into a stop codon.
Rimmed vacuole – Autophagic, multilaminated membranous structure surrounded by filamentous material and found in muscle fibers.
Splice site mutation – A mutation that creates or destroys signals for exon–intron splicing.

Definition and History

Marinesco–Sjögren syndrome (MSS, MIM 248800) is an autosomal recessive disorder with marked phenotypic variability. The two acknowledged original reports include a report of Marinesco and colleagues in 1931, where they described a Romanian family with four affected children. Later, Sjögren saw four similar cases and identified 10 more in three Swedish families in 1950. The syndrome is a panethnic disease with 200 published cases, but exact prevalence figures are not available. The patients described in the literature form a clinically heterogeneous entity, and can be divided into classical MSS and MSS-like groups. Typically, classical MSS is characterized by cerebellar atrophy with ataxia, early-onset cataracts, mild to severe mental retardation, and myopathy. Additional features include hypergonadotropic hypogonadism, short stature, various skeletal abnormalities, and strabismus. In the MSS-like group some, but not all, of the main features are present together with several atypical symptoms.

Pathogenesis

So far, *SIL1* is the only gene known to be defective in MSS. The main transcript of the *SIL1* gene has 10 exons and encodes a 461-amino acid protein. A total of 17 MSS-associated mutations have been described in *SIL1*. Most mutations are nonsense, frameshift, or splice site mutations predicted to result in loss of SIL1 protein function due to premature termination of translation or abnormal splicing of the transcript. A single missense mutation has so far been described. Not all patients with a clinical MSS diagnosis have detectable mutations in the *SIL1* gene implying genetic heterogeneity.

Several pieces of information suggest that MSS pathogenesis is linked to abnormal protein quality control in the ER. As cochaperone, SIL1 regulates the ATPase cycle of the 78 kDa glucose-regulated protein (GRP78). GRP78 belongs to the heat-shock protein 70 chaperone family and has multiple roles in processing proteins targeted to the secretory pathway. Most of the *SIL1* mutations described so far are predicted to lead to nonfunctional or absent SIL1 and are thus likely to result in decreased rates of GRP78 hydrolysis and abnormal protein translocation and folding. The accumulation of unfolded proteins in the ER causes ER stress, and if stressful conditions are not alleviated, this may lead to cell death. MSS may, thus, be added to the growing number of protein misfolding and accumulation disorders due to defective molecular chaperone function.

In MSS, the severe cerebellar atrophy is due to loss of Purkinje and granule cells in all cerebellar lobules except the vestibulocerebellum. The remaining Purkinje cells are mostly vacuolated or binucleated. The brain lesions are almost exclusively limited to the cerebellum. The hypothesis of defective protein folding in MSS is supported by data from the *wz* mouse, a naturally occurring mouse model for MSS. In the Purkinje cells of the *wz* mouse, loss-of-function of SIL1 causes induction of the unfolded protein response and abnormal accumulation of proteins, with subsequent neurodegeneration in cerebellar Purkinje cells and ataxia.

Clinical Features and Diagnostic Criteria

The cerebellar signs dominate the central nervous system symptoms in MSS. Delayed motor milestones are among the first clinical signs. Gait or truncal ataxia is one of the most frequent symptoms. Dysarthria, nystagmus, and intention tremor have been noted in many cases. MSS patients have variable degrees of developmental delay. In classical MSS neuroimaging studies such as magnetic resonance imaging (MRI) and computed tomography (CT) show cerebellar atrophy, which is usually more pronounced in the vermis than in the hemispheres. The cerebellar fissures are widened and the fourth ventricle is enlarged. The neuromuscular manifestations described so far show considerable variation. Hypotonia, slowly progressive muscle weakness, and atrophy suggesting chronic myopathy have been the most frequent findings. Electromyography (EMG) typically shows only myopathic features. Demyelinating polyneuropathy, axonal polyneuropathy, or both have also been described.

The bilateral cataracts have been stated as congenital, but there are several reports on rapid postnatal development of lens opacities. The eyes are typically operated on in the first decade of life. Strabismus is a frequent finding. The most distinguishable skeletal features are shortening

Table 1 Diagnostic criteria for MSS and comparison between the clinical features of *SIL1* mutation-positive and -negative patients

Diagnostic criteria	*Patients with SIL1 mutations (number of cases)*	*Patients without SIL1 mutations (number of cases)*
Major criteria		
Cerebellar ataxia	100% (29/29)	85% (11/13)
Cerebellar atrophy	100% (26/26)	79% (11/14)
Cataracts	100% (30/30)	67% (10/15)
Myopathic changes	92% (23/25)	44% (4/9)
Muscle weakness	100% (9/9)	
Truncal/limb hypotonia	100% (29/29)	82% (9/11)
Mental retardation (mild to profound)	100% (30/30)	93% (14/15)
Minor criteria		
Hypergonadotropic hypogonadism	90% (19/21)	20% (2/10)
Short stature	60% (18/30)	50% (5/10)
Orthopedic manifestations	62% (16/26)	42% (5/12)
Dysarthria	100% (6/6)	
Nystagmus	69% (20/29)	55% (6/11)
Strabismus	89% (24/27)	44% (4/9)

of metacarpals and metatarsals, shortening of phalanges, and deformation of the sternum. In addition, small posterior cranial fossa, scoliosis, and kyphoscoliosis, scalloped vertebral bodies, gracile bones, pes planovalgus, and valgus deformities of elbows and hips are present.

Although atypical findings like optic atrophy, seizures, hearing loss, and peripheral neuropathy have been reported, it is not known if these are rare manifestations of MSS or features of a distinct disorder. The common clinical features and diagnostic criteria of MSS are summarized in **Table 1**. The diagnosis of classical MSS requires the presence of the major criteria including cerebellar atrophy and ataxia, cataracts, myopathy, and psychomotor delay.

Differential Diagnosis

Other syndromes presenting with cerebellar atrophy and ataxia should be considered in the differential diagnosis. The evaluation of an affected child without family history is challenging, since all MSS features, for example, cataracts and hypergonadotropic hypogonadism, may not yet be present.

The congenital cataracts, facial dysmorphism, and neuropathy syndrome (CCFDN, MIM 604168) share with MSS the key features of ataxia, cataracts, psychomotor delay, and hypogonadism. The presence of more severe mental retardation, marked cerebellar atrophy leading to severe ataxia, myopathy with specific features on muscle biopsy, and absence of peripheral neuropathy and microcornea distinguishes MSS from CCFDN.

Some recent reports have described disorders clinically similar to, but genetically different from, MSS. An X-linked CASM syndrome (cataracts, ataxia, short stature, and mental retardation, MIM 300619), affects males while female carriers present only cataracts. A Marinesco–Sjögren-like syndrome was reported in two siblings sharing most of the clinical features found in MSS but without marked cerebellar atrophy. As additional symptoms the patients presented external ophthalmoplegia and dysphagia.

There are some other rare, mainly autosomal recessive disorders that partly resemble MSS. The clinical entities include the Cataract–ataxia–deafness–retardation syndrome (MIM 212710), familial Danish dementia (FDD, MIM 117300), VLDLR-associated cerebellar hypoplasia (Dysequilibrium syndrome; MIM 224050), aniridia, cerebellar ataxia, and mental deficiency (Gillespie syndrome; MIM 206700), and Ataxia–microcephaly–cataract syndrome (MIM 208870). In addition, several other syndromes share some of the main clinical features with MSS, but they are distinguishable due to additional features.

Diagnostic Work-up

The diagnosis of MSS is based on clinical evaluation and neuroimaging studies (MRI or CT). Molecular genetic testing for *SIL1* mutations may help confirm the diagnosis. Muscle biopsy specimen show variation in muscle fiber size, atrophic fibers, fat accumulation, and rimmed vacuole formation under light microscopy. Rimmed vacuoles are most evident in samples taken at older ages. In electron-microscopy, autophagic vacuoles with myeloid bodies beneath the sarcolemma or near the nucleus, and a perinuclear dense double-membrane structure suggested to be specific to MSS, are seen. Radiography of the bones may help determine the extent of skeletal involvement. EMG can be helpful in assessing the myopathy. Serum creatine kinase concentrations are normal or moderately increased, usually two- to four-fold the upper normal limits.

Management

After diagnosis, surveillance at regular intervals is recommended. Patients usually undergo cataract surgery during the first decade of life. Only symptomatic treatment is currently available to muscle manifestations. If hypergonadotropic hypogonadism is present, hormone replacement therapy should be considered to prevent secondary problems including osteoporosis. Genetic counseling is recommended to the families to determine the genetic risk and to discuss the reproductive options.

Prognosis

MSS patients are usually born after uncomplicated pregnancies. Muscular hypotonia is typically present in early infancy. Muscular weakness becomes evident during the first decade of life in the distal muscles of the extremities, and some patients are never able to walk without assistance. Later, patients show truncal ataxia, dysdiadochokinesia, and dysarthria. Their mental performance varies usually from mild to moderate mental retardation. The motor functions of the patients worsen progressively, but the duration of the disease does not alone explain the variation in the severity of the muscle involvement. The development of a child sometimes deteriorates after febrile illness. Although many of the patients are severely handicapped in their adulthood, the life span of patients with MSS is near to normal.

See also: Ataxia; Ataxia (Familial Cerebellar) with Muscle CoQ_{10} Deficiency; Ataxia with Isolated Vitamin E Deficiency; Ataxia-Telangiectasia; Friedreich's Ataxia and Variants; Spinocerebellar Ataxias Genetics.

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McLeod Syndrome

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Glossary

Acanthocytes – Contracted erythrocytes with thorny protrusions.

McLeod phenotype – An erythrocyte antigen pattern in which the Kx antigen is absent and the Kell antigen expression is markedly reduced.

McLeod syndrome – An X-linked recessive neurodegenerative disease due to mutation of the gene for the XK protein, characterized by involuntary movements (chorea) and acanthocytosis, in which there is reduced expression Kx and Kell antigens on erythrocytes.

Neuroacanthocytosis – A term for the group of neurological conditions in which there are abnormalities of red blood cell membranes resulting in thorny protrusions.

Definition and History

McLeod syndrome is one of the core neuroacanthocytosis syndromes (along with autosomal recessive chorea-acanthocytosis). It is transmitted in an X-linked recessive manner. McLeod syndrome is defined as a characteristic pattern of erythrocyte antigens, with decreased expression of the 23 Kell antigens, and absent expression of the Kx antigen, known as the McLeod phenotype, in combination with specific neurological signs. The abnormal red blood cell (RBC) phenotype is due to mutations of the *XK* gene resulting in absent or abnormal XK protein. The XK protein is linked by two disulphide bonds in the RBC membrane to the Kell protein, and thus, absent or abnormal XK causes decreased expression of the 23 antigens expressed on the Kell protein.

The RBC phenotype is often picked up many years before the appearance of any neurological abnormalities when carriers donate blood or have it cross-matched. This phenotype was discovered in the 1950s in a Harvard dental student, Hugh McLeod, when all the students were being screened for new blood antigen phenotypes. At that time, it was assumed to be benign, and it had not been until a number of years later that the connection was made with the neurological symptoms that developed in carrier individuals.

Some individuals have been incidentally identified by abnormalities of blood chemistry such as elevated creatine kinase (CK) or liver enzymes. Acanthocytosis, the appearance of contracted RBCs with thorny protrusions, is typically, but not invariably, present, and is not required to make the diagnosis. It is presumed that the membrane structural abnormalities are due to abnormal XK and reduced Kell expression, but this is neither confirmed nor well understood.

The neurologic features develop in middle age, often with a variable spectrum of cognitive and psychiatric problems, in additional to involvement of internal organs.

Pathogenesis

The relationship of abnormal XK to neurodegeneration of the central and peripheral nervous systems is not known. XK is widely expressed throughout the brain and various internal organs. In brain, it is not associated with Kell.

Neurodegeneration in the brain affects predominantly the caudate nucleus, putamen, and globus pallidus. Neuropathological findings consist of severe gliosis of this region, with mild gliosis of the cerebral cortex, but no inclusion bodies of any nature have been detected.

Epidemiology

McLeod syndrome is very rare. However, there are likely to be a number of undiagnosed cases. Cases have been reported from a variety of ethnic populations. In 2007, a summary was published of approximately 60 cases from 30 families in whom the mutations have been reported to date.

Typically males are affected, but occasionally, carrier females develop a milder phenotype thought to be due to X-chromosome inactivation.

Clinical Features and Diagnostic Criteria

The neurological features of McLeod syndrome typically develop in the 40s–50s and progress slowly over the next two decades. Often the initial presentation may be subtle cognitive or psychiatric symptoms. The use of neuroleptics may confound the recognition of the movement disorder. However, the appearance of seizures and the development of peripheral sensorimotor neuropathy and areflexia may suggest the diagnosis. The neuropathy, which along with the myopathy, causes hypotonia and peripheral weakness, is often a debilitating feature. Myopathy was initially thought to be a relatively benign feature, but has recently been recognized as being a significant cause of functional impairment. It may lead to a predisposition to neuroleptic malignant syndrome.

Nerve conduction studies show axonal loss, although occasionally demyelination can be seen. Electromyographic findings of myopathy may be seen at later stages.

A variety of movement disorders may be present and includes tics, parkinsonism, dystonia, and chorea. Additional somatic features consist of cardiomyopathy, skeletal myopathy, and hepatosplenomegaly. No specific features have been found in pathological examinations of cardiac or skeletal muscle.

Neuroimaging demonstrates bilateral atrophy of the caudate nuclei and may be reported as being similar to that seen in Huntington's disease.

Minimal symptoms can occasionally be seen if the mutation of *XK* interferes to a lesser extent than normal with XK protein function.

Differential Diagnosis

The differential diagnosis of McLeod syndrome depends upon the presentation. The full syndrome of a movement disorder, peripheral neuropathy, seizures, and cognitive changes is similar only to autosomal recessive chorea-acanthocytosis (ChAc), but can be distinguished by the absence of the self-mutilating lip and tongue

biting, which is characteristic of autosomal recessive chorea-acanthocytosis.

The initial workup may be that of a peripheral neuropathy or myopathy, especially if CK is elevated. Recognition of the syndrome may avoid the need for invasive and nondiagnostic tests such as muscle or bone marrow biopsy. Similarly, abnormalities of liver enzymes may prompt the performance of liver biopsy.

If there is a family history, this may indicate an X-linked disorder by the involvement only of males, and no male-male transmission. Maternal grandfathers or uncles may be affected.

Huntington's disease should be excluded, particularly if there is a possibility of non-paternity, or if the medical history of the father's family is not known.

Diagnostic Workup

The diagnosis is made by examination of the complete set of Kell antigens and Kx, which can be done at a regional blood center. The request should be made to 'exclude McLeod syndrome,' as just requesting the Kell status is not helpful. The diagnosis can be confirmed by sequencing *XK*.

McLeod syndrome may be suggested if acanthocytosis is found on peripheral blood smear. Sensitivity can be increased by incubating the RBCs with an equal volume of normal saline containing $10\,\mu l\,ml^{-1}$ heparin for 30–120 min on a shaker. Electron microscopy of glutaraldehyde-fixed RBCs is also confirmatory. However, the presence of acanthocytes in the neuroacanthocytosis syndromes is not constant, for reasons that are not well understood, and their absence does not preclude the diagnosis.

Elevated creatine kinase, often into the 1000s, is very suggestive of either McLeod syndrome or ChAc. Abnormal liver enzymes are also seen in both and require the exclusion of Wilson's disease as the only treatable neurodegenerative condition.

Echocardiography should be performed to evaluate for cardiomyopathy.

Electroencephalography may be helpful if seizures are a feature. Electromyography and nerve conduction velocity studies may document peripheral neuropathy or myopathy.

Management

Management is at present purely symptomatic. The involuntary movements do not typically impair function as much as the peripheral neuromuscular abnormalities. Psychiatric and cognitive symptoms should be treated appropriately.

Results of deep brain stimulation, predominantly targeted at reducing chorea and dystonia, have been variable. The optimal site and stimulation parameters remain to be determined.

Patients should be evaluated approximately annually by echocardiogram to monitor for the development of cardiomyopathy, arrhythmias, or congestive heart failure, which should be treated as appropriate.

Seizures usually respond to standard anticonvulsants, although carbamazepine and lamotrigine can worsen involuntary movements.

Evaluation by a speech therapist is essential to minimize problems due to dysphagia and weight loss. Physical and occupational therapists can assist with the difficulties with gait, balance, and activities of daily living.

As transfusion with heterologous (i.e. Kell+) blood may result in the generation of anti-Kell antibodies and a second transfusion may result in massive hemolysis (analogous to the reaction to Rhesus + blood in Rh− neonates), patients should be encouraged to bank their own blood, in case there is need for a blood transfusion.

Prognosis

McLeod syndrome is slowly progressive. Death is usually attributable to cardiac arrhythmias or seizure, but may be due to gradual, generalized debility, as seen in Huntington's or Parkinson's disease, with patients succumbing to pneumonia or other systemic infection.

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Relevant Websites

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Meige's Syndrome

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Glossary

Akathisia – Inner restlessness and irresistible urge to move, resulting in the inability to sit quietly (káthisis = sitting).
Dystonia – Sustained muscle contractions, frequently causing twisting and repetitive movements or abnormal postures.
Stereotypy – Involuntary, patterned, repetitive, coordinated, purposeless, or ritualistic movement, posture, or utterance.
Tardive dyskinesia (TD) – A variety of hyperkinetic involuntary movement disorders, associated with the use of dopamine receptor blocking drugs.

Definition and History

Meige syndrome is considered to be a type of segmental dystonia, because it involves contiguous body regions. It is characterized by blepharospasm (BSP), and oromandibular dystonia (OMD), but frequently dystonia may also be present in cervical and laryngeal muscles (**Figure 1**). More rarely, muscle groups beyond those of the cranial cervical structures can be affected. BSP refers to involuntary spasms of the orbicularis oculi (OO) muscle, resulting in forceful eyelid closure. OMD consists of contractions of the perioral or masticatory muscles, or both, resulting in jaw movements, lip or tongue protrusion, and lower facial twitching.

Meige syndrome can be primary (idiopathic), or secondary (symptomatic). The primary forms are the most prevalent. The disorder was named after Henry Meige, the French neurologist who first described its symptoms in detail in 1910. The term *craniocervical dystonia* (CCD) is preferred, because 'Meige syndrome' was originally used to refer only to the primary forms. *Cranial dystonia* is also appropriate, because cervical regions are not always necessarily involved. *Brueghel syndrome* has been used as an eponym, but it is preferably reserved for those cases where spasmodic jaw opening is the most prominent feature.

Epidemiology and Risk Factors

Idiopathic craniocervical dystonia (ICCD) is more common in women, with a 3:1 predominance, and usually

Figure 1 Patient with idiopathic CCD showing BSP, OMD, and anterocollis.

occurs in individuals older than age 50. A meta-analysis of major series of patients published in the English literature in the last 25 years showed that the mean age of onset is 38 years for hand dystonia, 41 years for cervical dystonia, 43 years for laryngeal dystonia and 56 years for BSP together with cranial dystonia. Evidence from epidemiological studies suggests that with increasing age, the site of onset of focal dystonias, shifts caudorostrally. Focal dystonias are more prevalent than generalized dystonias. Studies from various geographic areas indicate that BSP and cervical dystonia are the most frequent subtypes. Patients with BSP are more likely to experience spreading of symptoms to other body parts than patients with other focal primary dystonias. The greater risk of spread is within the first 5 years. Peripheral trauma is increasingly recognized as a trigger of dystonia. There are reports of OMD following jaw injury or surgery and of ocular trauma prior to the onset of BSP. Two case control studies found a significant association between BSP and diseases of the anterior segment of the eye (blepharitis, keratoconjunctivitis, and dry eyes). In one of those studies, the strength of the association increased when eye diseases first manifested around the fifth and sixth decades. Some authors proposed that this age range, together with the beginning of the physiological decline in the dopaminergic control over the trigeminal blink reflex circuit, might represent a temporal window of relative vulnerability to ocular diseases triggering BSP. A multicenter case control study in Italy, found that coffee drinking was associated with reduced likelihood of BSP.

Clinical Features

Clinical features of ICCD syndrome are fairly uniform. Most commonly, it begins in the upper face producing BSP. It may remain localized, but most frequently extends to other cranial muscle groups with variable rate and extent. When BSP is not associated with known etiologies, the term benign essential blepharospasm (BEB) is commonly used. Typically symptoms evolve gradually, reaching maximal disability after several months and then tend to remain stable. Occasionally, it can have a more abrupt onset and fluctuations can be seen during its evolution. Even though ICCD is a chronic disorder, spontaneous improvement may occur and there is a small potential of about 10% of remission of symptoms, particularly within the first 5 years. The clinical spectrum is wide causing variable degrees of social and occupational incapacity. Patients with BSP usually complain of eye discomfort, uncontrollable closing of the eyes or excessive blinking. It often interferes with the ability to read, drive, watch television, and other activities of the daily living. Sometimes this condition can be so severe, that it causes functional blindness.

BSP may coexist with apraxia of eyelid opening which is important to recognize as the latter condition does not respond well to botulinum toxin (BTX) injections.

Patients with involvement of the lower face and the oromandibular region complain of difficulty in speaking, chewing or swallowing and are socially most embarrassed. When vocal cords are involved a harsh, raspy voice, interrupted by voiceless pauses can be observed (spasmodic dysphonia). OMD may appear only when the patient attempts to eat, producing jaw opening or closing (trismus); as a result of lingual dystonia the food may be pushed out of the mouth. The severity of all these symptoms is influenced by various factors. For example, bright light, wind, or smoke tend to worsen BSP and patients generally like to use dark glasses. Other actions that frequently worsen symptoms include looking upward, walking, and reading. Various maneuvers called 'sensory tricks' may temporarily alleviate symptoms. These maneuvers include pulling at an upper eyelid, pinching the neck, talking, singing, humming, chewing, or opening the mouth, among others. Dental prosthetic devices may relieve jaw spasms. Patients with ICCD may have postural hand tremor and jerky movements in the arms. Sometimes they may seem talkative and anxious, but association with overt psychopathology has not been demonstrated. Intellect is normal and the remainder of the neurological exam is expected to be normal. In secondary forms additional neurological findings may be observed, depending on the disease entity. There are multiple reports of secondary CCD; potential etiologies include vascular or demylinating focal insults, head trauma, mass lesions, several neurodegenerative disorders such as Huntington's, Wilson's, and Parkinson's disease, neuroacanthocytosis, progressive supranuclear palsy, pantothenate kinase-associated neurodegeneration, and other metabolic, mitochondrial, and infectious disorders. Virtually all kinds of lesions, particularly those involving basal ganglia, thalamus, and rostral brainstem, may be associated with this syndrome. Tardive dystonia, produced by chronic neuroleptic administration, is a common cause of secondary CCD. The orofacial region is preferentially involved in tardive syndromes. Cases of tardive dystonia may resemble primary forms, but the presence of other hyperkinetic movements such as stereotypies, tics, akathisia, and respiratory dyskinesias are suggestive of prior neuroleptic exposure. CCD may also be induced by metoclopramide, levodopa, selective serotonin reuptake inhibitors, and more rarely by antihistaminics and stimulant drugs.

Pathophysiology

The underlying mechanisms of primary dystonia are still not well understood, but progress has been made based on different study results. The role of peripheral mechanisms

in focal dystonias has been studied in animal and human models. Schiatno and colleagues proposed a two factor model in which artificial dopamine depletion disinhibits the trigeminal blink circuits creating a permissive environment so that a prolonged external ophthalmic insult could precipitate BSP. Defazio, Martino, and colleagues found a significant association between disease of the anterior segment of the eye and BSP.

Pathology data have been scarce in cranial dystonia. Normal or nonspecific findings were present in nearly all specimens of idiopathic forms, except for increased contents of norepinephrine or copper and manganese in few autopsies. Recently, Defazio and colleagues reviewed the role of genetic factors in adult focal dystonia. They found an inheritance pattern compatible with an autosomal dominant trait and reduced penetrance in a few large families. More often the number of ascertained affected relatives was small, and inheritance did not appear to be Mendelian. Only DYT7 and DYT13 have been associated with cranial dystonia. The association of DYT1 and DRD5 polymorphisms with lifetime risk for focal dytonia is still controversial.

Novel neurophysiological and imaging studies in patients with cranial dystonia found: (1) impaired inhibitory control of motor mechanisms (at various levels of central nervous system) extending beyond affected muscles; (2) abnormally raised somatosensory spatial and temporal discrimination threshold; (3) increased excitability of brainstem interneurons mediating the blink reflex; (4) enlargement of putamen; (5) hyperechogenic lesions in the lenticular nucleus; (6) reduced postsynaptic dopamine D2 receptor binding in the striatum; (7) increased grey matter density in the primary sensory cortex and putamen; (8) overactivity of the primary sensorimotor cortex and the caudal part of supplementary motor area (SMA) in fMRI studies performed in the absence of a dystonia-inducing task; (9) overactivity of the primary sensorimotor cortex and SMA and deficient activation of primary motor and ventral premotor cortex within the mouth representation area; (10) abnormally reduced activity of the primary sensorimotor cortex after vibrotactile stimulation of affected and unaffected body regions.

Lots of the abnormalities described above for cranial dystonia are shared with other types of dystonia, suggesting common pathophysiologic mechanisms. Virtually in all cases of primary dystonia, there is dysfunction of the thalamus, frontal cortex, and basal ganglia. New data suggest that the cerebellum might also play an important role in this disorder. Physiological and imaging studies reflect an overactivation of sensory motor cortices that might be secondary to reduced inhibition. It seems that abnormalities in sensory processing accompany most types of dystonia, including cranial ones, and are concomitant with motor system modifications. These results have introduced the concept that patients with cranial dystonia also have impaired 'sensorimotor integration.' Animal models reinforce these observations and suggest that a disruption anywhere in the sensorimotor circuit can produce dystonia. The different localizations of the lesions producing secondary cranial dystonia also support the idea that any structure involved in these circuits can alter the activity patterns of all the others. Genetic susceptibility factors combined with certain environmental factors may enable these dysfunctional circuits to develop, leading to the expression of this movement disorder.

Differential Diagnosis

BSP should be differentiated from other conditions that can lead to eyelid closure, such as ptosis due to weakness of the levator palpebrae or Muller muscles. Ptosis may be seen in various disorders such as Myasthenia Gravis, third nerve lesions, or sympathetic denervation. Some patients are unable to open their eyes because of failure of the levator palpebrae to contract; this is called apraxia of eyelid opening. Vigorous frontalis contraction associated with delayed eye opening suggests this entity. EMG demonstrates an inactivity of the levator muscle despite the attempt to open the eyes. This entity is common in Parkinson's disease and other parkinsonian disorders, but can also be seen in isolation. Its treatment is difficult because it does not respond to BTX injections. Surgical approaches and special glasses may help.

Hemifacial spasm is typically characterized by unilateral, mostly clonic, facial muscle contractions. Twitching frequently begins in the OO and subsequently involves the lower face, including the platysma. Very rarely (3–5%) this condition can be bilateral, but usually there is a long latency before it affects the contralateral side. In contrast, BSP is typically bilateral. Commonly it is preceded by increased blinking and progresses to tonic, synchronous, OO contractions. Facial tics are multifocal, often suppressible, abrupt movements frequently preceded by a premonitory sensation. Hemimasticatory spasm consists of a unilateral contraction of muscles innervated by the motor trigeminal nerve resulting in painful jaw closing. Facial myokymia refers to continuous, undulating contractions of muscle fascicles.

Diagnostic Work-up and Tests

Diagnostic evaluation in adults presenting with dystonia should begin with a careful history. Although the majority of the cases of CCD are idiopathic in nature, physicians should be alert not to miss a reversible cause such as Wilson's disease. Review of all medications should query possible exposures to dopamine receptor blocking agents. If this is negative and the history suggests a gradual onset,

while there is no evidence of atypical features, such as rapid progression, abrupt onset, or onset at early age, imaging tests may not be required. All patients with possible heredodegenerative or secondary dystonia should undergo MRI imaging. The rest of the exams should be focused on the suspected etiologies. Genetic and functional imaging studies in CCD are not used routinely. Diagnosis remains largely based on careful clinical assessment. Referral to a movement disorder expert is recommended.

Management

Treatment of dystonia should be directed at the underlying cause. If no reversible etiologies are found, symptomatic treatment is the next step. Relief from pharmacotherapy is usually partial and short-lived. Anticholinergic agents (such as trihexyphenidyl), benzodiazepines (including clonazepam) and baclofen, are most commomly used. Recent communications reported improvement with clozapine and zolpidem. Levetiracetam showed inconsistent results. Tetrabenazine may benefit patients with tardive syndromes.

Periodic local injection of BTX is considered the therapy of choice for CCD. Side effects are local, and the duration of benefit is usually 2–6 months (average of 3 months). The pretarsal region of OO, particularly the Riolan muscle, seems to be the best place to inject BTX for BSP. If mild lower face spasms are associated with BSP, injections of BTX in periorbital muscles and slightly lower could be enough, otherwise, additional injections should be applied in the overflowing regions. Treating OMD with BTX is more challenging because of the risk of inducing dysphagia. In general, jaw-closing dystonia responds better than jaw-opening dystonia. Optimal doses reduce local side effects such as ptosis, diplopia, lower facial palsy, and dysphagia. For nonresponders to BTX in whom BSP is the main problem, myectomy is an option. Tinted lenses, in particular FL-41, may also help. Many patients benefit from combination therapies.

Sometimes this condition can be disabling and its medical treatment disappointing. Interest in the use of deep brain stimulation (DBS) for refractory forms of dystonia is thus increasing. Several recent case reports have suggested that this therapy may also be effective for CCD. Earlier communications in ICCD showed mild positive effects, but more recently Foote, Ostrem, Blomstedt, and Zauber showed more promising results, with improvements of around 70–75% in Burke-Fahn-Marsden (BFM) scores. It is important to note, that despite improvement in dystonia, some patients experienced mild and occasionally considerable worsening of motor function in previously nondystonic body regions. Other points of interest were that bilateral stimulation was necessary to achieve good results concerning axial symptoms; the latency of the benefit was shorter than in generalized dystonia; some patients developed stimulation induced dyskinesias, and speech and swallowing improvements were less significant.

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See also: Blepharospasm; Botulinum Toxin; Cervical Dystonia; Drug-induced Movement Disorders; Dyskinesias; Dystonia, Drug-induced (Acute); Dystonia, Secondary; Dystonia, Traumatic; Dystonia: Animal Models; DYT7, Autosomal Dominant Focal Dystonia; DYT13, Cranio-Cervical-Brachial; Fahn–Marsden Rating Scale; Geste Antagonistique; Hemifacial Spasm; Neuroleptics and Movement Disorders; PET Imaging in Movement Disorders; Psychogenic Movement Disorders; Rabbit Syndrome; rTMS; Spasmodic Dysphonia: Focal Laryngeal Dystonia; Surgery for Movement Disorders, Overview, Including History; Tardive Dystonia; Tardive Syndromes; Tics, Complex; Tics, Simple.

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http://www.ninds.nih.gov – National Institute of Neurological Disorders and Stroke.
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http://www.rarediseases.org/ – National Organization for Rare Disorders.
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Melanin

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Glossary

Complex I – Also called 'NADH-ubiquinone reductase,' an enzyme complex localized in the inner mitochondrial membrane. A part of the mitochondrial electron transport chain composed of complexes I–IV, which produce a proton 'gradient,' and transfer electrons to complex V (ATP synthase) producing ATP. In Parkinson's disease, Complex I activity is reduced.
***S*-Glutathionylation** – A term for the formation of 'mixed' disulfide bindings between reduced glutathione (GSH) and protein cysteine. *S*-Glutathionylation is catalyzed by reactive oxygen and nitrogen species (ROS–RNS), and this reversible posttranscriptional modification regulates various protein functions related to intracellular energy synthesis, signal transduction, and transcriptional activation.
Mitochondrial permeability transition (mPT) – The initial event in mitochondria-dependent intrinsic apoptosis. The permeability of the mitochondrial outer membrane is increased, leading to the release of proteins, such as apoptogenic molecules (cytochrome *c*, Smac/Diablo, HtrA2, etc.) from the intermembrane space into cytoplasm, accompanied by a decline of the membrane potential, $\Delta\Psi_m$, and Ca^{2+} influx. The mPT pore is a conductance pore spanning the inner and outer membrane, and consists of various membrane elements, the opening of which is regulated by the Bcl-2 protein family, cyclophilin D, and the mitochondrial redox state.
Ubiquitin–proteasome system – An intracellular macromolecular complex degrading misfolded, mutated, or oxidatively damaged proteins. Proteins are marked by covalent attachment of a polyubiquitin chain to lysine residues of protein and degraded in a large proteolytic complex, the 26S proteasome. The dysfunction of this system causes accumulation of inclusion bodies in neurodegenerative disease.

Characteristics of Melanin and Neuromelanin (NM) – Similarity and Dissimilarity

Melanin is a black pigment synthesized nonenzymatically or enzymatically from dopamine, L-DOPA and L-tyrosine. Melanin-containing cells, including catecholaminergic (CA) cells in the brain and melanocytes of the hair and skin, pigment cells in the inner ear, iris, and choroid of the eye, originate from the neural crest. However, the synthesis pathway, chemical structure, and function of melanin are quite different in the neural versus peripheral cells. In adult CA neurons of the substantia nigra (SN), locus coeruleus (LC), and additional brain stem loci, NM is produced in the cytoplasm mainly by autooxidation of dopamine. However, enzymatic synthesis of NM by tyrosine hydroxylase, peroxidase, prostaglandin H synthase, and macrophage migration inhibitory factor has also been proposed. In melanocytes, tyrosinase synthesizes L-DOPA and then DOPA-quinone from L-tyrosine in melanosomes. Tyrosinase mRNA and promotor activity are detected in the SN, but the tyrosinase-dependent synthesis does not occur in human brain, even though it does occur in the retinal pigmented epithelium.

NM isolated from the human SN is present in a large, aggregated structure, composed of three major components, melanin, protein, and lipid, with different electron density. Melanin polymer has the highest density and the protein component shows intermediate density, whereas the third lipid component is translucent. Melanin component is a mixture of melanin classes, black–brown 'eumelanin' and yellow–red 'pheomelanin' in a ratio of 4∼3 to 1. Eumelanin is composed of indole derivatives produced by autooxidation of dopamine, whereas pheomelanin contains benzothiazine molecules from incorporated cysteine or GSH with dopamine–quinone derived from dopamine by autooxidation. The protein components are covalently bound to NM, make up 5–15% of the isolated molecule, and include mostly lysosomal proteins, in addition to mitochondria-, cytosol-, and endoplasmic reticulum-associated protein, as detected by subcellular proteomics. The protein components are derived from a reaction of melanin polymer and proteins, or dopamine (quinone) bound to cysteinyl residue of peptide chains. The lipid components account for up to 20% of the mass and are identified to be 1% cholesterol and 14% polyisoprenoid dolichol. The lipid component is adsorbed to NM, not integrated in the structure. It was proposed that NM granules originate from lipofuscin, a lipid-containing pigment, but this hypothesis is now challenged by the fact that lipofuscin is localized in the lysosomes and produced also in glia and distributed ubiquitously in the brain.

The higher structure of the NM molecule is a multilayer three-dimensional structure similar to synthetic and naturally occurring melanin, as shown by X-ray diffraction studies. More recently, atomic force microscopy has revealed a spherical structure of NM granules with a diameter of ∼30 nm. The spherical structure of NM is composed of a pheomelanin core with a higher oxidation potential and a less redox-reactive eumelanin surface. However, this model cannot explain the occurrence of free sulfhydryl (SH) residues on the NM surface.

NM binds iron most strongly, and zinc, copper, manganese, chromium, cobalt, mercury, lead, and cadmium for 1.5% of the mass, and other 2–5% is due to sodium, potassium calcium and other inorganic compounds. Iron binds to NM at two distinct sites, the catechol groups forming metal centers in a lattice and the small-sized iron–oxygen frameworks in an insoluble NM matrix. In dopamine neurons of the SN, iron binds mainly to NM and accounts for 10–20% of the total iron, and the remainder is stored in microglia as bound to ferritin.

Physiological Function of NM

NM has been considered an inert waste product of dopamine autooxidation. However, recently, NM was found to function more actively in the brain. NM sequesters redox-active metals and toxic compounds, such as MPP^+, paraquat, and dopamine-(semi) quinone, preventing neuronal damage. NM also functions as an antioxidant and protects biomembranes from lipid peroxidation by scavenging ROS–RNS, such as hydroxyl radicals. Under physiological conditions, NM reduces ferric to ferrous iron and inactivates iron by accumulation as oxyhydroxide iron cluster. In addition, NM is ∼50% saturated with ferrous iron and can function as an iron-binding molecule to regulate iron homeostasis in NM-containing neurons.

NM in Aging and Parkinson's Disease

NM is first detected at 3–5 years of age as small, brown granules in the SN, and the size, number, and color of NM granules increase steadily until age 20. Thereafter, the NM color continues to darken until NM reaches its maximal levels around the sixth decades, when NM fills ∼47% of the cytoplasm. After then, the levels are relatively sustained in normal aging brains at 2.3–3.7 $mg\,g^{-1}$ of the SNpc in 50–90-year-old individuals. The number of NM-containing cells in normal SNpc is ∼95% of dopamine neurons, and decreases with age. With the onset of Parkinson's disease (PD), NM contents are reduced to 1.2–1.5 $mg\,g^{-1}$ of SNpc, suggesting that NM-containing dopamine neurons are more vulnerable than less-pigmented cells. The reduction of NM can be detected in vivo in the SN and LC of PD patients by use of 3 T MRI. Other studies indicate that NM contents decrease in the surviving neurons of SN, either because of reduced synthesis or increased degradation of NM.

NM isolated from PD patients contains highly cross-linked, proteasome-resistant lipoprotein with reduced NMR resonance. In PD (but not in control) brains, α-synuclein, a component of Lewy bodies, is cross-linked with dopamine *ortho*-quinone, aggregated and associated with NM lipid. In NM from PD SN, lipid composition also changes with reduced cholesterol, as shown by large volume of nonoxidized lipids in NM. In sporadic PD patients, insoluble extraneuronal NM granules released from dying neurons are detected and phagocytozed by microglia, the activation of which contributes to the inflammatory reaction observed in PD.

NM induces apoptosis in cellular models of dopamine neurons by activation of the mitochondrial apoptotic pathway, and it also deteriorates the ubiquitin–proteasome system. The cytotoxicity of NM depends on its protein component, since protease K treatment of NM completely reduces the cytotoxicity. NM liberates reduced glutathione (GSH) from mixed disulfide binding with SH residues of protein cysteine (*S*-glutathionylation) in mitochondria, and dissociates the higher structure of complex I. In PD, iron content increases by 30–35%, and GSH and antioxidant capacity reduce markedly, which induces oxidative stress. Increased ROS–RNS modify NM, activate SH residues in

NM protein, reduce the iron-binding capacity, and release sequestered iron in cytoplasm. These events finally induce the selective cell death of NM-containing neurons in the SNpc and the accumulation of Lewy bodies, the major pathological characteristics of PD.

See also: Alpha-synuclein; Complex I Deficiency; Dopamine; Mitochondrial Dysfunction; PARK1, Alpha Synuclein; Parkinson's Disease: Definition, Diagnosis, and Management; Proteasome Function in Movement Disorders; Substantia Nigra.

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Mercury

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Glossary

Mercury – An element that in organic and inorganic forms can be toxic to the nervous system.
Neurasthenia – A neurological condition marked most prominently by fatigue and lassitude. Many other symptoms may accompany these feelings including headache and other, often vaguely localized pains.
Tremor – A to-and-fro movement around a joint.

Mercury Compounds and the Nervous System

Human mercurial intoxication results from exposure to the metal, to its inorganic salts, to organic mercury-containing compounds that are degraded to the inorganic metal. Another form of mercurialism, with different chemical and clinical manifestations, results from intoxication with alkyl compounds, particularly methyl and ethyl mercury.

Inorganic mercury poisoning occurs as an industrial disease during paper manufacture, in the preparation of chlorine, and as a result of exposure to certain other chemical processes. Historically, mercurialism was associated with the hat manufacturing industry, because mercuric nitrate was used for processing felt. Acute poisoning has also followed the use of mercuric chloride as a local antiseptic, the excessive use of calomel as a diuretic, and following merthiolate ear irrigations. Dental amalgams release small amounts of mercury, available data do not indicate that this exposure represents a significant clinical risk of neurological intoxication.

The chief atmospheric source of mercury pollution is through the burning of coal and other fossil fuels. Metallic

mercury volatilizes at room temperature and condenses on skin and respiratory membranes. It is absorbed from the skin and the gastrointestinal and respiratory tracts. Elemental, nonionized mercury is transported in the blood, bound to plasma proteins and hemoglobin. Inorganic mercury has remarkable affinity for the kidney; as a result, symptoms of intoxication relate predominately to that organ. Brain uptake varies, depending on chemical form, but under appropriate conditions, the brain incorporates mercury rapidly. Once incorporated into the nervous system, mercury is very slowly eliminated.

Toxic Mechanisms

Serum concentrations are unreliable indicators of inorganic mercury toxicity, but toxic symptoms are usually present when concentrations exceed $500\,\mathrm{mg\,l^{-1}}$. Blood concentrations below $100\,\mathrm{mg\,l^{-1}}$ are considered to be safe. Urinary excretion is similarly an untrustworthy measure of toxicity. Inorganic mercury produces its toxic effects by altering membranes, particularly through combination with sulfur-containing bonds. Mercury inhibits energy metabolism by interacting with several enzyme systems that contain sulfur and by effects on chemicals including lipoic acid, coenzyme A, and pantetheine. Unlike lead, however, mercury forms complexes with amino groups of proteins.

Clinical Syndromes of Intoxication

Acute poisoning does not cause movement disorders but is associated with neurological signs that include emotional irritability, weakness in the lower limbs, psychosis with delirium, hallucinations, and locomotor hyperactivity when weakness does not occur. The chronic form of mercurialism is more common and occurs in industries that use mercury in low doses. The onset of illness may be subtle with postural and kinetic tremor, accompanied by weakness of the limbs and often a progressive personality change. The presence of tremor has been frequently associated with exposure to mercury, but tremor intensity and frequency had not been definitely correlated with current urinary levels of mercury. Other involuntary movements are described but have been poorly characterized in the literature. Muscle cramps and convulsions may develop. Occasionally a clinical picture resembling Parkinson's disease with slowness, gait difficulty, rigidity, and tremor develops, but in a large case–control study, no association between chronic mercury exposure and Parkinson's disease was found. Personality changes that can accompany or precede the motor phenomena include fatigue, apathy, and insomnia, often termed historically as *mercurial neurasthenia*. These symptoms may be interrupted or accompanied by periods of excitability and irritability, as typified in Lewis Carroll's Mad Hatter. The hyperirritability can be associated with violent behaviors, with some descriptions of assaultive and homicidal aggression.

Ataxia and gait instability has also been described in the context of chronic mercury exposure, and this syndrome can be associated with additional signs that include vertigo, nystagmus, blurred vision, narrowing of the visual fields, optic neuritis and atrophy of the optic nerve, and peripheral neuropathy. In children, far more often than in adults, chronic inorganic mercurialism is associated with acrodynia, but this syndrome involves generalized irritability and dysautonomia and has no associated movement disorder. Organic mercury readily enters the brain from the blood, and brain turnover is slow. In chronic exposure, ~10% of the body burden localizes in the brain. With acute intoxication, less than 3% is degraded into inorganic brain mercury, but this rate may change with chronic exposure. Specifically, inorganic mercury levels may account for 82–100% of brain mercury after organic mercury exposure if the autopsy is done several years after exposure. Once biotransformation to inorganic mercury occurs, excretion rates are extremely low since inorganic mercury cannot leave the brain easily. Anatomic changes in the brain involve especially the primary visual cortex and cerebellum followed by the putamen and frontal/parietal lobes. Peripheral nerves are also damaged. Because organic mercury is converted to inorganic metal, the intoxication syndrome seen after organic mercury exposure largely mimics the signs seen with inorganic exposure.

Alkyl mercury poisoning has followed the ingestion of contaminated sea food or exposure to alkyl mercury used in seed grain as an antifungal additive. Massive intoxication occurred in individuals living in the vicinity of Minamata Bay, Japan, as a result of ingestion of fish and shellfish containing methyl mercury. After effluent containing inorganic mercury from an adjacent chemical plant was deposited in sea water, mercury was methylated by microorganisms in the sediment, and methyl mercury so formed was incorporated into the protein of fish and shellfish. Alkyl mercury remains bound to protein for long periods as the half-life is several years. The intoxication occurred after humans consumed contaminated sea food. In 1972, another catastrophic epidemic of methyl mercury poisoning occurred in Iraq. Over 6000 patients were hospitalized for treatment, and 459 known fatalities occurred, principally as a result of eating homemade bread prepared from seed treated with a methyl mercury fungicide. At the cellular level, alkyl mercury compounds share many of the biochemical effects of their inorganic counterparts and form complexes with sulfhydryl radicals. The blood–brain barrier provides little impediment to the crossing of alkyl mercurials.

The primary neurological syndrome of this form of intoxication involves neuropathy, visual field defects, and blindness, many patients demonstrate evidence of cerebellar involvement, with unsteady gait, slurred speech, and poor coordination. Less frequent movement disorders include resting or postural tremor, chorea, athetosis, myoclonus, and rigidity. Prominent behavioral problems include labile affect, mental deterioration, comatose states, and even akinetic mutism.

Diagnosis

It is difficult to diagnose mercury toxicity from laboratory data because of variability of blood and urine measurements. While measurements in blood and hair are less variable than those in urine, these do not accurately reflect the degree of mercury toxicity. In urine, levels higher than $35\ \mu g\ g^{-1}$ creatinine are considered elevated. Hair samples must be collected according to specific protocols. For example, head samples must be taken close to the scalp and then washed to remove contaminants such as hair dyes or hair treatments. The advantage of hair samples is that they provide exposure information for the past year. Pubic hair has the advantage of being more likely free of mercury-containing surface contaminants. Subclinical slowing of finger tap speed has been detected in subjects with regular high fish consumption and levels of urinary organic and inorganic mercury that were higher than controls, but still far lower than the levels cited above.

Treatment

For treatment, mercury-binding compounds augment excretion of the metal in intoxicated patients regardless of the type of mercury exposure. The agents employed include D-penicillamine, *n*-acetyl-DL-penicillamine, and thiol resins. Dimer-caprol (BAL) is no longer utilized, because it increased the cerebral mercury concentrations in animals experimentally receiving the methyl form. Administration of chelating agents results in only irregular removal of mercury from the body. When chelating agents are administered, mercury concentrations of blood increase for 1–3 days, presumably as a result of rapid mobilization from the tissues and a slower rate of urinary and fecal excretion. After this period, blood concentrations decline. Thiol resins are not absorbed from the gastrointestinal tract, so they can be administered orally to bind mercury in bile and other fluids within the intestine. Fecal excretion is then enhanced by preventing reabsorption of methyl mercury so that redistribution of mercury in the body will not occur. Because thiol resins cannot reenter the body, they have no potentially adverse systemic effects. Spironolactone has also been employed in the experimental treatment of inorganic mercury poisoning. The protective effect appears to be related to increasing stool excretion through a yet unknown mechanism.

Prognosis

Most patients with severe mercury poisoning die within a few weeks of symptom onset, and those who survive have major neurological disability. In those with mild or moderate neurological symptoms, especially children and young adults, improvement may occur within the first 6 months. Examples have also been reported of ataxic, bedridden individuals who regained the ability to walk, and some children who were totally blind regained vision.

See also: Ataxia; Athetosis; Chorea; Tremor.

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Metachromatic Leukodystrophy

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Glossary

Auditory and visual evoked potentials – Evoked potential measurements record the time and strength of nerve responses to auditory (BAER) or visual (VER) stimulation.
Autosomal recessive – A genetic trait on one of the 22 nonsex chromosomes (autosomes) which requires the trait be present on both chromosome pairs to be expressed.
CSF protein – Protein content of the cerebral spinal fluid which is often elevated in the later stages of MLD.
EEG – An electroencephalogram (EEG) records brain electrical activity via electrodes on the scalp.
Heterozygote – An individual with a genetic trait on only one of a chromosome pair – a carrier.
Mucopolysaccharidosis – A genetic disorder in which the breakdown of one or more of a group of acidic carbohydrate polymers, the mucopolysaccharides or glycosaminoglycans, is impaired.
Nerve conduction velocity – The speed at which a nerve impulse is conducted along a peripheral nerve in the arm or leg.
Oligodendrocytes – Brain cells which provide the myelin sheath around axons in the central nervous system.
Periventricular – A brain imaging finding occurring next to or around the ventricles, usually on both sides of the brain.
Polyneuropathy – A generalized disorder of the peripheral nerves.
Schwann cells – Cells in the peripheral nervous system which provide the myelin sheath around axons.

Definition and History

Metachromatic leukodystrophy (MLD) is a group of genetic disorders resulting from defects in the catabolism of sulfated glycolipids commonly referred to as sulfatides or cerebroside sulfates. This leads to losses of myelin and results in motor, cognitive, and behavioral problems. Both central and peripheral nervous systems are impacted. Sulfatides occur throughout the body but are found in abundance in nervous tissue, kidneys, and testes. MLD is most often due to a profound deficiency of the lysosomal enzyme arylsulfatase A. The onset of symptoms can occur at any age beyond 1–2 years, but is preceded by a period of apparently normal development. MLD is generally divided into late-infantile, juvenile, and adult subtypes, based on the age of onset, which is an arbitrary classification. Sulfatide accumulation and MLD-like pathology also occur in two genetically distinct conditions: Saposin B deficiency and multiple sulfatase deficiency.

Metachromatic staining in the nervous system of individuals with neurodegenerative disease was noted as early as 1910, but a reliable staining protocol was only reported in 1955. Sulfatides, being the component responsible for the metachromasia, were not recognized until 1958. The gene for human arylsulfatase A was sequenced in1990, and a number of mutations and polymorphisms were recognized soon thereafter. The arylsulfatase A crystal structure was reported in 1998 and a unique active site structure revealed. A mouse model for arylsulfatase A deficiency was developed in 2000 and subsequently subjected to an extensive series of studies.

Pathogenesis/Pathophysiology

In the nervous system, sulfatides are most prevalent in white matter where they constitute 4–5% of the myelin lipids. In MLD, myelin appears to be formed normally by the oligodendrocytes and Schwann cells, but myelin turnover and repair are impaired resulting in the accumulation of excess sulfatides. This eventually leads to the disintegration of myelin and cell death. The cell debris is taken up by macrophages where the sulfatide accumulates. Neurons and axons tend to be relatively unaffected, and attempts at remyelination are evidenced by thin and poorly compacted residual myelin.

The cerebellum can be much more severely affected with a substantial loss of Purkinje cells and axonal tracts. Sulfatides are also increased in a variety of extraneural tissues and excreted in the urine. Liver and kidney sulfatides are substantially increased without apparent clinical consequences. The accumulation of sulfatides may occur in the gallbladder and may interfere with its function.

Epidemiology/Risk Factors

MLD is an autosomal recessive genetic disorder with a one in four chance of an affected child if both the parents are carriers (heterozygotes). The carrier frequency for the arylsulfatase A deficiency form of MLD ranges somewhere between one in 100 and one in 200 in the most studied European and European-derived populations. A number of inbred populations such as the Habbanite Jews in Israel have been described, in which the carrier frequency (1 in 6) and the incidence of MLD (>1%) are much higher. Saposin B and multiple sulfatase deficiency forms of MLD are rare, and reasonable estimates of the carrier frequencies have not been made. MLD occurs throughout the world, but reliable estimates of incidence in African and Asian populations are lacking.

Clinical Features and Diagnostic Criteria

MLD is characterized by a loss of motor and cognitive functions after a period of apparently normal development. The clinical subtypes are differentiated by the age of onset.

Late infantile: 1–2 years
Juvenile: 4–12 years
Adult: after sexual maturity

In late-infantile MLD, acquired skills such as walking and speech begin to deteriorate with a fairly rapid progression over a period of several months. There may be alternating periods of stabilization and decline. The patient eventually becomes bedridden, unable to speak or feed oneself. There may be seizures, and hypotonia eventually evolving to painful contractures is common. The child remains able to respond to the parents for a period, but eventually becomes nonresponsive. Swallowing becomes difficult, and tube feeding is usually recommended. With current levels of care, the child may survive for many years, but a secondary infection such as pneumonia eventually results in death.

Juvenile MLD (which is sometimes divided into early and late subforms) is usually detected during early schooling by a decrease in academic performance, difficulty in following directions, and behavioral abnormalities. This is typically followed by gait difficulties and slurred speech. Incontinence, abnormal postures, and loss of the ability to walk follow. The final stages of the disease are similar to the late-infantile form with survival for many years possible.

The initial indications of adult MLD occur after sexual maturity, but can range from 14 to >60. Initial symptoms can be clumsiness and loss of ambulation with the retention of intellectual processes or may be a change in personality, emotional labiality, and deteriorating job or school performance. Initial diagnoses such as MS on the one hand and psychiatric conditions such as schizophrenia on the other are common. Alcohol and drug abuse are frequent early signs. Eventually, there is a slow progressive loss of both motor and cognitive functions, which may extend over a period of 1–3 decades.

Multiple sulfatase deficiency has a clinical course similar to juvenile MLD, but may initially be diagnosed as a mucopolysaccharidosis due to mucopolysaccharide excretion and skeletal abnormalities.

The cases of saposinB deficiency recognized are too few to define a typical course, but the onset has ranged from infantile to adult, a juvenile MLD-like clinical course being most common.

Differential Diagnosis

In MLD, there is a period of normal development before symptoms emerge. Stumbling and loss of walking and/or speech regression in a 1–2 year old are typical of the late-infantile form. Gait problems and/or behavioral difficulties and emotional liability are the initial signs in juvenile or adult cases. It is difficult to distinguish MLD from a large spectrum of neurological and neuromotor disorders of genetic, environmental, and infectious etiology.

Diagnostic Work-Up/Tests

After a period of diagnostic uncertainty, the worsening of symptoms typically leads to a brain scan (CT or MRI) and indications of a leukodystrophy. In late-infantile cases, posterior periventricular white matter changes and severe bilateral polyneuropathy are noted. In later onset cases, anterior white mater changes are more common and polyneuropathy is often milder or completely absent. A series of enzymatic tests on white blood cells would reveal a profound deficiency of arylsulfatase A, leading to a preliminary diagnosis of MLD. Care must be exercised as there is a relatively common arylsulfatase A gene polymorphism with a substantially reduced enzyme expression, referred to as pseudodeficiency (PD). PD provides 5–10% of normal enzyme, enough to avoid clinical MLD even when present with a MLD-related gene. It is therefore necessary to show sulfatide storage or excretion to substantiate the diagnosis. In the past, this was a finding of sulfatide metachromasia in a brain or a nerve biopsy, and more recently, of sulfatide excretion into urine.

A number of additional tests are often included in the MLD work-up. CSF protein levels rise as the disease progresses in late-infantile and some juvenile cases reaching high levels in the later stages of the disease. Nerve conduction velocity is often decreased, and auditory- and visual-evoked potentials changes are commonly found. EEG alterations occur, sometimes before clinical symptoms are noted, and there may be seizures.

Management

Management mostly consists in the treatment of particular manifestations: Physical therapy is important for maintaining neuromuscular function and mobility. Contractures are treated with muscle relaxants. An enriched and challenging environment, memory training, and facilitated communication help sustain intellectual functioning. Seizures are treated using antiepileptic drugs. Genetic councilors and family support groups can be extremely valuable in helping parents and/or caregivers to anticipate when to employ walking aids, wheelchairs, feeding tubes, and other management needs.

Hematopoietic stem cell and bone marrow transplantation are the only therapies presently available for limiting the progression of central nervous system manifestations. This involves substantial risk and shows effects only after a period of continued regression. The best outcomes have been when the transplant is performed with later onset patients and before a substantial loss of function has occurred. Transplants do not correct peripheral nervous system manifestations, and long-term effects remain uncertain.

Prognosis

There is presently no cure for MLD, which eventually leads to immobility, dementia, and a loss of all but the most basic contact with the surroundings. Survival is correlated with the age of onset, but individual clinical courses can be variable, particularly with later onset cases. Death is usually due to pneumonia or some other infectious disease. The quality of care can substantially increase survival and enhance the quality of life.

See also: Alexander Disease; Ataxia; Athetosis; Electroencephalography (EEG); Gaucher's Disease; GM1 Type 3 Gangliosidosis; GM2 Gangliosidosis; Hallervorden–Spatz Syndrome (PKAN); Niemann–Pick Type C; Pelizaeus-Merzbacher Disease; Spasm.

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Micrographia

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Glossary

Basal ganglia – A collection of nuclei in the deep white matter of the brain, which is involved in motor control, cognition, emotions, and learning.
Bradykinesia – Slowness in movement, with the loss of voluntary and spontaneous movement.
Levodopa – Dopamine precursor produced by the brain, which is used as the best treatment for bradykinesia and rigidity in Parkinson diseases.
Micrographia – An acquired reduction in handwriting size, resulting in smaller amplitude strokes from slow and hypokinetic hand movements.
Parkinson's diseases – Degenerative disorders caused by loss of dopaminergic neurons from the substantia nigra parts compacta, commonly causing muscle rigidity, bradykinesia, resting tremor, and postural instability.

Definition and History

Micrographia is an acquired reduction in handwriting size, caused by hypokinetic hand movements resulting in smaller than normal sized strokes. It is more commonly associated with neurodegenerative diseases of the basal ganglia (BG), such as Parkinson's diseases (PD), but has also been described in focal BG lesions. This common clinical sign of parkinsonism can be the earliest manifestation of the syndrome. James Parkinson might have been aware of this feature in the first description of PD, when explaining 'the hand failing to answer with exactness to the dictates of the will' in *An Essay on the Shaking Palsy* (1817). Arnold Pick provided the first report of micrographia in 1903, in a patient with a syphilitic infarct involving the left thalamus and the genu of the internal capsule, and Froment was the first to associate it with PD.

Micrographia is usually defined by visual inspection of the patient's handwriting, and by comparing it to previous samples of their handwriting. Most often in PD micrographia worsens with continued writing. Recently, there has been an effort to further classify micrographia into two distinct types: constant micrographia (CM) and progressive micrographia (PM); and there also has been an effort to standardize an objective way to measure this clinical sign. CM was defined by the average size of the letter or figure written or copied by the patient, being two standard deviations below controls' size. PM was defined by the slope of reduction in size of letters as a function of the serial positioning of the letters/figures below two standard deviations of the mean. To better define and quantify micrographia, copying tasks instead of free writing should be used. There are currently no standard guidelines.

Pathogenesis/Pathophysiology

Micrographia is considered a component of bradykinesia in PD, and is thought to result from decreased pallidothalamic signals, secondary to dopamine depletion in the substantia nigra pars compacta. In this model, bradykinesia results from BG output failure. Cortical mechanisms cannot be reinforced in preparation and execution of movement, which then suffers and results in slow micrographic handwriting. This results in insufficient recruitment of muscle force during initiation of movement, leading to patients undershooting their targets and having to approach it using several smaller steps. In PD patients with micrographia, bradykinesia has been shown to result in decreased upstroke duration, thus in slower handwriting. However, upstroke amplitude (letter size) is unaffected with levodopa treatment, while stroke duration decreased, suggesting that other possible nondopaminergic components of micrographia and bradykinesia may exist.

It is thought that the overall deficit of reduced motor output in PD patients affects the modulation of upstroke amplitude and results in smaller handwriting. This deficit also results from focal lesions of the BG, and from lesions of the subcortical (thalamic and internal capsule) connections to the frontal lobe, especially to the supplementary motor cortex (which is involved in force modulation). Theoretically, in the absence of other lesions affecting the pyramidal system, patients with micrographia could have the force to increase handwriting amplitude, but they are less efficient at modulating force parameters given a compromised frontal–subcortical circuit. This resultant cortical abnormality may involve the underactivation of the supplementary motor cortex, which can specifically affect the 'open loop' circuit that is normally responsible for automatic motor programs, such as handwriting.

Despite this proposed primary cortical deficit in micrographia, frontal lobe function may also play a role in its improvement. This has been demonstrated in studies in which micrographia in PD patients significantly improved

with visual targets or constant auditory reminders. This is also described in bradykinesia, in which deficits can be ameliorated with external cues given to guide movement. Given that the underscaling of movement in automatic motor patterns improves with attention, the proposed mechanism involves the activation of the lateral premotor cortex (part of the 'closed loop' circuit) which can compensate, if attention is paid at preparing for movement or learning a motor task. The emergence of micrographia, despite compensatory mechanisms with improved attention, might suggest that in conditions such as PD, more extensive cortical dysfunction or other contributing cognitive processes maybe occurring.

Another possible mechanism for micrographia in PD suggests more extensive cortical dysfunction. In this model, micrographic handwriting is due to reduced motor output coupled with distortions in visual feedback. This was demonstrated in PD patients who initially produced smaller strokes (from reduced motor output), but then failed to recognize their micrographia secondary to reduced kinaesthesia, and subsequent strokes were produced to match the size of previously undersized strokes. Micrographia resulting from a sensory-motor deficit was also shown in a recent study in which simple eye closure eliminating distorted visual feedback significantly improved micrographia in PD patient during their 'off' periods.

Another theoretical mechanism for micrographia in PD could be that the dopamine depleted globus pallidus neurons result in a 'noisy' BG output, which reduces the signal-to-noise ratio in motor systems. The patient is more sensitive to any additional motor processing, and any additional simultaneous movement or additional motor load results in poorer handwriting. The deficit itself may be a compensation for this 'noisy' BG output, in which patients reduce their stroke size when other processing demands increase. Deep brain stimulation efficacy in PD may work in part by reducing or eliminating 'noisy' BG output.

Epidemiology/Risk Factors

The prevalence of micrographia ranges from severe micrographia in 15% to some micrographia in 75–90% of all PD patients. The self-reported prevalence of micrographia has been 6–14% in the elderly population, and 65–90% in PD cases.

Clinical Features and Diagnostic Criteria

Handwriting is an important skill in daily life. Any disease state that affects it will have a significant impact on the patient. When patients present with an initial complaint of micrographia, studies have shown that this symptom significantly increases the likelihood of having PD (with positive likelihood ratios of 3–6). The diagnosis of PD has to be considered, and other signs of Parkinsonism need to be searched for. Secondary causes of micrographia need to be considered.

Differential Diagnosis

Neurodegenerative

Parkinson's diseases (PD)
Secondary parkinsonism
Parkinson plus syndromes
Huntington's disease

Vascular

Ischemic (BG, left thalamus and genu of internal capsule)
Lenticular hematoma.

Toxic Exposure

Manganese poisoning.

Malignancy

BG tumors.

Immunologic

Multiple Sclerosis
Systemic lupus erythematosus (SLE)

Diagnostic Work-up/Tests

The most common etiology for micrographia is Parkinsonism. A complete history and neurological exam is essential to evaluate micrographia. Focus should be on determining if other features of parkinsonism including resting tremor, decreased hand and finger dexterity, cogwheel rigidity in the affected limb, and/or decreased arm swing when walking on the affected side exist. If a diagnosis of parkinsonism is made, then the diagnostic workup focuses on the syndrome. If no other associated signs are found in the presence of micrographia, then imaging of the brain with a computerized tomography (CT) or magnetic resonance imaging (MRI) is indicated.

Management

There is no specific treatment for micrographia. The same modalities used to treat bradykinesia in PD are utilized.

In one small study, handwriting was analyzed in PD patients across one levodopa treatment cycle. It showed that upstroke duration decreased when upstroke size was unchanged, 1 h after levodopa administration.

This suggested that at least one component of micrographia results from a nondopaminergic system. This is in keeping with the many reported cases of micrographia from focal subcortical lesions. Other treatments have improved stroke size including external application of weak electromagnetic fields, with resultant reversal of micrographia. Deep brain stimulation with high-frequency stimulation of the subthalamic nucleus made handwriting movements faster and smoother, perhaps indicating a partial restoration of 'open loop' automatic performance. Mean stroke length also increased demonstrating a stimulation-related reduction in micrographia in PD.

Prognosis

The prognosis in micrographia depends on the etiology. If part of parkinsonism, it may be partially treatable with drugs used to treat PD. However, there has been no clear correlation between motor scores on the Unified Parkinson's Disease Rating Scale (UPDRS) and micrographia. Therefore, prognosis is hard to predict with treatment. In other syndromes, micrographia can be the result of focal lesions of the BG, thalamus, internal capsule, and parietal lobe. If irreversible, as in the case of most ischemic or demyelinating lesions, the prognosis in terms of improvement may depend on the extent of the lesion and its potential to improve with physical/occupational therapy.

See also: Basal Ganglia; Beta-blockers and Movement Disorders; Bradykinesia; Complex I Deficiency; COMT Inhibitors in the Treatment of Parkinson's Disease; Deep Brain stimulation; Motor Output Variability; PARK7, DJ1.

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Milkmaid's Grip

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Glossary

Asterixis – Recurrent arrhythmic movement of the limbs typically occurring as a result liver failure.
Chorea – Jerky spasmodic movements of the limbs, trunk, and facial muscles common to diverse diseases of the central nervous system that involve the basal ganglia.
Encephalopathy – A disease of the brain.
Extrapyramidal – Situated outside of the pyramidal tracts, especially pathways involved in the control of motor function.

Motor impersistence – Inability to sustain a voluntary motor act despite the ability to perform the act briefly.
Myasthenia gravis – An autoimmune disease characterized by progressive weakness and fatigability of voluntary muscles caused by antibodies recognizing the acetylcholine receptor in the neuromuscular junction.
Myoclonus – Irregular, rapid, and typically multifocal involuntary muscle contraction.

Definition and History

Although the origin of the term 'milkmaid's grip' is difficult to define, this phenomenon is a characteristic feature of choreiform movement disorders such as Huntington's disease. Describing continuous and capricious increases and decreases in the pressure of handgrip; the terms 'milkmaid's grasp' or 'milking sign' have also been applied.

Pathogenesis/Pathophysiology

Striatal projections comprising the indirect pathway are believed to suppress undesired movements. Impairment/degeneration of this projection reveals movements that would ordinarily be inhibited. Hyperkinetic involuntary movements in Huntington's disease are thought to reflect the selective loss of medium spiny neurons of the indirect pathway. Functional alteration likely accounts for the occurrence of milkmaid's grip in other disorders. In addition, deficits in sensorimotor control during fine hand movements have been described in Huntington's disease and may contribute to the waxing and waning strength of grip.

Epidemiology/Risk Factors

Factors influencing the expression of milkmaid's grip depend upon the underlying diagnosis. Primarily genetic factors modulate risk in the autosomal dominant disorder Huntington' disease. Antecedent streptococcal infection and family history of chorea augment the risk of Sydenham's chorea and milkmaid's grip.

Clinical Features and Diagnostic Criteria

Considered a manifestation of motor impersistence, milkmaid's grip is often accompanied by impairment in sustained protrusion of the tongue and closure of the eyelids. While a precise description of milkmaid's grip was not included in George Huntington's monograph, 'On Chorea' (1872) he did recognize dyskinesia of the hands characterizing this as '. . .rolling – first the palms upward, and then the backs.' It is not only with the diagnosis of Huntington's disease that 'milkmaid's grip' has been reported. In post-infectious chorea, also identified as Sydenham's chorea or St. Vitus dance, an antecedent streptococcal illness has yielded milkmaid's grip. A precise description of this phenomenon is derived from the clinical notes of W.B. Cheadle at the Great Ormond Street Hospital. Describing a boy of 7 years and 9 months with endocarditis and chorea, Cheadle noted; '. . .when told to grasp the hand he is unable to give more than a spasmodic grasp and then looses it [while] the hand wanders round the object making ineffective attempts to hold it as constantly supinating and pronating the forearm' (1890). Milkmaid's grip has also been identified as a manifestation of the extrapyramidal syndrome that can complicate treatment with dopamine antagonists (i.e., tardive dyskinesia).

Differential Diagnosis

While commonly associated with choreiform disorders, milkmaids grip has been described in neuromuscular disorders. For example, handgrip fluctuating between weak and normal strength in myasthenia gravis has been characterized as milkmaid's grip. In the context of hepatic encephalopathy rhythmic squeezing when asked to grip the fingers, suggestive of milkmaid's grip, has been reported and considered a manifestation of asterixis (negative myoclonus) that complicates liver dysfunction.

Diagnostic Work-up/Tests

Elucidation of the etiology of milkmaid's grip is accomplished through determination of CAG repeat number ($\geq$37 CAG repeats) in the huntingtin gene, examination of immune measures to suggest prior streptococcal infection (i.e., antistreptolysin O titers) and magnetic resonance imaging of the brain to define basal ganglia anatomy. Laboratory assessment of hepatic function (asterixis) and determination of acetylcholine receptor antibodies (myasthenia gravis) will exclude uncommon causes.

Management

When symptoms are grave enough to require treatment, medications that curb choreiform movements can modulate the severity of milkmaid's grip. The most commonly utilized medications are dopamine antagonists. Most often an atypical neuroleptic will be prescribed due to the diminished risk of emergent tardive involuntary movements. Antagonism of the disinhibited, glutamatergic projection

from the subthalamic nucleus to the medial globus palidus with amantadine has also proven beneficial.

Prognosis

The natural history of milkmaid's grip is determined by the context in which it occurs. In Huntington's disease, improvement is unlikely given the degenerative nature of this diagnosis. In contrast, Sydenham's chorea is a self-limited disorder for which improvement is the rule. For toxic and metabolic etiologies of milkmaid's grip correction or improvement of the inciting imbalance will often result in restoration or resolution.

See also: Akathisia; Chorea; Chorea Gravidarum; Choreiform Disorders; Motor Impersistence; Sydenham's Chorea.

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Mitochondrial Dysfunction

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Glossary

Complex I – One of the polysubunit complexes of the mitochondrial electron transport chain.
DJ-1 – Protein of uncertain function whose gene mutations are found in rare forms of familial PD.
Haplotypes – Combination of alleles at multiple loci that are transmitted together on the same chromosome.
Lewy bodies – Intraneuronal proteinaceous inclusions found in affected brain regions, mainly in PD.
MPTP – Potent parkinsonian neurotoxin.
mtDNA – Mitochondrial DNA.
Parkin – E3 ubiquitin ligase whose gene mutations are found in rare forms of familial PD.
PINK1 – Mitochondrial kinase whose gene mutations are found in rare forms of familial PD.
Ubiquitin – Highly conserved regulatory protein of 76 amino acids that participates in the degradation process mediated by the proteasome complex.

Introduction

The second most common neurodegenerative disorder of the aging brain after the dementia of Alzheimer is Parkinson's disease (PD). This disease is progressive with a mean age at onset of 61, and exhibits an incidence that increases markedly with age. The cause of almost all occurrences of PD remains unknown. PD arises essentially as a sporadic condition, that is, in absence of any apparent genetic linkage, but occasionally the disease is inherited due to mutations in a variety of genes, including DJ-1 and PINK1. In both sporadic and familial (i.e., genetically inherited) PD, the primary hallmark is the degeneration of the nigrostriatal dopaminergic pathway, which, in depleting the brain of dopamine, leads to the emergence of abnormal motor manifestations such as resting tremor, rigidity, slowness of voluntary movement, and postural instability. At the onset of these manifestations, striatal dopamine has been depleted ~80%, and ~60% of substantia nigra dopaminergic neurons have been lost. However, the neuropathology of PD is far from limited to the nigrostriatal pathway, and histological changes can be found in many other dopaminergic and even nondopaminergic cell groups, including locus coeruleus, raphe nuclei, nucleus basalis of Meynert, and dorsal motor nucleus of the vagal nerve. Because a host of distinct neurological conditions share PD clinical features, a definite diagnosis of PD can only be achieved at autopsy and is customarily based not only on the loss of nigrostriatal dopaminergic neurons, but also on the identification of intraneuronal inclusions called Lewy bodies (LBs). These inclusions are spherical eosinophilic cytoplasmic aggregates composed of a variety of proteins, such as α-synuclein, parkin, ubiquitin, and neurofilaments, and

they can be found in every affected brain region. Whether identification of LBs should still be considered as necessary for the diagnosis of PD is controversial, since cases of inherited PD linked to parkin mutations typically lack LBs and are still regarded as cases of PD.

Why a Mitochondrial Defect Was Sought in PD

As mentioned above, the cause of sporadic PD is currently unknown. Over the years, a variety of pathogenic scenarios have been proposed to explain why and how neurodegeneration occurs in PD. The idea of mitochondrial dysfunction as a pathogenic mechanism in PD seems to have emanated from the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) story. Indeed, in the early 1980s, some drug users developed a rapidly progressive parkinsonian syndrome almost indistinguishable from PD. In these individuals, even the beneficial response and development of long-term motor complications from the administration of L-DOPA were virtually identical to those seen in PD patients. This cluster of patients with a young-onset PD-like syndrome was traced to intravenous use of a street preparation of 1-methyl-4-phenyl-4-propionpiperidine (MPPP), an analogue of the narcotic meperidine (Demerol). MPTP is the responsible neurotoxic contaminant, inadvertently produced during the illicit synthesis of MPPP in a basement laboratory. Subsequently, it was established that 1-methyl-4-phenylpyridinium (MPP^+), the active neurotoxic metabolite of MPTP, accumulates in the mitochondrial matrix where it inhibits oxidative phosphorylation. The use of several MPP^+ analogs and cationic inhibitors has demonstrated that MPP^+ binds at two distinct sites within the mitochondrial complex I of the electron transport chain comprised between N2 and ubiquinone. It is believed that, in response to MPP^+ binding to complex I, the flow of electrons along the respiratory chain is hampered, leading to an energy crisis, oxidative stress, and ultimately to cell death.

In light of the phenotypic similarity between PD and MPTP-induced parkinsonism in humans and the fact that the MPP^+ is a poison of the oxidative phosphorylation, many investigators have been prompted to search for mitochondrial respiratory defects in PD patients. Despite the fact that parkinsonism is hardly associated with genuine mitochondrial diseases, less than a decade later, as discussed in the next section, this idea has gained major enthusiasm among PD researchers.

Mitochondrial Dysfunction in PD

The direct relationship between mitochondrial dysfunction and PD came from the postmortem description of complex I deficiency in the substantia nigra of patients with PD. Subsequently, the deficiency was also reported in several tissues of PD patients including skeletal muscles and platelets. Notably, complex I deficiency in the substantia nigra and platelets has been consistently detected while the mitochondrial abnormality in skeletal muscle has been more difficult to identify reliably. Also worth noting is the fact that the substantia nigra samples used in the aforementioned studies were obtained from autopsies, which typically originate from very advanced cases of PD. We can, thus, safely assume that, in these PD samples, most of the neurons of interest, such as the dopaminergic neurons, are gone, and the number of glial cells, in contrast, has grown due to neurodegeneration-associated gliosis. Consequently, it is legitimate to posit that it is unlikely that the reported complex I deficit could have emanated from dopaminergic neurons only, since the vast majority of the cells contained in the studied samples are probably nondopaminergic neurons.

Mitochondrial complex I deficiency is not present in all patients with PD, either in the brain, platelets, or other tissues. The severity of the defect is about a 35% reduction in activity when the patient group is compared with control populations. At this point, in absence of a molecular marker, we cannot exclude that what we call sporadic PD is in fact not a disease per se (i.e., a single entity) but rather a syndrome made of heterogeneous pathological conditions sharing the same clinical phenotype. This view may have several significant implications. First, the aforementioned mitochondrial studies report on an etiologically heterogeneous population (e.g., patients with PD who had severe complex I deficiency and patients with PD who had healthy complex I activity). Second, there may be patients with a substantial complex I defect in whom the defect is directly related to their etiology, whereas other pathogenetic factors are important in other patients with PD. The small and unselected sample groups might explain why, for example, the mitochondrial abnormality has not been seen consistently in skeletal muscle. The complex I deficiency in the substantia nigra and platelets implies that this is a systemic defect in a proportion of cases (25% on the basis of platelet activities) and that this defect might be due to genetic or environmental (endogenous or exogenous) causes.

As for how the complex I defect may provoke neurodegeneration, it is important to mention that such a defect appears to be associated with a recruitment of the mitochondrial-dependent apoptotic pathway in intact cells. However, in isolated brain mitochondria, complex I dysfunction, caused by either pharmacological or genetic means, fails to directly activate this cell death pathway and to kill cells. Instead, defects of complex I lower the threshold for activation of mitochondrial-dependent apoptosis by Bax, thereby, rendering compromised neurons more prone to degeneration.

Mitochondrial DNA in Patients with PD

Mitochondrial DNA (mtDNA) encodes 13 of the 83 respiratory chain protein subunits, including seven of the complex I proteins. Thus, mutations in mtDNA were an obvious early target for analysis. The number of mtDNA deletions in individual neurons in the substantia nigra is substantially increased in PD patients older than 65 years. The deletions within a neuron are clonal and are associated with decreased cytochrome oxidase activity, as seen with histochemistry. While a high proportion of mtDNA deletions can be seen in controls, which increased with age, more mtDNA deletions are found in patients with parkinsonism and dementia. These results support the proposal that the human substantia nigra is a site of free-radical-mediated damage to mtDNA, and that this damage is enhanced in parkinsonism.

Sequencing of mtDNA from patients with PD has generally been done in unselected groups, with and without a mitochondrial deficiency. Although the results of some reports have suggested increased frequency of specific mtDNA polymorphisms in patients with PD, others have not. For instance, certain mtDNA haplotypes influence PD expression, and haplotype J has been associated with both a decreased and an increased risk of developing PD. Some evidence suggests that mtDNA haplotypes might influence cytosolic pH and mitochondrial calcium regulation which could influence neuronal function and integrity over time.

Genetic transplantation has been used to investigate the possibility that mtDNA from patients with PD is the origin of the complex I defect. Here, platelets from unselected patients with PD were fused and grown in mixed cultures or patients with PD were selected on the basis of a peripheral complex I deficiency and cells from these patients were fused with cells that lacked mtDNA (rho−) and grown in mixed or clonal cultures. In both instances, the mtDNA that was transferred from the patients with PD caused a complex I defect in the recipient cybrid cells, which suggests that the mtDNA in these patients caused the complex I deficiency through inherited or somatic mutations.

Finally, a mutation in mtDNA 12S RNA was found in a patient with maternally inherited, early-onset PD, deafness, and neuropathy, and a deletion in the gene encoding cytochrome b was found in a patient with parkinsonism. However, these mutations have not been identified in other patients with PD.

Mitochondrial Function and Familial PD

As indicated in the introduction, in rare instances, PD is linked to genetic defects and relevant to this review, some of these, including parkin, PINK1 and DJ-1, may affect mitochondrial function.

The Ubiquitin Ligase, Parkin

Parkin is transcribed ubiquitously, and intracellular localization studies have reported the association of parkin with the endoplasmic reticulum, Golgi apparatus, synaptic vesicles, and mitochondria. The function of parkin is unknown but the protein contains several domains for protein–protein interactions and E3 ligase activity. The ligase activity is a function of the ubiquitin proteasomal pathway, and several putative substrates for parkin have been reported, but whether any of these are bona fide parkin substrates remains to be established.

Recessive loss-of-function mutations in *parkin* were first reported in patients with juvenile-onset parkinsonism and have subsequently been shown to be the most common cause of PD in people younger than 20 years, although patients with later-onset cases have also been reported. An increase in striatal extracellular dopamine concentrations, reduced synaptic excitability, and mild, nonprogressive motor deficit at 2–4 months were described in a *parkin* knockout mouse line. However, no loss of dopaminergic neurons and no inclusion formations were noted. It has been reported that *parkin* knockout mice have decreased mitochondrial respiratory chain function in the striatum and reductions in specific respiratory chain and antioxidant proteins. More striking is the fact that *parkin* knockout *Drosophila* develop muscle pathology, abnormal mitochondrial morphology, and apoptotic cell death.

PINK1 (PTEN-Induced Putative Kinase 1)

The gene encoding PINK1 comprises 8 exons and encodes an insoluble, ubiquitously expressed, 581 amino acid, 63 kDa protein with an amino-terminal, mitochondrial-targeting sequence. There is some evidence that PINK1 is, at least in part, localized to the inner mitochondrial membrane, while its carboxy-terminus is exposed to the cytoplasm. The serine–threonine kinase domain of PINK1 has substantial homology with the CG4523 protein in drosophila. CG4523 interacts with a protein in the fly that is a homologue of the mammalian mitochondrial translation-initiating factor 3 (MTIF3), which makes this a candidate protein for interacting with PINK1. Analysis of genetic variants of MTIF3 in patients with PD found an allelic association between the C798T polymorphism and PD.

Mutations in *PINK1* are a cause of autosomal recessive PD. Mutations have been reported within and outside the kinase domain; however, the localization of PINK1 to the mitochondria is not affected by these mutations. Patients harboring the causative *PINK1* mutations have features typical of young-onset PD.

PINK1 knockout flies are viable but sterile or hypofertile, have a motor deficit, a shorter lifespan, an abnormal flight muscle with impaired function, disorganized mitochondrial morphology, reduced mitochondrial mass, lower

concentrations of ATP, and a small reduction in the number of dopaminergic neurons. This phenotype is very close to that seen in the *parkin* knockout flies. Relevant to these characteristics is the fact that parkin overexpression can rescue the mutant PINK1-related phenotype in flies, suggesting that parkin and PINK1 participate in the same pathogenetic pathway. While more work needs to be done to elucidate the role played in mitochondria by both PINK1 and parkin, mounting evidence indicates that, at least in insect cells, both proteins modulate the mitochondrial dynamics, including the fusion/fission.

Oncogene DJ-1

DJ-1 is a 23 kDa protein that is expressed in peripheral tissues and in parts of the brain, including the striatum, substantia nigra pars compacta, and reticulata in neurons and in glia, but is highly expressed in the cerebellum, hippocampus, and olfactory bulb. Studies of the intracellular distribution of DJ-1 show that it is found in several pools, including the mitochondria, where it is present presumably in the intermembrane space and matrix.

Thus far, studies on DJ-1 function have yielded confusing results, and its role at the level of the mitochondria remains enigmatic. DJ-1 seems to posses several functions, including that of an oncogene, a modulator of androgen-receptor-dependent transcription, and as a sensor of oxidative stress. More troubling is the fact that some studies have reported that oxidative stress and PD-associated mutations do not increase the mitochondrial localization of DJ-1, while others show that DJ-1 might translocate to the outer mitochondrial membrane during oxidative stress. The deletion or silencing of DJ-1 has been reported to sensitize cells to oxidative stress, and overexpression of DJ-1 protects cells. DJ-1 forms a nuclear complex with both RNA- and DNA-binding proteins that regulate gene transcription and can prevent apoptotic cell death by α-synuclein or oxidative stress.

Mutations in the gene encoding DJ-1 are a rare cause of autosomal recessive PD. Patients with mutations in *DJ-1* have young-onset PD that progresses slowly, responds well to levodopa, and might be coupled with dystonia. Mutations in *DJ-1* that cause familial PD lead to protein instability or decreased nuclear localization, decreased transcriptional activation, and decreased protection against apoptosis. The L166P mutation is also associated with increased mitochondrial localization, although this was not confirmed in other studies.

Conclusion

In the past decade, there have been some major discoveries on the role of mitochondria in neurodegenerative diseases in general and PD in particular. We now understand that through depletion of ATP, generation of ROS, and release of apoptogenic proteins, mitochondria may hold a key role in neurodegenerative processes. Initiation of these events, either individually or, more likely, in combination, would potentially lead to neuronal death. We also understand that the potential role of mitochondrial dysfunction in PD may not be restricted to a defect in respiration but may involve alterations in mitochondrial dynamics, which is increasingly recognized as a pathogenic factor. Some aspects of mitochondrial genetics, such as heteroplasmy, mitotic segregation, and the threshold effect, may contribute to our difficulty in linking common neurodegenerative diseases to mitochondrial defects. It is also important to remember that most studies on the mitochondrial link to neurodegeneration have been mainly performed in autopsy material, which often originates from terminally ill patients and is devoid of almost all neurons of interest, those that are proposed to die from mitochondrial dysfunction. Thus, many, if not all of these studies reflect analyses performed on a population of surviving cells (e.g., glia) not necessary representative of the actual neuronal death mechanism. Finally, it is also crucial to remember that mitochondrial defects reported in postmortem tissues may simply reflect nonspecific alterations that occur in dying neurons. The development of better in vivo experimental models of neurodegenerative diseases may provide us with the necessary tools to appropriately examine the mechanistic relationship between neurodegeneration and mitochondrial dysfunction and to address once and for all many of the pending issues that cloud the field of sporadic *mitochondrial* neurodegenerative diseases.

See also: Complex I Deficiency; Mitochondrial Dysfunction; MPTP; PARK2, parkin; *PARK6, PINK1*; PARK7, DJ1; Parkinson's Disease: Definition, Diagnosis, and Management; Parkinson's Disease: Genetics.

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Mitochondrial Encephalopathies

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Glossary

Dystonia – A movement disorder that causes involuntary sustained muscle contractions, repetitive twisting movements, and abnormal postures of the trunk, neck, face, or arms and legs.
LHON (Leber's hereditary optic neuropathy) – A disorder consisting of acute or subacute painless visual loss in one or both eyes due to optic atrophy, usually caused by a point mutation in one of the mitochondrial DNA encoded complex I genes.
MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes) – This is a disorder caused by various mitochondrial DNA mutations, most commonly an A to G point mutation at position 3243 in the tRNA-Leu(UUR) gene.
MERRF (myoclonus epilepsy with ragged-red fibers) – MERRF is characterized by myoclonus, generalised epilepsy, ataxia, and ragged-red fibers in muscle biopsy.
MPTP (1-methyl 4-phenyl 1,2,3, 6-tetrahydropyridine) – A toxin that inhibits the activity of complex I of the mitochondrial electron transport chain.
3-NP (3-nitropropionic acid) – A toxin that inhibits the activity of complex II of the mitocohondrial electron transport chain.

Mitochondria are the 'energy factories' of our cells. They generate ATP through the mitochondrial electron transport chain, which includes a series of protein complexes within the inner mitochondrial membrane that transfer electrons to molecular oxygen. This process is coupled to the generation of a proton gradient, and the energy stored in this proton gradient is used to generate ATP. Mitochondrial dysfunction can result in several deleterious consequences (**Table 1**) that may contribute to the pathogenesis of mitochondrial encephalomyopathies.

Table 1 Potential consequences of mitochondrial dysfunction

Low ATP levels
Increased reactive oxygen species (ROS)
Impaired calcium buffering
Opening of the mitochondrial permeability transition pore → release of pro-apoptotic factors

The mitochondrial encephalomyopathies, sometimes also referred to as mitochondrial encephalopathies or simply mitochondrial disorders, represent a diverse set of disorders involving abnormalities of mitochondrial function. Classic mitochondrial genetic disorders are associated with mutations in mitochondrial DNA (mtDNA), which are inherited strictly along the maternal line. MtDNA mutations also can be acquired during life (somatic mtDNA mutations), a phenomenon hypothesized to play a role in some age-related disorders. The situation is complicated by the fact that a predisposition to accumulating somatic mtDNA mutations can be inherited (see discussion of Polg mutations later in this section). A total of 13 proteins are encoded on the mtDNA, each of which is a component of the mitochondrial electron transport chain, along with 22 tRNAs and 2 rRNAs. Thus, most of the estimated 1500 proteins that function within the mitochondria are encoded on the nuclear genome. Not surprisingly, many disorders caused by mutations in nuclear genes have been associated with mitochondrial dysfunction, including Friedreich's ataxia and Huntington's disease. However, this section focuses on disorders associated with mtDNA mutations. Inherited mitochondrial genetic disorders are relatively rare, and the literature on movement disorders associated with these disorders is even rarer.

Classic mitochondrial encephalopathies are relatively rare, and not all physicians are familiar with the range of clinical presentations of these disorders. Recognition of the potential for prominent movement disorders in mitochondrial encephalopathies can help to avoid delays in diagnosis. This review briefly summarizes the movement disorders reported in association with some of the classic mitochondrial disorders.

Leber's Hereditary Optic Neuropathy Plus Dystonia

The first human disease demonstrated to be caused by a mtDNA mutation was Leber's hereditary optic neuropathy (LHON), most commonly caused by a point mutation in one of the mitochondrial genes encoding a subunit of complex I of the mitochondrial electron transport chain, either G3460A, G11778A, or T14484C in most cases. LHON is associated with acute or subacute painless visual loss in one or both eyes due to optic atrophy. Subsequently, rare families were identified in which LHON occurred in some family members and dystonia, either alone or together with LHON, in others. This syndrome

Table 2 mtDNA mutations associated with dystonia

Syndrome/disease	*Gene*	*Site of mutation*	*Types of mutations*
MELAS	tRNA-Leu(UUR)	3243	A to G substitution
Dystonia + cataracts	ND1 (complex I)	3308	Frame shift
LHON	ND1 (complex I)	3460	Missense
	ND4 (complex I)	11778	Missense
LHON + Dystonia	ND4 (complex I)	11696	Missense
	ND6 (complex I)	14459	Missense
	ND6 (complex I)	14596	Missense
Leigh's syndrome	tRNA-Lys	8344	A to G substitution
	ATP-6 (complex V)	8993	Missense
Kearns–Sayr	Multiple		5.9 kb deletion

of LHON plus dystonia can be caused by a point mutation at position 14459 in the ND6 subunit of complex I. Subsequently, other mtDNA mutations have been linked to a similar syndrome (**Table 2**).

LHON associated mtDNA mutations also rarely can be associated with other neurological features. For example, we reported a family with maternally inherited parkinsonism plus dystonia and dementia in association with a heteroplasmic G11778A 'LHON' mutation. Others have reported postural tremors, tics, parkinsonism, chorea, and dystonia, as well as other neurological findings.

Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-Like Episodes

Another mitochondrial syndrome, MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes), as the name implies, typically is characterized by stroke-like episodes as well as seizures, myopathy, ataxia, headaches, and recurrent vomiting. An A3243G point mutation in the tRNA-Leu(UUR) gene accounts for about 80% of cases. Dystonia also can be a feature of MELAS, and Sudarsky et al. reported a patient with MELAS for whom dystonia was the predominant presenting symptom. Some patients have been reported to have myoclonus as well, though myoclonus is more typical of myoclonus, epilepsy, ragged-red fiber (MERRF) (see below). Chorea also can occur in MELAS.

Leigh Syndrome

Maternally inherited Leigh syndrome (MILS) is a severe usually infantile- or early childhood-onset mitochondrial disorder associated with bilateral basal ganglia and brainstem degeneration that is genetically diverse, and can be caused by various different mtDNA mutations and also by autosomal recessive or X-linked mutations in nuclear encoded genes leading to mitochondrial dysfunction. Because of the propensity for basal ganglia pathology, it is not surprising that MILS can be associated with many different movement disorders, including prominent dystonia, myoclonus, chorea, parkinsonism, and tics.

Myoclonus, Epilepsy, Ragged-Red Fibers

Myoclonus, epilepsy, ragged-red fibers (MERRF) is a syndrome characterized by myoclonus, generalized seizures, ataxia, and myopathy, usually due to a point mutation in the tRNA-Lys gene (A8344G, T8356C, or G8363A). In addition Rita Horvath et al. reported a patient with parkinsonism as a prominent clinical feature in a patient harboring the 8344 'MERRF' mutation.

Treatment of myoclonus in MERRF is complicated by the fact that valproic acid can inhibit cytochrome oxidase activity and has been reported to cause ultrastructural changes in mitochondria. A case report has been published of improvement in myoclonus with levetiracetam in a patient with MERRF. Unfortunately, controlled trials are lacking regarding treatment of movement disorders specifically in MERRF or in other classic mitochondrial disorders.

Multiple mtDNA Deletions Associated with Parkinsonsism

Familial parkinsonism can result from an inherited predisposition to accumulating multiple somatic mtDNA deletions. This form of parkinsonism, associated with progressive external ophthalmoplegia (PEO) and premature ovarian failure, results from a mutation in the mtDNA polymerase γ (Polg) gene, resulting in increased errors during mtDNA replication. Polg is a nuclear encoded gene, and thus this predisposition to accumulating mtDNA deletions is inherited in an autosomal dominant manner.

mtDNA Mutations and Mitochondrial Toxins in Parkinson's Disease and Dystonia

Mitochondrial complex I activity is deficient in the substantia nigra in Parkinson's disease (PD). Cell lines expressing mtDNA from PD patients also manifest

complex I deficiency, suggesting that mtDNA mutations may account for the defect in PD, though specific mutations have yet to be identified that definitively account for the complex I defect in PD. Large mtDNA deletions have been found to accumulate with age in substantia nigra neurons with modestly higher levels in PD compared to controls, but the significance of these deletions in the pathogenesis of PD remains uncertain. Interestingly, patients with adult-onset idiopathic dystonia also are reported to have a defect in mitochondrial complex I activity, but the significance and origin of mitochondrial dysfunction in such cases remains unknown.

Though this review focuses on mtDNA mutations, it is worth noting that mitochondrial toxins also can cause parkinsonism and dystonia. The mitochondrial complex I inhibitors 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (MPTP) and rotenone (a pesticide) can induces loss of dopaminergic neurons resulting in parkinsonism in animal models. MPTP also induces transient dystonia in baboons. Another mitochondrial toxin, 3-nitropropionic acid (3-NP) inhibits complex II and induces behavioral changes and striatal lesions similar to those of Huntington's disease. 3-NP also can induce a delayed-onset progressive dystonia following systemic injections in monkeys. Accidental exposure in humans following ingestion of 3-NP contaminated sugar cane is reported to have induced a transient encephalopathy followed by a progressive movement disorder including dystonia and chorea.

See also: Chorea; Complex I Deficiency; Dystonia; Dystonia, Secondary; Leigh Syndrome; Mitochondrial Dysfunction; MPTP; Myoclonic Epilepsy with Ragged Red Fibers (MERRF); Myoclonus; Myoclonus, Epileptic; Parkinson's Disease: Definition, Diagnosis, and Management; Parkinson's Disease: Genetics; Pelizaeus-Merzbacher Disease; Pesticides; Pseudobulbar Symptoms; Staircase (Skilled Reaching) Test.

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MMSE - Mini-Mental State Examination

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Glossary

Factor analysis – A statistical method for reducing correlational data to a smaller number of factors which are regarded as the basic variables that account for the interrelationships among the data.

Reliability – The regularity with which a test produces the same score under similar retest conditions, or the regularity with which different parts of a test provide similar findings.

Validity – The degree to which a test measures what it purports to measure.

Definition and History

The Mini-Mental State Examination (MMSE), published by Folstein et al. in 1975, is a widely used test for screening and scaling cognitive impairment. The MMSE was initially developed as a simplified, quick, scored form of cognitive mental status since the batteries available at that time to evaluate mental status were lengthy and time-consuming. In the original article, Folstein et al. administered the MMSE to a total of 206 patients with dementia syndromes and other psychiatric diagnoses (affective disorder, affective disorder with cognitive impairment, mania, schizophrenia, and personality disorders) and 63 normal, elderly controls. Comparing 69 psychiatric inpatients (diagnosed with dementia or affective disorder with or without cognitive impairment) and 63 normal, elderly controls, the authors reported that the MMSE significantly differentiated the three diagnostic groups of patients from each other and from the normal group. Based on the examination of an additional 137 psychiatric inpatients for standardization, Folstein et al. found scores of 20 or less in their patients with dementia, delirium, schizophrenia, or affective disorder but not in the normal elderly or in patients with neurosis or personality disorder. The MMSE scores demonstrated high concurrent validity with the Weschler Adult Intelligence Scale, Verbal and Performance scores. In a subset of patients retested after 28 days, there was no significant difference in scores. Folstein et al. acknowledged that the MMSE did not replace a complete clinical evaluation for diagnostic purposes, but highlighted its reliability and validity, clinical pertinence, and usefulness in training residents in skillful evaluation of cognitive aspects of mental status.

Over time, the MMSE has remained a brief test of mental status that is easy to administer and score. Administration time is approximately 10 min. There are authorized translated versions of the MMSE in many languages. In addition, population-based normative data such as age and years of education are available for interpreting the MMSE scores; total scores are affected by increased age and low education (especially education less than 8 years), which may represent psychometric bias.

Scale Structure

The total possible score is 30, and a score of 23 and below is generally considered to be within the impaired range. In patients with significant physical or sensory limitations, not all items can be administered (e.g., patient may be unable to copy the design due to motor impairment, or may be unable to name objects because of visual defect). In this case, the score is out of the number of items which are administered (e.g., out of 28 or 29). Items on the MMSE assess a number of domains, including orientation (10 points), registration of three words (3 points), attention (5 points), recall of three words (3 points), language (8 points), and visuoconstruction (1 point).

Psychometric Properties

The MMSE demonstrates moderately high levels of reliability. It has been reported to be internally consistent. The MMSE has been found to have short-term test–retest reliability in patients with dementia, as well as long-term reliability in cognitively intact individuals. The MMSE has been shown to have construct validity, since it is moderately correlated with other dementia screening exams (e.g., Blessed Orientation-Memory-Concentration Test), as well as measures of general cognitive abilities (e.g., Wechsler Intelligence Scale).

The MMSE has been found to be sensitive to the severity of dementia in patients with Alzheimer's disease (AD). The total score is useful in documenting cognitive change over time. Patients with AD typically show an annual decline of 3 points on the MMSE. The MMSE is not used as the sole criterion for diagnosing dementia, since there are nonneurological reasons that lead to low scores (e.g., low education, difficulty with the English language, visual or auditory defects). Rather, the score is used in conjunction with the clinical history, the neurological examination, and other neuropsychological tests in order to establish a diagnosis of dementia. Besides being routinely used in clinical practice, the MMSE has been used to assess cognition in epidemiological studies of dementia. The MMSE also has been used in clinical trials as an exclusion–inclusion criteria (e.g., screening for cognitive impairment) and as part of neuropsychological test batteries in research studies.

Since individual items of the MMSE load on different factors across factor analytic studies, caution should be used in interpreting performance on individual items. For example, there is a tendency to associate not recalling the three words with cortical, generalized dementia, and difficulty spelling WORLD backwards with frontal–subcortical dysfunction. However, the items of the MMSE should not be substituted for a detailed neuropsychological evaluation for differential diagnosis.

Use in Movement Disorders

The MMSE has been used to detect cognitive decline in patients with Parkinson's disease (PD). For example,

researchers followed 69 patients with idiopathic PD who initially scored within the normal range (MMSE $\geq$ 24). At two-year follow-up, 12 patients (17%) had significant cognitive decline, as defined as a decline of $\geq$4 points on the MMSE.

A score of less than 24 on the MMSE in patients with parkinsonism is generally supportive of dementia; however, the MMSE does not differentiate coexisting AD versus dementia with Lewy bodies in patients with parkinsonism and dementia. In a study of 115 newly diagnosed patients with Parkinson's disease, subjects were excluded who had possible dementia, as defined by a MMSE score of less than 24. Of these patients, 24% had mild cognitive impairment, as defined as impairment on at least three tests from a neuropsychological test battery. In a recent study of 106 patients with PD who had normal MMSE scores, mild cognitive impairment was found in 29.2% of the patients, as defined as impairment on at least two tests within a cognitive domain. These findings have led some researchers to suggest that the MMSE has a ceiling effect when assessing the mild cognitive changes associated with PD.

The MMSE has also been used with patients with of Huntington's disease (HD). In a study comparing 145 patients with AD and 84 patients with HD, the HD patients were generally impaired in performing serial subtractions, while the AD patients had more difficulty recalling the three words.

Criticisms and Strengths

The MMSE has been criticized as being not very effective in separating patients with mild dementia from normal subjects, as well as being insensitive to mild cognitive impairment. Recently, the Montreal Cognitive Assessment (MoCA) has been proposed as a screening instrument that is sensitive to mild cognitive impairment and the early cognitive changes of Parkinson's disease. The MoCA assesses a broader range of domains affected in PD, including attention, executive functions, and visuoperception. In a study of 131 patients with PD, 52% of patients with normal MMSE scores had mild cognitive impairment, as suggested by a score of less than 26 on the MoCA.

In addition, the MMSE has received criticism for being a highly verbal based test, for all items not being equally sensitive to cognitive impairment, for lacking assessment of subcortical functions, and for being limited in the evaluation of change in more severely demented patients. There also may be influences of age, education, and cultural background; some of these factors such as age or education can be accounted for with use of normative data.

However, the MMSE has several strengths including that it can be readily and quickly administered in both clinical and research settings. It has demonstrated utility in its widespread and long-standing use as a cognitive screening test. Translations into multiple languages are available, as are age and education-based normative data. Its psychometric properties and use in studies of dementia demonstrate that the test largely meets its proposed goals as a screening instrument of cognitive function and serial measurement of cognitive change.

See also: Cognitive Assessments and Parkinson's Disease; Dementia with Lewy Bodies; Dementia, Movement Disorders; Executive Dysfunction.

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Monoamine Oxidase Type B Inhibitors

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Introduction

The monoamine oxidase type B (MAO-B) inhibitors, rasagiline and selegiline, have been studied extensively in regard to both symptomatic and possible neuroprotective or disease-modifying properties in Parkinson's disease (PD). Selegiline and rasagiline are propargylamine pharmacophores and irreversibly inhibit the MAO-B isozyme, but they differ substantially in chemical scaffolding and metabolic by-products. Considering the pharmacological differences between the two compounds, it cannot be assumed that selegiline and rasagiline demonstrate similar clinical benefits.

In addition to rasagiline and selegiline, other MAO-B selective inhibitors (e.g., lazabemide and mofegiline) have been tested in clinical trials for the treatment of PD. However, these agents have not made it to the market.

MAO Inhibitor Pharmacology

MAO are ubiquitous enzymes that exist in mammalian tissues in two genetically distinct forms, referred to as MAO-A and MAO-B. The physiologic role of MAO is to catalyze the biotransformation of a variety of arylalkylamine neurotransmitters, such as dopamine, norepinephrine, and serotonin as well as to detoxify biogenic amines, such as tyramine. The overall reaction involves oxidative deamination and can be characterized as: $RCH_2NH_2 + H_2O + O_2 \rightarrow RCHO + NH_3 + H_2O_2$. Each isozyme demonstrates distinct substrate specificity, inhibitor selectivity, and a unique tissue distribution. MAO-A is primarily responsible for degrading serotonin and norepinephrine, as well as exogenous monoamines such as tyramine. MAO-B is primarily responsible for degrading dopamine. Both MAO isoenzymes are present in the tissues of the brain, gastrointestinal tract, and liver; however, MAO-A predominates in the gastrointestinal and hepatic tissues and in the human basal ganglia, MAO-B is more abundant than MAO-A, accounting for 80% of total MAO activity.

Although the mechanism by which MAO-B inhibitors exert beneficial effects in PD are multifactorial, the main pharmacologic activity is the selective inhibition of MAO-B resulting in a reduced deamination of dopamine and thus in a greater dopaminergic activity. Both drugs contain a propargylamine moiety that is essential for conferring irreversible inhibition of MAO-B.

Medical interest in MAO inhibitors initially emerged in the early 1950s for the treatment of psychiatric disorders (i.e., depression). The nonselective MAO inhibitors, such as phenelzine and tranylcypromine, were shown to be associated with an increased incidence of hypertensive crisis, which was initially observed in association with the consumption of aged cheese. This 'cheese reaction' is known to be due to the increased bioavailability of tyramine, a dietary sympathomimetic amine, into the systemic circulation due to MAO-A inhibition in the gut. Subsequently, inhibitors selective for the MAO-B isozyme were developed and are nowadays used to treat PD. Despite the proven safety of selective MAO-B inhibitors, concerns persist regarding unlikely interactions with tyramine-containing foods/beverages and drugs with serotonergic augmentation. Practically speaking, at therapeutic doses, these selective MAO-B inhibitors are unlikely to induce a 'cheese reaction' (transient hypertension, headache) unless extraordinary amounts of dietary tyramine (400 mg or greater) are ingested, unlike the nonselective MAO-A/B inhibitors, which require as little as 10 mg or less of dietary tyramine. Studies in rasagiline-treated patients receiving a tyramine challenge test did not yield significant findings on blood pressure or heart rate changes. It should also be noted that there were no dietary restrictions with respect to tyramine in the rasagiline clinical trials. Thus, rasagiline 0.5–1.0 mg daily can be used safely without over concern regarding dietary tyramine restrictions.

Additionally, the potential for a hypertensive effect resulting from concomitant administration of sympathomimetic agents (e.g., ephedrine, phenylephrine, pseudoephedrine), which are substrates of MAO, is low and the available data demonstrate that the risk of a severe hypertensive episode associated with occasional administration of over-the-counter sympathomimetic agents (e.g., cold products, weight-reducing agents) appears to be minimal.

Concomitant use of MAO-B inhibitors with meperidine and other selected analgesics is contraindicated due to a small risk of serotonin syndrome. Concomitant use of serotonergic antidepressants is not contraindicated (with the exception of rasagiline and mirtazapine) and they can be used together safely. In one survey, the frequency of serotonin syndrome in patients on concomitant selegiline and a selective serotonin reuptake inhibitor (SSRI) was reported to be only 0.24%, with 0.04% of patients experiencing serious symptoms.

Selegiline

At daily doses of <20 mg, selegiline (*N*-propargyl-methamphetamine), also known as L-deprenyl, is an irreversible inhibitor of the MAO-B isozyme. For treatment in PD, conventional selegiline is administered 5 mg twice daily and orally disintegrating selegiline 1.25–2.5 mg once daily. Synthesized in 1961, selegiline was the first selective MAO-B inhibitor. It is a propargylamine derivate of methamphetamine and able to selectively and irreversibly block MAO-B activity in the brain. The inhibition of MAO-B activity results in a reduced oxidative deamination of dopamine and phenylethylamine.

Several randomized, controlled trials, including the large Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP), demonstrate that selegiline monotherapy provides a symptomatic benefit and is well tolerated. As monotherapy, the side effects of selegiline include nausea, benign cardiac arrhythmias, dizziness, and headache. The outcomes data for conventional selegiline as an adjunct to levodopa are conflicting. Several studies have demonstrated improvements in motor symptoms and reduction in off-time. However, several other studies, have shown minimal or no benefit from adjunctive selegiline therapy. When used in combination with levodopa or dopamine agonists, treatment emergent side effects include nausea, dizziness, fatigue, constipation, insomnia, peak-dose dyskinesias, psychiatric complications (e.g., hallucinations), and orthostatic hypotension.

The clinical value of conventional selegiline is compromised by low bioavailability as >90% of an orally administered dose undergoes first-pass metabolism by hepatic microsomal P-450 dependent monooxygenases before reaching the systemic circulation. This extensive hepatic first-pass effect not only reduces the systemic exposure to selegiline, but is also associated with the production of metabolites, namely *N*-desmethylselegiline (DMS), L-methamphetamine (*m*-amph), and L-amphetamine (amph) (**Figure 1**). The latter two metabolites have been implicated in contributing towards adverse cardiovascular and psychiatric side effects during selegiline treatment (e.g., orthostatic hypotension, hallucinations, insomnia, vivid dreaming).

The putative neuroprotective effects of selegiline and its metabolite, DMS, have been investigated clinically as well as in cell culture and animal models. Selegiline and DMS prevent neurotoxin-induced cell death by virtue of their ability to induce antiapoptotic molecules and down-regulate proapoptotic molecules. In fact, the protective efficacy of DMS may be greater than that of selegiline, as it is active at lower concentrations and provides significantly greater levels of protection at the same concentrations, suggesting that DMS might be the active compound responsible for the neuroprotective properties of selegiline. Despite preclinical evidence of neuroprotection, the amphetamine-like metabolites of selegiline may actually be neurotoxic and counteract any disease-modifying effect of selegiline.

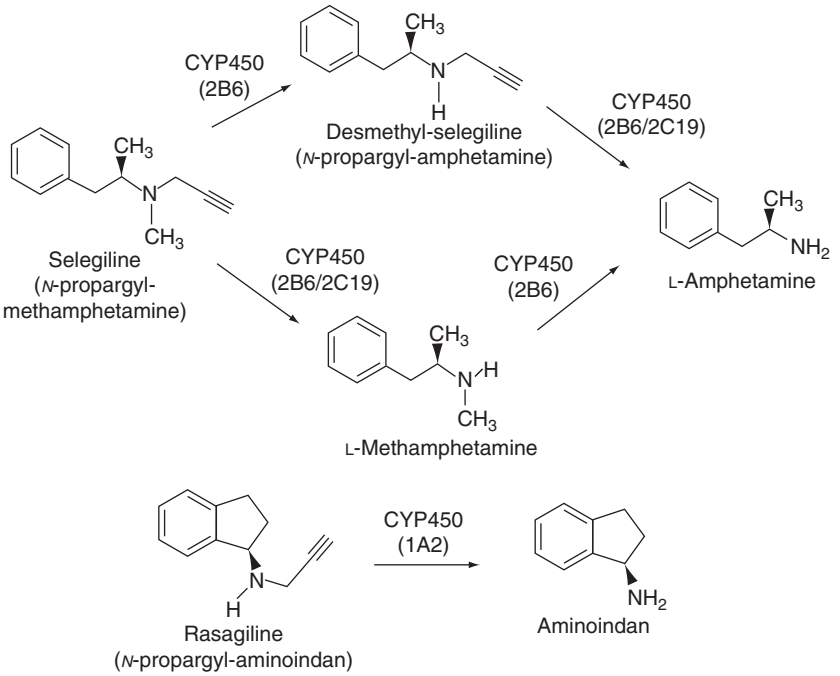

Figure 1 Molecular structure and metabolic pathways of rasagiline and selegiline.

Since the selegiline molecule can be absorbed transbuccally, selegiline is also formulated as an orally disintegrating tablet that dissolves in the mouth on contact with saliva. Subsequent transbuccal absorption minimizes first-pass hepatic metabolism and provides higher plasma concentrations of selegiline and lower levels of metabolites (DMS, *m*-amph, amph). In pharmacokinetic studies, about one-third of the dose of an oral disintegrating tablet was absorbed pregastrically within a minute, and selegiline plasma levels were approximately 5 fold higher than those achieved with the same dose of the conventional oral formulation.

Rasagiline

Rasagiline (*N*-propargyl-1(*R*)-aminoindan) is a nonamphetamine propargylamine and at doses of up to 1 mg once daily is a selective and irreversible MAO-B inhibitor. Results from in vitro and in vivo preclinical studies have demonstrated that rasagiline increases the release of dopamine in the striatum. Large, randomized, clinical studies have demonstrated that rasagiline is effective as monotherapy in patients with early PD and that earlier initiation of rasagline is associated with improved long-term outcomes compared with delayed therapy. As an adjunct to levodopa, rasagiline reduces off-time in patients experiencing motor fluctuations (e.g., wearing off).

In a clinical trial, patients initiated on rasagiline monotherapy early in PD had less functional decline than patients whose treatment was delayed for 6 months. Using a delayed-start onset design, the TVP-1012 in Early Monotherapy for Parkinson's Disease Outpatients (TEMPO) study indicated that rasagiline might furthermore have neuroprotective properties in addition to its symptomatic effects. In this study, patients treated with 1 mg rasagiline per day for 12 months showed less functional decline than subjects whose treatment with rasagiline was delayed for 6 months. This suggests that early initiation with rasagiline (even before the onset of functional impairment) is associated with better long-term outcomes.

For the management of patients with motor fluctuations, the efficacy of rasagiline appears similar to that of entacapone as demonstrated in the Lasting Effect in Adjunct Therapy with Rasagiline Given Once Daily (LARGO) study. Thus, when an adjunctive agent is required for managing motor fluctuations, rasagiline is considered as a first line agent. Rasagiline has an absolute bioavailability of 36% and its major metabolite is 1-R-aminoindan (**Figure 1**), which is devoid of amphetamine-like effects. Accordingly, clinical studies demonstrated good tolerability of rasagiline treatment and found no difference in the frequency of cardiovascular and psychiatric adverse events between rasagiline and placebo-treated patients.

Overall, the data associated with rasagiline for reducing 'off' time are of high quality. In addition to demonstrated efficacy in reducing 'off' time in patients experiencing motor fluctuations while receiving levodopa, rasagiline has demonstrated good tolerability in patients receiving numerous other adjunctive therapies (e.g., dopamine agonists, catechol–*O*–methyl–transferase (COMT) inhibitors): a common scenario in the real-world management of PD. The use of conventional selegline for reducing 'off' time is supported by less robust quality of data. However, the orally disintegrating selegiline tablet appears to offer a similar benefit in reducing 'off' time to that by rasagiline, albeit no direct comparative data are available.

Clinical Neuroprotection or Disease Modification

MAO-B inhibitors with a propargylamine molecular scaffolding, such as rasagiline and selegiline, have been investigated for neuroprotective (disease-modifying) properties. These agents exhibit several mechanisms that either protect neurons from toxic insults or attenuate neuronal degeneration. The published literature is abundant with data on the antioxidant and antiapoptotic properties of rasagiline and selegiline. Clinically, results of randomized, placebo-controlled studies in patients with early PD suggests that either agent may provide positive disease-modifying effects, in addition to symptomatic effects. However, due to disagreement regarding the validity of neuroprotection study methodologies, the medical and scientific community remains hesitant to confirm or refute the disease-modifying properties of MAO-B inhibitors.

The DATATOP clinical trial represents one of the earliest attempts to identify a neuroprotective benefit in PD. Untreated patients with early PD were randomized to receive treatment with either placebo, selegiline, vitamin E, or the combination selegiline and vitamin E. The primary outcome was the time it took patients to develop sufficient disability to require L-dopa. Individuals treated with selegiline reached this endpoint nearly 9 months later than individuals not treated with selegiline. Although initially lauded as a major breakthrough in PD therapeutics, it soon became clear that the effect of selegiline on progression was at least in part accounted for by a symptomatic benefit of selegiline. Several subsequent studies have also attempted to demonstrate the clinical neuroprotection-like effects associated with selegiline; but all have been confounded by methodological or interpretive issues. Thus, despite the availability of clinical data, the matter of whether selegiline confers neuroprotection remains unsettled.

The TEMPO (rasagiline mesylate TEMPO) study employed a delayed-start design to evaluate early treatment with rasagiline versus delayed treatment in an

attempt to elucidate a potential neuroprotective benefit over a 1-year period. Untreated patients with early PD were randomized to receive treatment with either placebo, rasagiline for 1 year, or placebo for 6 months and then rasagiline for the remaining months (delayed treatment group). The primary outcome was the change in the total Unified Parkinson Disease Rating Scale (UPDRS) score from baseline to 1 year. Individuals randomized to early treatment with rasagiline showed a statistically significant benefit at 1 year compared with those in the delayed treatment arm, albeit the effect was small (~2 points on the total UPDRS). Overall, the TEMPO study and its open-label follow-up demonstrate that early intervention in patients with PD can be associated with measurable benefits that endure for several years. Subsequently, the Attenuation of Disease Progression With Azilect Once Daily (ADAGIO) study was conducted. The ADAGIO 18-month study was a randomized, delayed-start, multicenter, double-blind, placebo-controlled, parallel-group study that prospectively examined the potential disease-modifying effects of rasagiline. The delayed-start protocol was based on recommendations and input from the FDA. More than 1100 patients with early and untreated PD were enrolled, making it one of the largest of its kind. Patients were randomized to early-start treatment (18 months of rasagiline 1 or 2 mg once daily) or delayed-start treatment (9 months placebo phase followed by 9 months rasagiline phase). The three primary analyses of the trial were based on the change in total UPDRS (baseline vs. end of study) as well as slope superiority of rasagiline over placebo in the placebo-controlled phase (i.e., if the rate of disease progression in the rasagiline-treated group is lower vs. the placebo-treated group) and noninferiority of early-start versus delayed-start slopes during weeks 48–72 of the active phase (i.e., if the rate of disease progression is at least similar once both groups are on active treatment). The rasagiline 1 mg group met all the three primary end points for statistical significance while the rasagiline 2 mg group did not satisf the predefined criteria for disease modification.

Utilizing a design that is somewhat similar to a delayed-start methodology, a follow-up of the controlled trial DATATOP, evaluated 310 patients (of the originally 800 enrolled) who did not reach the primary end point of disability requiring levodopa therapy. After a 2-month washout and while maintaining the blindness of the original treatment (selegline or placebo), the 310 patients were administered selegiline 5 mg twice daily and were monitored for up to 18 months. The primary end point was the need for levodopa. During this extended trial, there was no statistically significant difference in the time for levodopa initiation between the 189 patients who had been assigned originally to active selegiline and the 121 patients who delayed the start of selegiline. Thus, earlier treatment with selegiline did not lead to superior survival with respect to the end point of disability requiring levodopa. However, since this was an open-label extension, an important limitation of the between group comparison is that patients were not matched for the level of disability at the beginning of this open-label extension period. This contrasts with the rasagiline delayed-start studies in which patients were randomized a priori to the early- and delayed-start groups, thus minimizing the potential confounding effects of mismatches in functional level. It is also important to note that the main outcome measures of the delayed-start rasagiline studies (i.e., change in total UPDRS score and/or slope analyses) are different than that of the extended selegline study (i.e., time required for addition of levodopa).

Summary

Rasagiline and selegiline are irreversible inhibitors of MAO-B but differ substantially in molecular and pharmacologic characteristics. In spite of chemical differences between the two compounds current, evidence supports the use of either agent as symptomatic monotherapy in early stage PD and as adjunctive therapy for the management of motor fluctuations. Additionally, the fully published results of the ADAGIO study suggest that rasagiline. 1mg perday provides benefits that are consistent with a possible disease-modifying effect. However, given the negative findings for the 2mg dose, it cannot be definitively concluded that rasagiline has disease modifying effects.

See also: COMT Inhibitors in the Treatment of Parkinson's Disease; Dopaminergic Agonists in Parkinson's Disease; Neuroprotection in Movement Disorders; Parkinson's Disease: Definition, Diagnosis, and Management.

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Motor Evoked Potential

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Definition and History

The term 'motor evoked potential' (MEP) most commonly refers to the action potential elicited by noninvasive stimulation of the motor cortex through the scalp. MEPs were originally reported following electrical stimulation (high voltage: 1000/1500 V, and short duration: 50/100 μs, pulses) of the motor cortex, first introduced by Merton and Morton. Subsequently, magnetic stimuli (rapidly transient fields with variable flow direction and intensity up to 1.5/2.5 Tesla) were introduced by Barker and collaborators to evoke MEPs. The latter method, transcranial magnetic stimulation (TMS), is largely preferred since magnetic fields pass unattenuated through the skull and scalp, without nociceptive activation, and penetrate easily into the brain generating an electrical current that activates the neural tissue.

Origin of MEPs

In humans, MEPs can be recorded using surface electromyography from all skeletal muscles. They are characterized by a preferential contralateral distribution, short latency with proximo-distal progression, a variable amplitude (larger in distal muscles), and sensitivity to voluntary contraction. Such features support the notion that MEPs are mainly mediated by fast-conducting corticomotoneuronal connections projecting monosynaptically to the alpha-motoneurons in the contralateral spinal cord. It has been suggested that MEPs probably reflect the transynaptic activation of corticospinal neurons (including large pyramidal neurons and intracortical interneurons). Indeed, the recorded MEP is the sum of multiple descending volleys produced by a single high-intensity TMS pulse: a shorter latency direct D-wave (reflecting the *direct* excitation of the corticospinal axon) is followed by several later indirect I-waves (reflecting the *indirect* excitation of tangentially oriented axons in the deep cortical layers).

MEP Parameters

MEP recordings are largely used in clinical practice as well as in experimental research and several parameters can be considered. The threshold refers to the lowest intensity of the magnetic stimulus able to evoke a MEP of minimal size during either muscle relaxation or contraction. MEP threshold reflects the excitability of the corticospinal connections. The latency of the response, expressed in milliseconds, indicates the time taken by descending impulses to reach the target muscle. MEP latencies, therefore, vary as a function of the muscle distance (or subject height) and may be used to assess conduction along the central motor pathways (central motor conduction time, CMCT) by subtracting the peripheral conduction time. The peak-to-peak amplitude of the response is usually expressed as a percentage of the amplitude of the maximum response (direct M-wave) recorded in the same muscle on supramaximal electrical stimulation of the corresponding peripheral nerve. MEP size provides a measure of the portion of the spinal motoneurons discharged by TMS. This is clearly demonstrated by the observation that the MEP amplitude can be differently modulated by various motor tasks (reach, grasp, locomotion) and even by motor imagery and observation.

When TMS is delivered during a voluntary contraction of the target muscle, the MEP is followed by a pause of the ongoing electromyogram (EMG) activity lasting up to 200–300 ms. This period of inhibition is defined 'cortical silent period' and depends on GABA-mediated mechanisms controlling cortical excitability. Finally, when a focal coil is used for TMS, MEP recordings can be used for noninvasive and painless mapping of the somatotopic representation of muscles within the motor cortex. The cortical maps are constructed by stimulating different points on the scalp at a constant intensity and analyzing the number of sites from which MEPs can be elicited in the target muscle.

Applications of MEPs

Immediately after the introduction of the techniques of single-pulse TMS, it became evident that recording the MEP represented a reliable method to detect abnormalities of impulse propagation along the corticospinal tract. Afterwards, new techniques of paired-pulse or repetitive TMS have been progressively introduced to test the excitability of motor cortical areas. TMS, therefore, represents a noninvasive neurophysiological technique that allows studying both 'conductivity' and 'excitability' of the corticospinal system in man and may be regarded as an important new tool in clinical and experimental neurology.

Several abnormalities of standard MEP parameters can be documented in clinical studies. The MEP can be

absent, the onset-latency can be delayed, and the amplitude can be decreased together with a raised threshold. Different mechanisms may underlie such changes: failure of conduction due to damage to the corticospinal tract, dispersion of multiple descending volleys causing desynchronization of alpha-motoneurons discharges, depression of cortico-motoneuronal excitability, or intracortical conduction block. MEP recordings are currently used in routine clinical practice in order to document the functional impairment (even subclinical) of central motor conduction in various neurological conditions such as demyelinating syndromes, amyotrophic lateral sclerosis, myelopathies, stroke, and cerebrovascular disorders. On the other hand, central conduction is usually normal in neurodegenerative disorders not involving the corticospinal tracts.

Changes of the MEP size may reflect the efficiency of inhibitory systems within the human motor cortex. Using paired-pulse stimulation, it has been shown that the test MEP can be suppressed by subthreshold or suprathreshold conditioning stimuli delivered respectively a few milliseconds or 50–200 ms before (short- or long-interval intracortical inhibition – SICI or LICI). All these inhibitory phenomena are thought to depend on the activation of intracortical circuits, which are able to suppress the corticospinal output. The modulation of MEP amplitude by conditioning-test paradigms has been largely used to investigate motor cortical excitability in movement disorders (Parkinsonism, dystonia, chorea, dyskinesias).

See also: Basal Ganglia, Functional Organization; Blepharospasm; Botulinum Toxin; Dystonia; Multiple System Atrophy; Paired Pulse TMS; rTMS; Single Pulse TMS; Theta Burst TMS.

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Motor Fluctuations

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Glossary

COMT – An enzyme that catalyzes the degradation of catecholamines, including the neurotransmitters dopamine, epinephrine, and norepinephrine.
MAOI – The brain and liver enzyme that normally breaks down the catecholamines norepinephrine, serotonin, and dopamine.
Pharmacodynamics – The study of how drugs act at target sites of action in the body.
Pharmacokinetics – The study of the uptake, distribution, metabolism, biotransformation, and elimination of drugs by the body.

Definition and History

Motor fluctuations are defined as variations in motor ability or performance over time, typically measured in

minutes to hours. This problem was recognized shortly after oral levodopa (LD) was introduced for the treatment of Parkinson's disease (PD). In 1969, Barbeau described 'a marked variation in individual performance from day to day or within the same day. Occasional short-lasting refractory periods varying from a few minutes to 3 or 4 h will occur in patients who are otherwise perfectly controlled.' The problem of fluctuating motor ability is not a small one. In a review of the literature from 1966 to 2000, Ahlskog and Muenter determined that by the 4–6 year of LD therapy, ~40% of patients will have developed motor fluctuations. Risk factors for developing fluctuations include younger age at disease onset, longer disease duration, greater disease severity, longer time of treatment, and higher LD intake.

Pharmacological Basis of Motor Fluctuations

Although subtle motor fluctuations may occur with other antiparkinsonian medications such as dopamine agonists, the vast majority of fluctuations are related to LD. The most important pharmacokinetic property of LD is its short plasma half-life of ~90 min. It follows that the dopamine produced from this short-lived precursor is also available relatively briefly. Coupled with progressive loss of functional dopaminergic nerve terminals in the striatum, it is not surprising that the response to single doses of LD in advanced PD as demonstrated in F^{18} fluorodopa PET studies is equally short. Furthermore, in the setting of the dopaminergically denervated striatum in PD, the relative rise and fall of dopamine concentrations are much larger than in the normal striatum.

The short plasma half-life of LD and the dependence of striatal dopamine synthesis on external LD in PD mean that alterations in absorption, metabolism, and distribution to brain of LD will translate into clinical effects. To understand how this impacts on PD patients, one must be familiar with the concept of the 'short duration effect.' This is the short-duration antiparkisonian response that approximates the plasma LD concentration and by extension, the striatal synaptic levels of dopamine. Most recognize that it is this phenomenon that underlies motor fluctuations and in the more severely affected, the ON–OFF cycle.

LD is absorbed through the small bowel, and thus, any interference with the delivery of drug to the intestinal region will also delay the rise in plasma levels of drug and, therefore, the production of dopamine by the brain. At the level of the brain, LD entry is limited by the capacity of an amino acid transporter that is responsible for moving several dietary-derived amino acids into the brain. Competition with LD here can also reduce dopamine production overall. These latter-described factors can be best thought of as contributors to the unpredictability of fluctuations, but they are important to recognize, because they are also more amenable to treatment.

Evolution of Motor Fluctuations

It is clear that at the beginning of treatment, patients are often unaware of their variable motor performance despite being detectable with careful observation. At some point, however, patients will notice that their medication effect wanes as the hours pass, and the etiology of this evolving awareness of motor fluctuations is the subject of some debate. One attractive view because of its simplicity is that an earlier finishing of the short-duration response due to disease progression leads to motor fluctuations. Another hypothesis is that the shortening of the response is not the largest factor, but that the alteration in the magnitude of the response (difference between OFF and ON motor function) is the most important etiologic factor. More specifically, the absolute magnitude of the short-duration response increases, because the trough or worst motor function related to disease severity becomes deeper over time and additionally because the peak response may increase with ongoing LD treatment. These two causal theories about the evolution of motor fluctuations suggest two treatment approaches, which can be complementary.

The first approach is perhaps more intuitive and widely applied with the aim of using pharmacokinetic manipulation to prolong the action of each dose of LD. This is achieved by either lengthening the absorption time with controlled release preparations or inhibiting the loss of LD outside the CNS by inhibiting aromatic amino acid decarboxylase (i.e., carbidopa, benserazide) and catechol-*O*-methyltransferase, as well as augmenting the effects of centrally produced dopamine with dopamine agonists or monoamine oxidase inhibitors. More directly, attempting to continuously administer drug to the brain via duodenal LD infusions or a subcutaneous/transcutaneous application of dopamine agonists will also reduce motor fluctuations. A second approach utilizes pharmacodynamic principles in attempting to lessen the amplitude of motor disability and is discussed later.

Clinical Phenomenology and Types of Motor Fluctuations

In their extreme, fluctuations can be one of the most dramatic phenomena witnessed in clinical medicine. A PD patient may be profoundly immobile or frozen, slumped in a wheel chair, even unable to control drooling. After a dose of dopaminergic medication, the patient may suddenly find it easy to rise, walk independently, and perform normal activities. When this dramatic, the mobile phase is often accompanied by dyskinesia or excessive unwanted movements of the body that most often appear

choreiform or jerky. After minutes to hours, the effect wanes and the patient returns to the wheelchair-bound state. These transitions between parkinsonism, (often referred to as the OFF state), and the more mobile or active ON state may occur over seconds, making them all the more striking in appearance. It has been likened to turning a light switch on and off; hence, the descriptive term 'ON-OFF' phenomenon has gained widespread use. Although most motor fluctuations are not this dramatic, patients with fluctuations are aware of, and observers can perceive, clear variations in motor ability. Often, the less severe motor fluctuations are seen as the 'wearing off' of the effects of a dose of medication or 'end of dose' effect. While motor fluctuations are often associated with dyskinesia, this association is not absolute.

Other types of motor fluctuations have been recognized. Delayed onset of responses to single (especially first morning) doses of LD was detailed by Melamed over 20 years ago and has become known as the 'delayed ON.' The complete failure of a drug dose to reverse parkinsonism has been termed 'no ON' or dose failure. Other types of motor fluctuations have been described in PD, including the 'sleep benefit' or diurnal fluctuation, and the more rarely observed paradoxical kinesia. This refers to the unexpected motor improvement that comes with extraordinary situations such as being able to easily mobilize in a dangerous setting.

Nonmotor fluctuations have been described and may or may not coincide with motor fluctuations. Nonmotor symptoms may be cognitive/psychiatric, visceral, or dysautonomic in nature and could involve pain or fatigue. For some patients, these nonmotor fluctuations can be more disruptive than motor fluctuations. It is worth exploring for coincidental timing of motor and nonmotor fluctuations, because if they do occur together, there is a good chance that both will be improved using strategies to smooth motor fluctuations. There is much less understanding of how to improve nonmotor fluctuations that do not respond to dopaminergic manipulation.

Diagnosis

It is critical for clinicians to recognize motor fluctuations, because not addressing this problem will inevitably lead to undertreatment of the patient and dissatisfaction. One way to probe the patient for the appearance of fluctuations is to ask whether he or she experiences changes in stiffness, slowness, walking, or tremor lasting minutes to hours. Another good question to ask is what the effects are of missing one or two doses of LD. During the beneficial period of a fluctuation, PD symptoms will be lessened; patients may report that shuffling is much better; they feel more fluid in their movements; or their movements are faster overall. Tremor can respond in this fashion as well, although it may not respond as consistently as rigidity or bradykinesia. The transition from OFF to ON can be gradual and hardly perceptible in the early stages of the disease and treatment. In this early period, fluctuations also tend to be more predictable. For example, a patient may report his/her symptoms worsening only if he/she missed a dose of medication several hours earlier. As months to years pass, the gradual nature of the transitions becomes steeper or abrupt, and to the patient, it appears that ON-time shortens. In other words, during early disease, a dose of medicine causes long-lasting benefit, but in advanced stages, the dose benefit can last as short as an hour or two. Accompanying these changes in the rate of a fluctuation comes the deepening of the 'trough' or the extent of parkinsonian symptoms while in the OFF state. For example, an early fluctuator may notice that walking slows mildly or tremor returns if one or sometimes, even several doses in a row are missed. The advanced fluctuator described earlier can suffer a profound loss of movement ability within moments of drug levels dropping below a critical threshold. In addition, during advancing stages, the duration of fluctuations can become more unpredictable, and this feature can be quite bothersome to daily life.

Although the diagnosis of motor fluctuations can usually be made with careful questioning of the patient, at times, the picture is unclear and some clinicians then prefer to examine the patient after a dose of medication is withheld for hours or even overnight and compare it with an examination an hour or so after medication is taken. On the other hand, frequent dosing with LD as well as other drugs can make the picture very confused; putting the patient on 3-h dosing may make the pattern clear.

Management of Motor Fluctuations

Treatment goals for motor fluctuations need to be realistic. The principles most likely to lead to improvements begin with transforming unpredictable fluctuations into predictable ones (so that interventions will in turn predictably succeed). The next goal is to try and make an ON-cycle as long as possible. However, it is impossible to lengthen ON-cycles and diminish troughs enough to abolish fluctuations in most cases, because inevitably, it leads to the escalation of antiparkinsonian medication usage and severe dyskinesia, psychiatric adverse events, or other toxicity.

Treatment options range from changing dietary intake to altering the pattern of medication use or using additional medications to improve ON time and/or reduce dyskinesia (as dyskinesia can be provoked by strategies that improve ON time). Currently, surgical options are mostly used for medically refractory fluctuations.

Improving Systemic Absorption of LD

Making motor responses more predictable can be achieved by altering the absorption of LD. For example, speeding up absorption by adding in or switching to regular release LD (versus the controlled release formula), suspending LD in liquid, and making doses large enough to attain therapeutic thresholds all can increase consistent results. In fact, a complicated fluctuating pattern of response can be converted into a stable, predictable wearing off pattern by giving adequate doses at 3 or 4 h intervals. Then, the wearing off pattern is much more rationally approached with methods to prolong or overlap ON time.

It has been demonstrated that dietary protein intake can reduce the effectiveness of LD because of competition with other amino acids at the large neutral amino acid transporter site in the gut and at the blood brain barrier. This effect is not important for other classes of PD medication. As patients become more advanced in their condition and especially if their fluctuations are brittle in nature, a meal with even modest amounts of protein can cause dose failures. If the patient adopts a low protein meal strategy or is able to time medication intake such that LD is taken on an empty upper GI tract, he or she may have more reliable responses and fluctuate less. This can take a toll on the patient who is taking medication very frequently, as it may be hard to find a window where protein delivery will not come close to dose times. Nevertheless, many more PD patients will find this to be an inexpensive change that makes a noticeable difference.

A poor absorption of the drug through the small intestine can obviously worsen fluctuations. Methods of improving this absorption include crushing the drug and consuming it in the form of a suspension with or without acidification, that is, ascorbic acid. Iron supplements must be administered at alternate times, as iron will bind to and, thus, contain LD in the GI tract, decreasing drug absorption and reducing benefit.

Improving Constancy of Dopaminergic Stimulation

It is generally thought that a smoother delivery of medication is beneficial to reducing fluctuations and dyskinesia. This concept has become codified as 'continuous dopaminergic stimulation' with the aim of constantly delivering medication to the striatum and avoiding troughs of medication and, thereby, periods of reduced dopaminergic stimulation. This constancy of stimulation is believed to reduce the sensitization that underlies both motor fluctuations and dyskinesia. A continuous delivery of LD or apomorphine will reduce 'OFF' time, but as this benefit occurs immediately, it is likely that this is achieved through pharmacokinetic means, by maintaining drug delivery above a threshold level throughout the day. It is important to note that patients will sometimes turn OFF despite having adequate plasma levels of LD or apomorphine, indicating that the constant delivery of drug to the systemic circulation is not the only factor determining if a patient is ON or OFF. The effects of continuous dopaminergic stimulation on dyskinesia is less clear. It is important to note that no controlled trials have demonstrated the efficacy of continuous dopaminergic stimulation over months.

Despite these reservations, in practical terms, most patients will benefit from trying to simulate a more constant drug level in the brain. This is not very important in early disease, as patients will begin medications two or three times a day initially and perceive no troughs. Over time, the troughs appear as a given dose wanes in effect. Patients will then alter medication intake to bridge the OFF periods. It is not unusual for some patients to require taking doses every few hours. The complexity arises in the number of strategies that is available to choose from to achieve the steady benefit.

The most obvious method is to decrease the interval between drug doses. For example, if a patient finds that the motor worsening occurs often an hour before the next dose is due, the natural remedy is to take subsequent doses an hour earlier than before. The disadvantage of this strategy is that more doses in a day translate into more inconvenience and chances of forgetting a dose.

This early wearing off phenomenon is well recognized with LD use, and the advent of dopamine agonists was heralded by the observation that the experience of wearing off was muted and delayed in those who began agonist therapy in favor of LD. Examples of dopamine agonists include pramipexole, ropinerole, rotigotine (24 h-transdermal patch), lisuride, and apomorphine. Pergolide and bromocriptine are not often used anymore due to the concerning risk of cardiac valvulopathy and other possible connective tissue abnormalities. All of these agonists with the exception of apomorphine are united in their relatively long half-life. For example, the LD $T_{1/2}$ is 45–90 min, whereas the plasma half-life of pramipexole is 8 h. Although the duration of benefit is not explained fully by pharmacokinetics alone, it is likely that the longer persistence of the agonist benefit is at least partly associated with its more durable half-life. Thus, it is not an uncommon strategy for patients to begin a dopamine agonist as monotherapy in the earliest stages of disease requiring symptomtic treatment. In a Cochrane review of dopamine agonists, the authors determined that the odds ratio of developing motor fluctuations was 0.75 (95% CI 0.63–0.9, $p = 0.002$) compared with LD-treated early PD subjects. On the other hand, the results of the PDRG-UK study published in 2008 indicated that initial treatment with an agonist may delay the onset of motor complications, but over time, the benefit is not sustained and may be at the expense of therapeutic benefit. Still, other investigators have explored the ability

of dopamine agonists not only to delay the onset of fluctuations but also to reduce them once fluctuations have become established. Some studies have shown that continuous infusions of lisuride or apomorphine with or without low dose LD supplementation can reduce fluctuations and dyskinesia, although blinded studies are lacking. Adverse skin reactions can be expected in a substantial minority of patients using a subcutaneous administration system.

Another promising effort to achieve more continuous dopaminergic stimulation is to deliver LD in novel ways. The controlled release preparation of carbidopa/LD was introduced with the hope that it would smooth motor fluctuations. Studies showed that initial use of the controlled release preparation (versus the regular release formulation) was equally or more effective in delaying the onset of fluctuations. In established fluctuators, however, the results have been mixed. More recently, continuous duodenal or jejunal infusions, which create more steady plasma drug levels, have been reported to reduce OFF time significantly and to possibly reduce dyskinesias, although device problems were not uncommon. Other formulations, including prodrug transdermal species and more reliable controlled release preparations of LD, are also in development.

Catechol-*O*-methyltransferase inhibitors (COMTI) have become established adjunct therapies to prolong the LD effect. This class of medication works by inhibiting the loss of LD peripherally by conversion to an inert compound 3-*O*-methyldopa (3-OMD), thus, allowing more LD to enter the brain. Two inhibitors are available commercially: entacapone and tolcapone. The former is a peripheral inhibitor of COMT; the latter is able to penetrate the CNS and may also inhibit the O-methylation of dopamine, and thus, may, extend its effect. With tolcapone, individuals can rarely develop transaminase elevation and liver failure; therefore, periodic monitoring of liver enzymes is recommended, especially during the initial months of use. Generally, side effects necessitating the discontinuation of COMTI are unusual, but may include diarrhea or a harmless alteration in urine color. More frequently, adverse effects as a result of too much dopaminergic stimulation may occur; thus, it is not unusual to concomitantly reduce the LD dose. A Cochrane review of COMTI concluded that entacapone increased clinically meaningful ON time by $1\,\mathrm{h\,day^{-1}}$, while tolcapone results were approximately twice of that. With repeated doses throughout the day, the peak levels of LD can also rise and result in the problems of excessive dopamine effect if not compensated for by LD dose reductions.

Monoamine oxidase type B (MAO-B) inhibitors, including selegiline and rasagiline, have been investigated for their ability not only to provide benefit against PD symptoms but also to reduce motor fluctuations. The initial hope for MAO-B inhibition was to serve as a neuroprotectant; however, this effect has still not yet been definitively proved, and these medications are currently not FDA approved for this indication. On the other hand, the inhibition of MAO-B has proved beneficial against motor fluctuations, while providing some relief from parkinsonian symptoms.

There are important limitations to these approaches, which cannot be ignored. Not surprisingly, these strategies can be associated with more dopaminergic adverse events such as worsened dyskinesia, orthostasis, sleep disruption, and psychiatric toxicity. Around-the-clock administration of dopaminergic drugs is generally avoided to reduce psychiatric complications, although it has been used successfully in a few patients. Another interesting consideration is that even with continuous administration of drugs like LD or apomorphine, there is NOT complete amelioration of OFF states, even when plasma levels of LD or apomorphine are in the therapeutic range. In addition, there is the question of tolerance developing to continuous dopaminergic stimulation. While the evidence for tolerance to LD is not persuasive in PD subjects, in humans, there is certainly other evidence of tolerance to drugs that alter dopamine levels, for example, cocaine, and also animal evidence of tolerance to long-acting dopamine D-1 agonists. Therefore, to avoid any possibility of developing tolerance to continuous dopaminergic stimulation, it may be beneficial to restrict it to the daytime and if possible, establish a drug-free interval overnight.

While the wide variety of medications to sustain dopaminergic stimulation has been clearly helpful (especially in reducing OFF time), more continuous drug delivery has not eliminated the problem, underscoring the idea that pharmacokinetics alone cannot explain motor fluctuations. A second, more pharmacodynamic approach toward the treatment of motor fluctuations is to improve the trough or OFF motor function.

An interesting phenomenon called the 'long-duration response' (LDR) to LD has been discovered, and in contradistinction to the short-duration response, which in broad terms parallels the plasma level of drug, the LDR builds up over weeks and likewise dissipates slowly. The LDR improves trough function and may partially account for why motor fluctuations are not appreciated early in LD therapy.

Methods to augment the LDR would likely diminish motor fluctuations. Unfortunately, since the underlying mechanisms for the LDR are poorly understood, there have been only few strategies or therapies to address it. Deep brain stimulation (DBS) of the globus pallidus (GP) or the subthalamic nucleus (STN) has been the most important advance that appears to reduce motor fluctuations by augmenting the LDR, or in other words, by improving trough function. In most cases, surgery will reduce the magnitude of fluctuations, and hence, they may be less clinically apparent, keeping in mind that most patients will still require medication for the optimal functioning.

The benefit seen with DBS is due to the reduction of the depth of the OFF symptomatology, or in other words, the shallowing of the troughs. DBS does not increase the peak or ON-benefit of LD, or increase the duration of benefit. In this setting, STN stimulation with its prokinetic effect often results in a reduced medication use and subsequently in less dyskinesia. With GP stimulation, there is a direct antidyskinetic effect in addition to the reduction in motor fluctuations; this effect is less dependent on the reduction in medication intake.

Other means to improve trough motor function remain experimental and utilize neural grafting, neurotrophic factors, and gene therapy.

Conclusion

The problem of motor fluctuations is extremely common in PD treatment. It is critical that the medical provider is aware of and alerted to the appearance of this evolving motor variability, as treatment options are numerous and usually successfully lead to improved patient outcomes and satisfaction. In general, using pharmacokinetic and pharmacodynamic principles, one can try to achieve a smoother overlap of therapeutic cycles to maximize ON time and minimize OFF time by altering LD absorption through the gut and into the brain, retarding the breakdown of synthesized dopamine and by use of other classes of dopaminergic medications or surgery. The advancing fluctuator presents a treatment challenge however, and options become more complex to employ due to the ceiling limitations of dyskinesia and psychiatric and other adverse effects, coupled with the increasing disability associated with deepening OFF periods. Surgery is applicable for some PD patients who have reached the limits of medical optimization.

See also: Deep Brain stimulation; Dopamine; Dyskinesias; Levodopa.

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Motor Impersistence

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Glossary

Anosagnosia – Unawareness of the presence of disease or deficit.
Apraxia – Inability or impaired ability to plan and execute motor acts in the absence of muscle or sensory impairment.
Hemiplegia – Paralysis affecting one side of the body.
Motor impersistence – Inability to sustain a voluntary motor act despite the ability to perform the act briefly.

Definition and History

Coined by Fisher, motor impersistence describes an inability to sustain voluntary motor acts (i.e., eyelid closure or tongue protrusion) despite the ability to briefly perform the act. In his observation of hemiplegic patients, Fisher described an inability to (a) take a deep breath, hold one's breath, or say 'ah' for a prolonged period; (b) exert steady pressure during hand grip; (c) keep the eyes fixed centrally during visual fields testing; (d) hold the eyelids shut; and (e) hold the mouth open or tongue protruded. He also described other gaze disturbances, including conjugate deviation to the side of the lesion, gaze restriction to the hemiplegic side, and inability to maintain steady conjugate gaze.

Fisher viewed impersistence as being akin to the limb kinetic form of apraxia, while others have speculated that symptoms of impersistence reflect a reversion to primitive drives (i.e., maintenance of vigilance and a defensive posture). Joynt and colleagues suggested that motor impersistence represents the oscillation of function typically seen following cerebral damage.

Pathogenesis/Pathophysiology

Available evidence suggests that right hemisphere dysfunction is crucial. In reviewing ten cases with right hemisphere damage, Fisher noted motor impersistence in all, and although four of the ten studied had prior left hemisphere or bihemispheric injury, he suggested that this past damage did not meaningfully affect the syndrome's expression. He viewed cortical injury as vital with variable expression reflecting lesion location.

In 16 patients (15 with right hemisphere lesions and one with bilateral lesions), Berlin found signs of impersistence in all. In 14, right parietal structures were involved. He did not observe impersistence in patients with right hemiplegia.

Kertesz and colleagues compared the performance of 45 acute stroke patients (31 right and 14 left hemisphere, matched for lesion size) and 17 control subjects on 11 tasks assessing motor impersistence. They found that right hemisphere lesions showed significantly more impersistence and suggested an essential role for frontal and central structures.

Although impersistence occurred more often in patients with bilateral or right hemisphere lesions in Joynt's sample, the authors cautioned that evidence did not strongly support localization to the right hemisphere, in contrast to prior opinion.

Contrasting with other authors, Garfield found that pathological impersistence was more common in children with right (75%)-versus-left hemiplegia (20%), although the difference was not statistically significant.

Epidemiology/Risk Factors

As motor impersistence is a symptom not a diagnosis, the underlying disorder defines the epidemiology and risk factors. Many cases reported in the literature result from hemispheric vascular insults. Therefore, factors associated with enhanced stroke risk (i.e., hypertension, dyslipidemia, etc.) need to be considered. Family history modulates risk in Huntington's disease, while antecedent streptococcal infection is important in Sydenham's chorea.

Joynt and colleagues examined impersistence in a sample of 101 patients with hemispheric dysfunction and 74 control subjects. 'Pathological' impersistence (defined performance worse than 97% of controls) was observed in 23% of patients.

In Garfield's sample, when children with hemispheric lesions were compared with a larger normative sample for impersistence, 68% met criteria (as against 3% of uninjured children).

Clinical Features and Diagnostic Criteria

In his sample, Fisher noted an inability to keep the eyelids closed and the tongue protruded as being most central. Left hemiplegics with impersistence were said to show more significant cognitive dysfunction with memory impairment, confusion, and anosagnosia observed in most. In Joynt's sample, motor impersistence was related to mental impairment and a trend was apparent between marked motor impersistence (performance worse than all controls) and advancing age.

Berlin reported an impersistence triad (i.e., an inability to maintain the mouth open, the tongue protruded, and the eyelids closed), but unlike Fisher, orientation and memory were preserved.

Kertesz reported that an inability to maintain the mouth open, tongue protruded, eyelids closed, and gaze fixed right best discriminated right from left hemisphere lesions. A correlation was noted between impersistence and performance on spatial tasks (all patients) and on a measure of apraxia (right hemisphere lesions only).

In Garfield's pediatric sample, there was no apparent relationship between impersistence and age, sex, or IQ.

Differential Diagnosis

In addition to hemispheric injury, motor impersistence is commonly associated with hyperkinetic movement disorders such as Huntington's disease and Sydenham's chorea.

Diagnostic Work-up/Tests

The imaging of the brain is central to the evaluation of motor impersistence to examine hemispheric anatomy and evaluate the integrity of the basal ganglia. Specific testing for Huntington's disease examines CAG repeat number ($\geq$37 CAG repeats) in the huntingtin gene. Immune markers can suggest prior streptococcal infection (i.e., antistreptolysin O titers) in Sydenham's chorea.

Management

The nature of motor impersistence is such that treatment is not usually warranted. This is good, since efforts to treat the dyskinesia have met with limited success. Dopamine receptor antagonists may diminish the frequency and severity with atypical agents being most often prescribed.

Prognosis

Impersistence has been observed acutely but also years after the initial insult. DeRenzi and colleagues studied the incidence of eyelid movement disorders in a large sample of acute stroke patients on ten impersistence tasks. In some cases, the left eye was the only affected, and impersistence persisted 3 months post-stroke in 26% of right hemisphere strokes.

In his sample, Berlin found that with clinical improvement, impersistence of eye closure was often modified; first, the eye on the hemiplegic side (usually the left) would open before the second eye, and the left eye would open only later, and finally both eyes would remain closed for 30 s or more.

When noted in hyperkinetic movement disorders, prognosis is defined by the primary diagnosis. In Huntington's disease, improvement is doubtful, while for Sydenham's chorea resolution is the rule.

See also: Akathisia; Chorea; Chorea Gravidarum; Choreiform Disorders; Milkmaid's Grip; Sydenham's Chorea.

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Motor Output Variability

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Glossary

Force variability – The involuntary inconsistency in the force output.
Motor-output variability – The involuntary inconsistency in the output of voluntary muscle contractions.
Noise – Motor-output variability is assumed to be noise superimposed on the motor command at any level of the nervous system (e.g., synaptic noise).
Trial-to-trial variability – The involuntary variability of a motor-output characteristic (e.g., peak force or time to peak force endpoint variability) among different trials.
Within-trial variability – The involuntary inconsistency in the output within a trial (e.g., trajectory variability).

Definition and History

Motor-output variability refers to the involuntary inconsistency in the output of voluntary muscle contractions. The variability in the motor output can be observed within a trial (e.g., trajectory variability) and from trial to trial (e.g., end-point variability). Initial studies on

motor-output variability were performed by Fullerton and Cattell (1892).

It is generally accepted that within-trial and trial-to-trial variability increases with force level; however, most studies suggest that this increase in variability is not proportional to the level of force. In addition to force, the amplitude of motor-output variability is influenced by numerous other factors including the input–output properties of the motor neurons, the muscle group performing the task, the type of contraction performed, and the age of the individual. For example, acute elevations of physiological arousal can increase the gain of input–output relations of the motor neurons and increase the variability in force exhibited by the same individual attempting to maintain a constant force. Similarly, lower limb muscles display greater trial-to-trial variability compared with the upper limb muscles and eccentric contractions exhibit greater within- and between-trial variability compared with isometric and concentric contractions. Finally, a number of studies have focused on the effects of age on motor-output variability. It is generally accepted that the within-trial variability is greater for older adults compared with young adults, especially, for intensity levels lower than 20% of maximum. These age-associated impairments appear to be even greater for trial-to-trial variability. Interestingly, older adults appear to exhibit greater variability in the temporal characteristics of movement (time-to-peak force, impulse duration) than force.

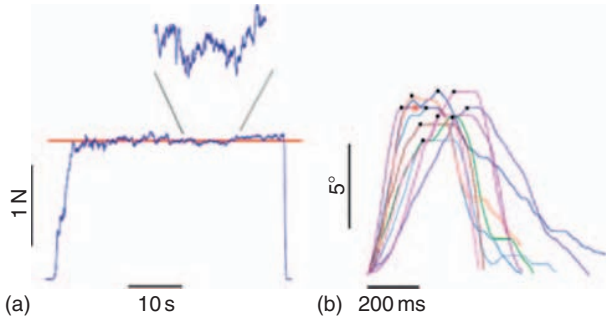

Figure 1 Within-trial and trial-to-trial motor-output variability. The recording on the left (a) demonstrates the involuntary variability in the force output despite the efforts of a young adult to exert a constant isometric contraction with no variations. This variability is dominated by low-frequency oscillations (inset). The recording to the right (b) demonstrates the trial-to-trial variability during goal-directed movements exerted by a young adult. It is evident from the 10 trials graphed that variability exists across trials for both the spatial and time components of movement.

Theoretically, motor-output variability is assumed to be noise superimposed on the motor command at any level of the nervous system. The neural activation of muscle appears to interact with the noisy motor command in the following three ways: first, increased variability in motor unit discharge, which has been shown to be related with synaptic noise, appears to be a major contributor to force variability during constant isometric contractions. Second, changes in the rhythmical discharge of motor units, which has been attributed to oscillatory input from higher centers, can influence the variability of motor performance. Third, increasing coactivation of the antagonist muscles can reduce trajectory variability possibly by minimizing the influence of noise to the antagonist muscles via joint stiffness and damping. Nonetheless, further research is needed to understand the neural mechanisms that contribute to within-trial and trial-to-trial motor-output variability.

Independent of the exact causal mechanisms, the functional significance of motor-output variability is that it can impair the ability of humans to perform accurate movements. Recent findings provide evidence that during aiming isometric contractions, older subjects who exhibit greater trajectory (within-trial) and end-point (trial-to-trial) variability exhibit impaired accuracy in force and time. Therefore, these findings demonstrate that both forms of motor-output variability are strongly associated with functional performance in humans (see **Figures 1** and **2**).

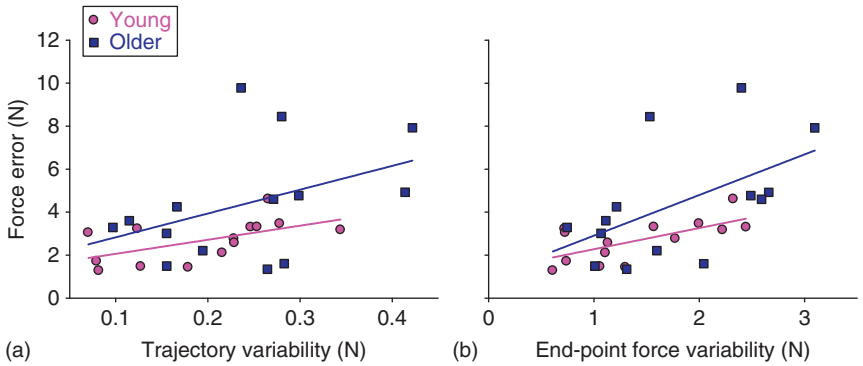

Figure 2 Functional significance of motor-output variability. The variability in the force trajectory (left; within-trial variability) and end-point (right; trial-to-trial variability) is associated with the end-point accuracy of force. In this example, subjects that exerted smoother force trajectories (left) and lower peak force variability (right) exhibited greater end-point accuracy in force. In addition, this example demonstrates the age-associated increases in motor-output variability and the associated impairment in end-point accuracy.

See also: Motor Impersistence; Motor Unit; Motor Unit Synchronization; Movement Time.

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Motor Unit

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Glossary

α-Motor neurons – Neurons that innervate extrafusal muscle fibers of skeletal muscles to directly control their contraction. Also known as lower motor neurons; they are grouped in nuclei in the anterior horn of the spinal cord or in brainstem nuclei.
Innervation ratio – The number of muscle fibers innervated by a single motor neuron.
Motor unit – A single α-motor neuron together with all the muscle fibers it innervates.
Neuromuscular junction – The synaptic linkage between the axon terminal of a motor neuron and the excitable region (end plate) of the innervated muscle fiber.
Tetanic contraction – A condition of continuous contraction in a skeletal muscle caused by a steady high rate of firing of motor units.

Definition and History

In mammals, each skeletal muscle fiber is innervated by only one motor neuron. An individual motor axon, however, branches to innervate several muscle fibers. Sir Charles Sherrington (1857–1952) was the first to recognize that a single motor neuron and the colony of muscle fibers which it innervates constitute the basic unit of contraction, and in 1925 he coined the term *motor unit* to describe it (**Figure 1**). By definition, all the muscle fibers belonging to a single motor unit contract together. These fibers are always within the same muscle but are generally distributed over a relatively wide area within the muscle to ensure a uniform contraction. Such organization also decreases the probability that damage to one or a few motor neurons will significantly alter the action of a muscle.

The transmission mechanisms in the neuromuscular junction are very similar to those at central synapses. Upon the arrival of an action potential at the axon terminal, voltage-dependent calcium channels open and Ca^{2+} ions flow into the terminal. The influx of Ca^{2+} triggers the exocytosis of neurotransmitter called acetylcholine (Ach) into the synaptic cleft. The Ach then diffuses across the neuromuscular junction to bind at nicotinic receptor sites located on the end plate. These receptors are ligand-gated ion channels so when bound by Ach they open, allowing sodium and potassium ions to flow in and out. This results in a local depolarization of the end plate, which then spreads across the surface of the muscle fiber to trigger muscle contraction. The action of Ach is terminated by the enzyme acetylcholinesterase which hydrolizes the neurotransmitter.

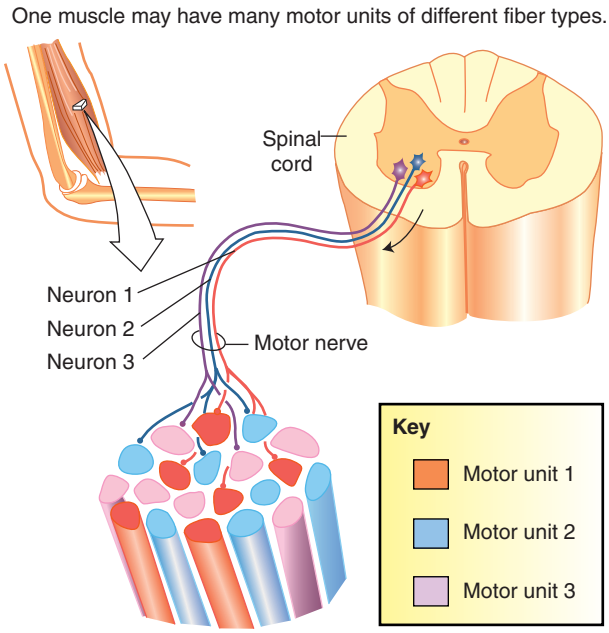

Figure 1 Diagram illustrating the motor unit components.

Innervation Ratio

The number of muscle fibers innervated by a single motor neuron varies across motor unit types and muscles. The variation in innervation ratio is the most significant factor that contributes to differences in motor unit force. A low innervation ratio allows for finer grading of the muscle total force by the nervous system. Thus, muscles used for fine motor control have low innervation ratios (e.g., 5:1 for the lateral rectus muscle of the eye). In these muscles, activation of one motor unit elicits a relatively small response because only a few fibers contract. On the other hand, muscles used for gross motor actions, such as standing or walking, have high innervation ratios (e.g., 2000:1 for the gastrocnemius muscle in the leg).

Types of Motor Units

During embryological development, each motor neuron secretes a growth factor which aids the differentiation of all muscle fibers in their motor unit so that they develop into the same fiber type. Thus, motor units can be categorized according to the physiological and biochemical properties of their muscle fibers. There are three types of motor units: *Slow fatigue-resistant* motor units consist of comparatively small muscle fibers (type I) that contract slowly and generate relatively small forces. These fibers are red due to rich blood supply and myoglobin content. With plentiful mitochondria, they rely exclusively on oxidative metabolism and are highly resistant to fatigue. Slow motor units are important for activities that require sustained muscle contraction, such as the maintenance of upright posture. *Fast fatigable* motor units, on the other hand, consist of larger fibers (type IIb) that contract rapidly and generate the greatest force. Their force is 10–100 fold greater than the force of type I fibers. These fibers are pale due to limited blood supply and have sparse mitochondria. They rely on anaerobic glycolysis and are therefore easily fatigued. Fast fatigable motor units are especially important for brief exertions that require great forces, such as jumping. The third type of motor unit is the *fast fatigue-resistant* that has physiological properties that lie between those of the other two. In this motor unit, the fibers (type IIa) are of intermediate size and are only slightly slower than type IIb fibers. However, because they have more mitochondria and better blood supply, they have greater capacity for oxidative metabolism and are more resistant to fatigue. These fibers can generate about twice as much force as the type I fibers.

All three types of motor units can be found in most muscles, but in different proportions that are appropriate for different muscle functions. For example, slow motor units are prevalent in muscles that participate in motor acts that require sustained effort, such as the soleus muscle that is important for posture.

Regulation of Muscle Force

Although each motor unit in a skeletal muscle contracts in an all-or-none fashion, the nervous system can regulate the contraction force of a muscle. The force produced by a single muscle can be regulated in two ways. The first is *orderly recruitment*. The force of muscle contraction can be increased by recruiting additional motor units. However, the motor units within a muscle are not activated in a random manner. As a general rule, motor units are recruited in the order of their size. When muscle is initially activated, small motor units are the first to be recruited since they require the lowest threshold for activation. When more force is needed, the synaptic input increases in strength to progressively recruit lager motor units. The sequential recruitment of larger motor units results in a smooth increase in muscle force. This principle, known as the *size principle*, is functionally important as it simplifies the task of modulating muscle force by the nervous system. Instead of selecting specific combinations of motor units to produce the needed amount of force, higher brain centers only need to determine the strength of synaptic drive to be delivered to the motor neuron pool as a whole.

The second mechanism for force regulation is *rate coding*. The rate at which motor neurons discharge action potential has a pronounced influence on the force that the motor unit exerts. The contraction and relaxation time for a muscle twitch is much longer than that of an action

potential. Thus, an increase in the frequency of firing allows the forces of successive twitches to summate. This effect is typically characterized by a sigmoidal association between firing frequency and force. For a motor unit, the force–frequency relationship depends on the time course of its twitch response and the quantity of contractile proteins.

In a given motor unit, firing rates stay within a relatively narrow range (about 6–30 Hz). The force that a single motor unit can exert will vary by ~3–15 times when discharge rate is increased from a minimum to a maximum. When the frequency of action potentials is relatively low, successive stimuli activate the fibers only after the peak force of each twitch, in the relaxation phase, so that individual twitches can still be distinguished. This is called *unfused tetanus*. As the firing rate increases the individual twitches merge and can no longer be observed giving rise to a constant increase in force. This is called *fused tetanus*. The muscle as a whole contracts smoothly even in cases of unfused tetanus because individual motor units are activated at different times allowing individual twitches to be averaged out.

Motor Unit Disorders

Damage to or dysfunction of the motor unit due to genetic or acquired (e.g., toxic, traumatic, infectious) conditions can result in various disorders. The distinctive features of these disorders vary depending on which of the functional components of the motor unit is primarily affected. Disorders that primarily affect the cell body of the motor neurons or its axon are classified as *neurogenic* diseases. In these diseases, death of motor neurons results in the associated denervated muscle fibers becoming spontaneously active (termed fibrillation), and the muscle gradually becomes weak and wasted. The axons of the remaining motor neurons give off small branches that innervate some of the denervated muscle fibers, resulting in an increased innervation ratio of the surviving motor units. In addition, visible muscle twitches (fasciculations) can occur resulting from spontaneous activity of motor neurons. Changes in reflexes (e.g., tendon reflexes) may also be observed. Dysfunction of the neuromuscular junction can also occur and lead to impaired motor unit function (e.g., myasthenia gravis).

Disorders that mainly affect the muscle fibers are called *myopathic* diseases. The main symptoms of myopathic diseases (e.g., muscular dystrophies) are due to weakness of the skeletal muscle which often includes difficulty in walking or lifting. Other infrequent symptoms include myotonia (inability of the muscle to relax), cramps, and pain. In these diseases, the number of muscle fibers in each motor unit is reduced, but there is no change in the number of motor units firing during a contraction.

See also: Acetylcholine; Botulinum Toxin; Cholinesterase Inhibitors in Parkinson's Disease; Concentric Needle EMG; Electromyography (EMG); Motor Unit Synchronization.

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Motor Unit Synchronization

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Glossary

Electromyography (EMG) – A technique for recording muscle signals in order to evaluate the activation of a muscle. EMG is performed using surface electrodes to record the electrical activity generated by muscle fibers both at rest and during contraction.

Intramuscular recordings – A technique for recording the action potentials of muscle fibers using fine-wire electrodes that are inserted into the muscle. Intramuscular recordings are often used in nerve

conduction studies involving deep or proximal muscles and in other electrodiagnostic tests.

α-Motor neurons – Neurons that innervate extrafusal muscle fibers of skeletal muscles to directly control their contraction. Also known as lower motor neurons; they are grouped in nuclei in the anterior horn of the spinal cord or in brainstem nuclei.

Motor unit synchronization – The simultaneous or near-simultaneous discharge of motor units that occurs more often than would be expected by chance.

Motor unit – A single α-motor neuron together with all the muscle fibers it innervates.

Neuromuscular junction – The synaptic linkage between the axon terminal of a motor neuron and the excitable region (end plate) of the innervated muscle fiber.

Measurement of Motor Unit Synchronization

The excitability of motor neurons can be measured in humans by inserting fine-wire electrodes into the muscle and recording the action potentials of the muscle fibers belonging to the same motor unit (intramuscular recordings). This technique provides a reliable indication of the firing properties of the motor neuron due to the high synaptic efficacy at the neuromuscular junction, where an action potential in a motor neuron will consistently produce an action potential in its associated muscle fibers. Synchronization between motor neurons can be consequently quantified by time- and frequency-domain analyses of the discharge times of pairs of motor units.

The most direct method to measure the level of motor unit synchronization in human is by cross-correlation of discharge times from pairs of concurrently active motor units, where the discharge times of one motor unit are used as a reference, and a histogram is constructed based on the perievent discharge times of the second motor unit. In case of a tendency toward synchronization, a peak in the cross-correlation histogram is observed. Theoretically, if there is no difference in conduction velocities between the two motor neurons, the cross-correlation peak will be centered around time zero, which is the time of firing of the reference motor unit. The size of the central peak in the cross-correlation histogram is proportional to the strength of the common input to the two motor neurons.

Additional information about the properties of the shared input responsible for motor unit synchronization can be acquired from coherence analysis, the frequency-domain equivalent measure of cross-correlation. While cross-correlation approximates the strength of the shared input between the two motor neurons, coherence also provides its frequency when the synchronization varies periodically in time. For example, when applied to human hand muscle, significant coherence was detected between pairs of motor units at frequencies of 1–12 and 16–32 Hz during isometric abduction of the index finger. The presence of coherence between motor unit pairs indicates common periodicity at the presynaptic input.

Mechanisms of Motor Unit Synchronization

The most widely accepted explanation for motor unit synchronization is that branched inputs delivered by presynaptic neurons at the level of the spinal cord generate a common input that increases the probability of simultaneous discharge in the motor neurons sharing this input. It is important, however, to note that such input can be responsible only for 'short-term' synchronization, which is characterized by a narrow central peak in the cross-correlation histogram with duration of less than 10 ms. Based on the models of branched-axon input, direct common input is likely to evoke action potentials that occur within a few milliseconds of each other. Thus, central peaks with broader durations must involve indirect common inputs to the motor neurons via interneurons that are themselves synchronized by a common input. This type of synchronization is termed as 'broad-peak' synchronization. In most human studies, the duration of the central peak varies between 10 and 20 ms, perhaps reflecting a combination of these two forms of input.

Several observations in humans suggest that short-term synchronization is likely to be generated by branched input from supraspinal centers. For example, in patients with sporadic amyotrophic lateral sclerosis, a progressive degenerative disorder that involves the loss of large diameter corticospinal neurons and decreased conduction velocity of the surviving axons, almost no motor unit synchronization could be detected in the dominant extensor carpi radialis muscle. This is in contrast to strong synchronization normally seen in healthy subjects. Another interesting study was conducted on a patient with Klippel–Feil syndrome, who had abnormally branched, fast-conducting corticospinal tract fibers that projected to motor neuron pools bilaterally. In this patient, peculiar synchronization was detected between motor units from the two hands – a phenomenon that was never observed in normal subjects. These studies suggest that branched corticospinal axons are an important cause of short-term synchrony in motor units. Conversely, strong vibration of a hand muscle, which is known to activate muscle spindle afferents, has no effect

on the strength of motor unit synchronization, indicating that peripheral afferents are unlikely to contribute to its generation.

It is important, however, to note that the branched common input theory fails to account for certain observations. In 1993, De Luca and colleagues reported the existence of 'long-term' synchronization that, compared to short-term synchronization, is characterized by lower amplitude peaks that are centered at long latencies ranging from 8 to 76 ms. These long latencies of synchronization cannot be explained by common presynaptic branches, considering the conduction velocity differences and the distances involved. An alternative mechanism is that such synchronization might be the product of synchronous oscillatory activity of the pairs of cortical neurons that synapse on two or more motor neurons. Indeed, activities that are likely to involve synchronized oscillations in higher order neurons, such as attention-demanding tasks, are often accompanied by increased motor unit synchronization. Motor cortical neurons themselves can also be synchronized. This is particularly evident during precision tasks or following training.

Functional Significance of Motor Unit Synchronization

It was initially postulated that synchronization of motor-units can temporarily increase the force generated by the muscle due to a superposition of motor-unit force twitches. However, several studies failed to find a relation between the level of synchronization and net force output, and this hypothesis remains controversial. Nevertheless, this does not indicate that motor unit synchronization does not have a significant physiological function. Various studies have demonstrated that the level of motor unit synchronization can be altered significantly depending on the task conditions. For example, correlated motor unit activity can be altered in human limb muscles during the performance of an action that requires significant attention, or during the changes in muscle length (lengthening vs. shortening contraction). In addition to the task-related changes, it has been shown that certain types of exercise can alter motor unit synchronization. In 1975, Milner-Brown and colleagues carried out one of the earliest and most influential studies on the functional role of motor unit synchronization in the control of movement. They found that weight lifters exhibited greater motor unit synchronization in the first dorsal interosseus muscle than the control subjects. Their study also demonstrated an increase in synchronization following 6 weeks of strength-training program in control subjects. It was therefore suggested that supraspinal inputs from motor cortex directly to spinal motor neurons are enhanced as a result of training to the point where they produce a significant synchronization of motor units. However, this study utilized an indirect method in which averaging the surface electromyography (EMG) signal with respect to motor unit discharge provided a global estimate of synchronization, and the validity of this technique has been challenged.

In a later study, Semmler and Nordstrom (1998) used the more direct method of cross-correlation of motor unit discharges, to compare motor unit synchronization between highly trained musicians, weight lifters, and untrained subjects. Similar to the earlier Milner-Brown et al. findings, strength-trained weight lifters displayed the highest level of synchronization in both hands during a simple index finger abduction task. Furthermore, the amount of motor unit synchronization was lowest in both hands of the musicians and the dominant hand (usually used for skilled movements) of untrained subjects. These findings further support the idea that motor unit synchronization may be a form of adaptation that occurs as a consequence of strength training, allowing for greater force production. However, in a more recent study carried out by the same group, it was shown that significant increases in strength of a hand muscle after several weeks of training were not accompanied by alterations in motor unit synchronization, suggesting that correlated motor unit activity is not important for the expression of muscle strength. Alternatively, the divergent level of motor unit synchronization observed in weightlifters and musicians might reflect reduced motor unit synchronization due to long-term skill training, rather than an increase in synchrony that is caused by strength training. It has been therefore suggested that the weak motor unit synchronization in musicians might reflect a neural adaptation that occurs to lower the strength of common inputs to motor neurons in order to promote the accurate performance of skilled tasks.

Although increased motor unit synchronization is not directly associated with the development of muscle strength, it has been shown to contribute to larger force fluctuations and to increase the rate of force development during rapid contraction. In addition, motor unit synchronization has been implicated in the coordination of the activity of multiple muscles. Evidence for this view comes from cross-correlation analysis of single motor units related to functionally linked, but anatomically distinct muscles. For example, motor unit synchronization has been shown to exist between left and right masseter muscles during jaw clenching and left and right rectus abdominus muscles during trunk curl, but not for the coactivation of homologous muscles of the left and right upper limbs. The functional significance of the motor unit synchronization may therefore lie in the selection and activity of common inputs between muscles. It is possible that the increase in motor unit synchronization observed in a single muscle of weightlifters may also reflect increased common inputs between muscles. This might be a nervous system adaptation to facilitate the

coactivation of many muscles to produce force rapidly. Conversely, the weaker synchronization in musicians may reflect minimal common inputs between muscles to promote independent and skilled muscle synergies.

See also: Motor Unit.

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Movement Disorders: Overview

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Glossary

Basal ganglia – The basal ganglia are that group of gray matter nuclei lying deep within the cerebral hemispheres (caudate, putamen, and pallidum), the diencephalon (subthalamic nucleus), and the mesencephalon (substantia nigra).
Dyskinesia – Abnormal, unnatural movement.
Hyperkinesias – Involuntary movements where there is an excess of movement.
Hypokinesias – Involuntary movements where there is a paucity or poverty of movement.

Definitions

Movement disorders are neurological syndromes in which there is either an excess of movement or a paucity of voluntary and automatic movements, unrelated to weakness or spasticity. The former are commonly referred to as hyperkinesias (excessive movements), dyskinesias (unnatural movements), and abnormal involuntary movements). These terms are used interchangeably. The five major categories of dyskinesias, in alphabetical order, are chorea, dystonia, myoclonus, tics, and tremor. The list of the hyperkinetic disorders is presented in **Table 1**.

The syndromes with a paucity of movement are referred to as hypokinesias (decreased amplitude of movement), bradykinesias (slowness of movement), and akinesias (loss of movement), and these terms are also used interchangeably. The list of the hypokinetic diosorders is presented in **Table 2**. The parkinsonian syndromes comprise the vast majority of such paucity of movement. Other hypokinetic disorders represent only a small group of patients.

Conveniently, movement disorders can be divided into parkinsonism and all other types. There are about an equal number of patients in each of these two groups,

Table 1 Hyperkinetic disorders

A. Abdominal dyskinesias	L. Jumpy stumps
B. Akathitic movements	M. Moving toes/fingers
C. Asynergia/ataxia/dysmetria	N. Myoclonus
D. Athetosis	O. Myokymia
E. Ballism	P. Myorhythmia
F. Chorea	Q. Paroxysmal dyskinesias
G. Dystonia	R. Restless legs
H. Hemifacial spasm	S. Stereotypy
I. Hyperekplexia	T. Tics
J. Hypnogenic dyskinesias	U. Tremor
K. Jumping disorders	

Source: Fahn S and Jankovic J (2007) *Principles and Practice of Movement Disorders*. Philadelphia: Churchill Livingstone Elsevier.

Table 2 Hypokinetic disorders

A. Akinesia/bradykinesia (parkinsonism)
B. Apraxia
C. Blocking (holding) tics
D. Cataplexy and drop attacks
E. Catatonia, psychomotor depression, and obsessional slowness
F. Freezing phenomenon
G. Hesitant gaits
H. Hypothyroid slowness
I. Rigidity
J. Stiff-muscles

Source: Fahn S and Jankovic J (2007) *Principles and Practice of Movement Disorders*. Philadelphia: Churchill Livingstone Elsevier.

as seen from the perspective of movement disorder specialty clinics. It should be noted that this listing is merely a categorization of movement phenomenolgy and not etiology. There are usually multiple etiologies for each of them, including a psychogenic etiology.

Neurologists, neurosurgeons, and nurses who specialize in these disorders are known as movement disorder specialists; their international professional society is The Movement Disorder Society, Inc. (www.movementdisorders.org), which holds annual meetings and publishes a scholarly journal that includes videotape demonstrations of various conditions.

The Origins of Abnormal Movements

Most movement disorders originate within the central nervous system (CNS), particularly the basal ganglia or their connections. The basal ganglia are that group of gray matter nuclei lying deep within the cerebral hemispheres (caudate, putamen, and pallidum), the diencephalon (subthalamic nucleus), and the mesencephalon (substantia nigra). There are some exceptions to this general rule. Pathology of the cerebellum or its pathways typically results in an impairment of coordination (asynergy, ataxia), misjudgment of distance (dysmetria), and intention tremor. Myoclonus and some forms of tremors do not appear to be related primarily to basal ganglia pathology, and often arise elsewhere in the CNS, including cerebral cortex (cortical reflex myoclonus), brainstem (cerebellar outflow tremor, reticular reflex myoclonus, hyperekplexia, and rhythmical brainstem myoclonus such as palatal myoclonus and ocular myoclonus), and spinal cord (rhythmical segmental myoclonus and nonrhythmic propriospinal myoclonus). The peripheral nervous system can give rise to abnormal movements also, such as the moving toes-painful legs syndrome. It is not known for certain which part of the brain is associated with tics, although the basal ganglia and the limbic structures have been implicated. Certain localizations within the basal ganglia are classically associated with specific movement disorders: substantia nigra – bradykinesia and rest tremor; subthalamic nucleus – ballism; caudate nucleus – chorea; and putamen – dystonia.

Evaluation of a Dyskinesia

Not all postures and movements should be considered abnormal and therefore a movement disorder. One must consider whether the suspected movements might be purposeful voluntary movements, such as exaggerated gestures, mannerisms, or compulsive movements, or whether sustained contracted muscles might be physiologic reflex muscle tightness to reduce pain, so-called guarding. It should also be noted that, as a general rule, abnormal involuntary movements are exaggerated with anxiety and stress, and most diminish or disappear during sleep. They may or may not lessen with amobarbital or with hypnosis.

Once it has been decided that abnormal movements are present, the next question is to determine the category of the involuntary movement, such as chorea, dystonia, myoclonus, tics, and tremor. To do so, one evaluates features such as rhythmicity, speed, duration, pattern (e.g,. repetitive, flowing, continual, paroxysmal, diurnal), induction (i.e., stimuli-induced, action-induced, exercise-induced), complexity of the movements (complex vs. simple), suppressibility by volitional attention or by sensory tricks, and whether the movements are accompanied by sensations such as restlessness or the urge to make a movement that can release a built up tension.

After the type of hyperkinesia is determined, the neurologist then tries to determine their etiology, namely, whether the movement disorder is hereditary, sporadic, or secondary to some known neurological disorder. As a general rule, the etiology can be ascertained on the basis of the history and judicially selected laboratory tests. Once the type of disorder and its etiology have been determined, the neurologist determines how best to treat it.

Phenomenology of Hyperkinesias (as listed in Table 1)

Abdominal Dyskinesias

Abdominal dyskinesias are continuous movements of the abdominal wall or sometimes the diaphragm. The movements persist, and their sinuous, rhythmic nature has led to their being called belly dancer's dyskinesia. They may be associated with abdominal trauma in some cases, and a common result is segmental abdominal myoclonus. Another common cause is tardive dyskinesia. Hiccups, which is regularly recurring diaphragmatic myoclonus, does not move the abdomen and umbilicus in a sinewy fashion, but with sharp jerks and typically with noises as air is expelled by the contractions, and hence should not present a problem in diagnosis.

Akathitic Movements

Akathisia (from the Greek, meaning unable to sit still) refers to a feeling of inner, general restlessness, which is reduced or relieved by moving about. The typical akathitic patient, when sitting, may caress his scalp, cross and uncross his legs, rock his trunk, squirm in the chair, get out of the chair often to pace back and forth, and may even make noises such as moaning. Akathisia can be generalized or focal; the latter often produces a sensation of burning or pain, again relieved by moving that body part. Common sites for focal akathisia are the mouth and vagina.

The most common cause of akathisia is iatrogenic. It is a common complication of antidopaminergic drugs, including those that block dopamine receptors (such as antipsychotic drugs) and those that deplete dopamine (such as reserpine and tetrabenazine). Akathisia can occur when drug therapy is initiated (acute akathisia), subsequently with the emergence of drug-induced parkinsonism, or after chronic treatment (tardive akathisia). Acute akathisia is eliminated upon withdrawal of the medication. Tardive akathisia is usually associated with the syndrome of tardive dyskinesia. Like tardive dyskinesia, tardive akathisia is aggravated by discontinuing the neuroleptic.

Asynergia/Ataxia/Dysmetria

Asynergia or dyssynergia refers to decomposition of movement due to breakdown of normal coordinated execution of a voluntary movement. It is one of the cardinal clinical features of cerebellar disease or of lesions involving the pathways to or from the cerebellum. Instead of a smooth, continuous movement; the limb wanders off its trajectory attempting to reach a target, with corrective maneuvers that resemble oscillations of the limb. The limb usually misses the target (dysmetria). Ataxia of gait is typified by unsteadiness on walking with a wide base, the body swaying, and an inability to walk on tandem (heel-to-toe). Asynergia of a limb is also called limb ataxia.

Athetosis

Athetosis has been used in two senses: (1) to describe a class of slow, writhing, continuous, involuntary movements and (2) to describe the syndrome of athetoid cerebral palsy. This syndrome commonly occurs as a result of injury to the basal ganglia in the prenatal or perinatal period or during infancy. When producing abnormal posture, athetosis blends with dystonia. When the speed of athetosis is high, it blends with those of chorea, and the term choreoathetosis is used. Pseudoathetosis refers to distal athetoid movements of the fingers and toes due to loss of proprioception, which can be due to sensory deafferentation (sensory athetosis) or due to central loss of proprioception.

Ballism

Ballism refers to very large amplitude choreic movements of the proximal parts of the limbs, causing flinging and flailing limb movements. Ballism is most often unilateral, which is referred to as hemiballism. This is often the result of a lesion in the contralateral subthalamic nucleus or its connections, or to multiple small infarcts (lacunes) in the contralateral striatum.

Chorea

Chorea refers to involuntary, irregular, purposeless, nonrhythmic, abrupt, rapid, unsustained movements that seem to flow from one body part to another. A characteristic feature of chorea is that the movements are unpredictable in timing, direction, and distribution (i.e., random). The prototypical choreic movements are those seen in Huntington's disease, in which the brief and rapid movements are irregular and occur randomly as a function of time. In Sydenham chorea and in the withdrawal emergent syndrome, the movements have a restless-like appearance.

Choreic movements can be partially suppressed, in which the movements are incorporated into semipurposeful movements, known as parakinesia. Chorea is usually accompanied by motor impersistence ('negative chorea'), the inability to maintain a sustained contraction. A common symptom of motor impersistence is the dropping of objects. Motor impersistence is detected by examining for the inability to keep the tongue protruded and by the presence of the 'milk-maid' grip due to the inability to keep the fist in a sustained tight grip.

Dystonia

Dystonia refers to twisting movements that tend to be sustained at the peak of the movement, are frequently repetitive, and often progress to prolonged abnormal postures. In contrast to chorea, dystonic movements

repeatedly involve the same group of muscles, that is, they are patterned. Agonist and antagonist muscles contract simultaneously (cocontraction) to produce the sustained quality of dystonic movements. The speed of the movement varies widely from slow (athetotic dystonia) to shock-like (myoclonic dystonia).

When dystonia first appears, the movements typically occur when the affected body part is carrying out a voluntary action (action dystonia) and are not present when that body part is at rest. With the progression of the disorder, dystonic movements can appear at distant sites (overflow) when other parts of the body are voluntarily moving, such as occurs also in athetosis and in dopa-induced dyskinesias. With further progression, dystonic movements become present when the body is 'at rest.' Even at this stage, dystonic movements are usually made more severe with voluntary activity. Primary dystonia often begins as action dystonia and may persist as the kinetic (clonic) form, whereas secondary dystonia often begins as sustained postures (tonic form). Rarely, primary dystonia can appear initially at rest and clears when the affected body part or some other part of the body is voluntarily active; this type has been called paradoxical dystonia.

One of the characteristics and almost unique features of dystonic movements is that they can often be diminished by tactile or proprioceptive 'sensory tricks' (geste antagoniste). Thus, touching the involved body part or an adjacent body part can often reduce the muscle contractions.

When a single body part is affected, the condition is referred to as focal dystonia. Common forms of focal dystonia are spasmodic torticollis (cervical dystonia), blepharospasm (upper facial dystonia), and writer's cramp (hand dystonia). The involvement of two or more contiguous regions of the body is referred to as segmental dystonia. Generalized dystonia indicates the involvement of one or both the legs, the trunk, and some other part of the body. Multifocal dystonia involves two or more regions, not conforming to segmental or generalized dystonia. Hemidystonia refers to the involvement of the arm and leg on the same side.

Sustained contractions of ocular muscles, resulting in tonic ocular deviation, usually upward gaze, is referred to as oculogyric crisis. It is most common today as a complication of dopamine receptor blocking agents. Paroxysmal tonic upgaze can be seen in infants and children and often eventually subsides.

In contrast to this continual type of classical torsion dystonia, a variant of dystonia also exists in which the movements occur in attacks, with a sudden onset and limited duration – known as paroxysmal kinesigenic dyskinesias (PKDs) and paroxysmal nonkinesigenic dyskinesias (PNKDs). These are categorized among the paroxysmal disorders (see below). Among the other disorders to be differentiated from dystonia are tonic tics (also called dystonic tics), which also appear as sustained contractions.

Hemifacial Spasm

Hemifacial spasm, as the name indicates, refers to unilateral facial muscle contractions. Generally, these are continual rapid, brief, repetitive spasms, but can also be more prolonged sustained tonic spasms, mixed with periods of quiescence. Often the movements can be brought out when the patient voluntarily and forcefully contracts the facial muscles; when the patient then relaxes the face, the involuntary movements appear. The disorder involves the facial nerve, and sometimes it is due to compression of the nerve by an aberrant blood vessel.

Hyperekplexia

Hyperekplexia ('startle disease') is an excessive startle reaction to a sudden, unexpected stimulus. The startle response can be either a short 'jump' or a more prolonged tonic spasm causing falls. This condition can be familial or sporadic.

Hypnogenic Dyskinesias

Most dyskinesias disappear during deep sleep, although they may emerge during light sleep. The major exception is symptomatic rhythmical oculo-palatal myoclonus, which persists during sleep, in addition to being present while the patient is awake. There are, however, a few movement disorders that are present only when the patient is asleep. The most common hypnogenic dyskinesia is the condition known as periodic movements in sleep. They appear as slow flexor contractions of one or both legs, with dorsiflexion of the big toe and the foot, and flexion of the knee and hip. They occur in intervals, approximately every 20 s. Periodic movements in sleep are a frequent component of the restless legs syndrome.

Another rare nocturnal dyskinesia is hypnogenic paroxysmal dystonia or other dyskinesias that occur only during sleep. Hypnogenic dystonia can be complex and with sustained contractions, similar to that occurring in torsion dystonia. As depicted in its name, such movements occur as a paroxysm during sleep and last only a few minutes. They may or may not awaken the patient. Some may be frontal lobe seizures.

Jumping Disorders

Jumping disorders are similar-appearing syndromes with names like Jumping Frenchmen of Maine, latah, myriachit, and Ragin Cajun. The names were coined for the ethnic groups in different parts of the world, although their clinical features are similar. All of these appear to be influenced by social and group behavior. After the initial jump to the unexpected stimulus, there is automatic speech or behavior, such as striking out. In some of these, there is automatic obedience to words as 'jump' or 'throw.'

Jumpy Stumps

Jumpy stumps are uncontrollable and sometimes exhausting chaotic movements of the stump remaining from amputated limbs. When they occur, it is after a delayed period of time after the amputation.

Moving Toes and Fingers

The painful legs, moving toes syndrome refers to a disorder in which the toes of one foot or both feet are in continual flexion-extension with some lateral motion, associated with a deep pain in the ipsilateral leg. The constant movement has a sinusoidal quality. The movements and pain are continuous, and both occur even during sleep, although they may be reduced and the normal sleep pattern may be altered. The leg pain is much more troublesome to the patient than are the constant movements. In some patients with this disorder, there is evidence for a lesion in the lumbar roots or in the peripheral nerves. An analogous disorder, 'painful arm, moving fingers,' has also been described.

Myoclonus

Myoclonic jerks are sudden, brief, shock-like involuntary movements caused by muscular contractions (positive myoclonus) or inhibitions (negative myoclonus). The most common form of negative myoclonus is asterixis, which commonly accompanies various metabolic encephalopathies. In asterixis, the brief flapping of the outstretched limbs is due to a transient inhibition of the muscles that maintain posture of those extremities.

Myoclonus can appear when the affected body part is at rest or when it is performing a voluntary motor act, so-called action myoclonus. Myoclonic jerks are usually irregular (arrhythmic), but can be rhythmical (such as in palatal myoclonus or in ocular myoclonus, with a rate of $\sim$2 Hz). Rhythmical ocular myoclonus due to a lesion in the dentato-olivary pathway needs to be distinguished from arrhythmic and chaotic opsoclonus or dancing eyes. Rhythmic myoclonus is typically due to a structural lesion of the brainstem or spinal cord (therefore also called segmental myoclonus), but not all cases of segmental myoclonus are rhythmic, and some types of cortical epilepsia partialis continua can be rhythmic. Oscillatory myoclonus is depicted as rhythmic jerks that occur in a burst and then fade. Spinal myoclonus, in addition to presenting as segmental and rhythmical, can also present as flexion axial jerks triggered by a distant stimulus that travels via a slow-conducting spinal pathway, and called propriospinal myoclonus. Respiratory myoclonus can be variable and has been called diaphragmatic flutter and diaphragmatic tremor.

Myoclonic jerks occurring in different body parts are often synchronized: a feature that may be specific for myoclonus. The jerks can often be triggered by sudden stimuli such as sound, light, visual threat, or movement (reflex myoclonus). Myoclonus has a relationship to seizures in that both seem to be the result of hyperexcitable neurons.

Action or intention myoclonus is often encountered after cerebral hypoxia-ischemia (Lance–Adams syndrome) and with certain degenerative disorders, such as progressive myoclonus epilepsy (Unverricht–Lundborg disease) and progressive myoclonic ataxia (Ramsay Hunt syndrome). In the opsoclonus–myoclonus syndrome, originally described by Kinsbourne and subsequently called both 'dancing eyes, dancing feet' and 'polymyoclonia' by Dyken and Kolar, the amplitude of the myoclonus is usually very tiny, resembling irregular tremors. Because of the small amplitudes of the continuous, generalized myoclonus, these are called minipolymyoclonus.

Myokymia

Myokymia is a fine persistent quivering or rippling of muscles. Electromyography reveals regular groups of motor unit discharges, especially doublets and triplets, occurring with a regular rhythmic discharge. Myokymia occurs most commonly in facial muscles. Most facial myokymias are due to pontine lesions, particularly multiple sclerosis, and less often due to pontine glioma. Myokymia is also a feature of neuromyotonia (see stiff muscles, below). Myokymia can persist during sleep.

Myorhythmia

The term, myorhythmia, has been used in different ways over time. Herz used it to refer to the rhythmical movements seen in patients with torsion dystonia. Today, this is recognized as a patterned feature of dystonic movements and not as a separate phenomenon. Monrad-Krohn and Refsum and Masucci et al. used the term myorhythmia to label what is called rhythmical myoclonus today, such as palatal myoclonus. Fahn and Jankovic advocate using the term to represent a somewhat low frequency ($<$3 Hz), prolonged, rhythmical or repetitive movement, in which the movement does not have the sharp square wave appearance of a myoclonic jerk. Therefore, it would not apply to palatal myoclonus. Myorhythmia would also not be applied to the sinusoidal cycles of most tremors (parkinsonian, essential, cerebellar), because the frequency of these tremors is higher than what is defined for myorhythmia.

The most typical disorder in which the term myorhythmia is applied is in Whipple disease, in which there are slow-moving, repetitive, synchronous, rhythmical contractions in ocular, facial, masticatory, and other muscles, so-called oculo-facio-masticatory myorhythmia. The abnormal movements of facial and masticatory muscles can persist in sleep.

Paroxysmal Dyskinesias

The paroxysmal dyskinesias represent various types of dyskinetic movements, particularly choreoathetosis and dystonia, that occur 'out-of-the-blue' and then disappear after being present for seconds, minutes, or hours. The patient can remain normal for months between attacks, or there can be many attacks per day.

PKD is the best described and easiest to diagnose, because it is characteristically triggered by a sudden movement, and the abnormal movements last only seconds to a few minutes. PKD can be hereditary or symptomatic and is usually successfully treated with anticonvulsants. The abnormal movements easily habituate, that is, they fail to recur if the sudden movement is immediately repeated. These movements can be dystonic, ballistic, and choreic. There may be many brief paroxysmal bursts of movements each day.

PNKD can be familial, sporadic, or symptomatic; is triggered by stress, fatigue, caffeine, or alcohol; and can last minutes to hours. Sporadic PNKD is more often a psychogenic movement disorder, particularly if it is a combination of both paroxysmal and continual dystonias.

Paroxysmal exertional dyskinesia (PED) can be due to glucose transporter 1 deficiency or can be sporadic. The attacks of dyskinesias occur about 30 min after exercising.

When the paroxysmal dyskinesias consist of ataxia or tremor, they have been called episodic ataxias and tremors. They are usually familial, and may include vestibular signs and symptoms.

Restless Legs

The term restless legs syndrome refers to more than just the phenomenon of restless legs, where the patient has unpleasant crawling sensations in the legs, particularly when sitting and relaxing in the evening, which then disappear on walking. The complete syndrome consists of several parts, in which one or more may be present in any individual. While the unpleasant dysesthesias in the legs are the most common symptom, the clinical spectrum may also include periodic movements in sleep (see hypnogenic dyskinesias), myoclonic jerks, more sustained dystonic movements, or stereotypic movements that occur while the patient is awake, particularly in the late evening.

Stereotypy

Stereotypy refers to coordinated movements that repeat themselves continually and identically. However, there may be long periods of minutes between movements, or they may be very frequent. When they occur at irregular intervals, stereotypies may not always be easily distinguished from motor tics (see below), compulsions, gestures, and mannerisms. In their classic monograph on tics, Meige and Feindel distinguished between stereotypies and motor tics by describing the latter as acts that are impelling but not impossible to resist, whereas the former, while illogical, are without an irresistible urge. Stereotypies typically occur in patients with tardive dyskinesia and with schizophrenia, mental retardation, and autism.

Compulsions are repetitive, purposeless, usually complex movements seen in patients with obsessive-compulsive disorder (OCD). They are associated with an irresistible urge to make the movement. Patients realize they are making the movements in response to this 'need to do so.' In this respect, compulsions resemble tics, and not stereotypies, which are not accompanied by any urge. Like stereotypies, compulsions could be carried out in a uniform repetitive fashion for long periods of time, but do so at the expense of all other activities because compulsions may be impossible to stop. In contrast, stereotypies can usually be stopped on command, and the patient will have normal motor behavior until they start up again, usually as soon as the patient is no longer paying attention to the command.

Gestures are culturally developed, expressive, voluntary movements calculated to indicate a particular state of mind and which may also be used as a means of adding emphasis to oratory. Mannerisms are sets of movements that include gestures plus more peculiar and individualistic movements not considered as bothersome. Mannerisms can be considered to represent a type of motor signature that individualizes a person. Sometimes mannerisms can be bizarre, and these could be considered as tics or on the borderline with tics. Since gestures and mannerisms rarely continually repeat themselves, they would not likely be confused with stereotypies, but they may have problems at times being distinguished from tics.

Tics

Tics consist of abnormal movements (motor tics) or abnormal sounds (phonic tics). When both types of tics are present, the designation of Gilles de la Tourette syndrome or Tourette syndrome is commonly applied. Tics vary in severity over time and can have remissions and exacerbations.

Motor and phonic tics can be simple or complex and occur abruptly for brief moments from a background of normal motor activity. Thus, they are paroxysmal in occurrence unless so severe as to be continual. A single simple motor tic may be impossible to distinguish from a myoclonic or choreic jerk; each of these would be an abrupt, sudden, isolated movement. Examples include a shoulder shrug, head jerk, blink, dart of the eyes, and twitch of the nose. Most of the time such simple tics are repetitive, such as a run of eye blinking or a sequence of several simple tics in a row. In this more complex pattern, tics can be easily distinguished from the other

hyperkinesias. Even when tics are simple jerks, more complex forms of tics may also be present in the same patient, allowing one to establish the diagnosis by 'the company it keeps.' One type of simple tic is quite distinct, namely ocular. Eye movements are not a feature of chorea or myoclonus, but are common in tics.

Complex motor tics are very distinct, consisting of coordinated patterns of sequential movements that can appear in different parts of the body and are not necessarily identical from occurrence to occurrence in the same body part. Examples of complex tics include such acts as touching the nose, touching other people, head shaking with shoulder shrugging, kicking of legs, and jumping. Obscene gesturing (copropraxia) is another example.

Like akathitic movements, tics are usually preceded by an uncomfortable feeling or sensory urge that is relieved by carrying out the movement, that is, like 'scratching the itch.' Thus, the movements and sounds can be considered 'unvoluntary.' Unless very severe, tics can be voluntarily suppressed for various periods of time, but when suppressed, inner tension builds up and is only relieved by an increased burst of more tics.

Tics can vary in speed, from being as rapid as myoclonic jerks to being slow and sustained contractions, resembling dystonic movements. The complex sequential pattern of muscular contractions in dystonic tics makes the diagnosis obvious in most cases. Moreover, torsion dystonia is a continual hyperkinesia, whereas tics are paroxysmal bursts of varying duration.

Phonic tics can range from simple throat-clearing sounds or grunts to verbalizations and the utterance of obscenities (coprolalia). Sniffing can also be a phonic tic, involving nasal passages rather than the vocal apparatus. Like motor tics, phonic tics can also be divided into simple and complex. Throat-clearing and sniffing represent simple phonic tics, whereas verbalizations are considered complex phonic tics.

Tremor

Tremor is an oscillatory, usually rhythmical and regular, movement affecting one or more body parts, such as the limbs, neck, tongue, chin, or vocal cords. Jerky, irregular 'tremor' is usually a manifestation of myoclonus. Tremor is produced by rhythmic alternating or simultaneous contractions of agonists and antagonist muscles. The rate, location, amplitude, and constancy vary depending on the specific type of tremor and its severity. It is helpful to determine whether the tremor is present at rest (with the patient sitting or lying in repose), with posture-holding (with the arms or legs extended in front of the body), with action (such as writing or pouring water), or with intention maneuvers (such as bringing the finger to touch the nose). Tremors can, thus, be classified as tremor-at-rest, postural tremor, action tremor, or intention tremor, respectively. Some tremors may be present only during a specific task (such as writing) or with a specific posture, such as standing as in orthostatic tremor. These are called task-specific or position-specific tremors, respectively, and may overlap with task-specific and position-specific action dystonias, which may also appear as tremors (dystonic tremor). Etiologies and treatment of tremors differ according to the type of tremor phenomenology it fits.

Phenomenology of Hypokinesias (as listed in Table 2)

Akinesia/Bradykinesia

Akinesia, bradykinesia, and hypokinesia literally mean absence, slowness, and decreased amplitude of movement, respectively. The three terms are commonly grouped together for convenience and usually referred to under the term of bradykinesia. These phenomena are a prominent and most important feature of parkinsonism, and are often equated as a *sine qua non* for parkinsonism. Although akinesia means lack of movement, the label is often used to indicate a very severe form of bradykinesia. Bradykinesia is mild in early Parkinson disease (PD) and becomes more severe in advanced PD and other forms of parkinsonism. Parkinsonism is a neurological syndrome manifested by any combination of six cardinal features: tremor-at-rest, bradykinesia, rigidity, flexed posture, freezing, and loss of postural reflexes.

Akinesia/bradykinesia/hypokinesia can be detected in various parts of the body. Cranially, it is manifested by masked facies (hypomimia), decreased frequency of blinking, impaired upgaze, impaired ocular convergence, soft speech (hypophonia), loss of inflection (aprosody), and drooling of saliva due to decreased spontaneous swallowing. In the arms, bradykinesia is manifested by slowness in shrugging the shoulder and lowering the shrugged shoulder; slowness in raising the arm; loss of spontaneous movement such as gesturing; smallness and slowness of handwriting (micrographia); decreased armswing when walking; slowness and decrementing amplitude of repetitively opening and closing the hands, tapping a finger, and twisting the hand back and forth; and difficulty with hand dexterity for shaving, brushing teeth, and putting on make-up. In the legs bradykinesia is manifested by slowness and decrementing amplitude in repetitively stomping the foot or tapping the toes; by slowness in making the number eight with the foot; and by a slow, short-stepped, shuffling gait with reduced heel strike when stepping forward. In the trunk, bradykinesia is manifested by difficulty in arising from a chair, getting out of automobiles, and turning in bed.

Bradykinesia encompasses a loss of automatic movements, slowness in initiating movement on command, and reduction in amplitude of the voluntary movement. An early feature of reduction of amplitude, besides the

decrementing of the amplitude with repetitive finger tapping or foot tapping, there is also a breakdown of the smooth, regular rhythm of the tapping. Carrying out two activities simultaneously is impaired, and this difficulty may be a manifestation of bradykinesia. With the stimulation of a sufficient sensory input, bradykinesia, hypokinesia, and akinesia can be temporarily overcome (kinesia paradoxica).

Akinesia needs to be distinguished from the freezing phenomenon (see below), both of which are features of parkinsonism.

Apraxia

Apraxia is a cerebral cortex, not a basal ganglia, dysfunction. Apraxia is traditionally defined as a disorder of voluntary movement that cannot be explained by weakness, spasticity, rigidity, sensory loss, or cognitive impairment. It can exist and can be tested for in the presence of a movement disorder provided that akinesia, rigidity, or dystonia is not so severe that voluntary movement cannot be executed. There are three classical categories of apraxia:

1. In ideational apraxia, the concept or plan of movement cannot be formulated by the patient. Some examiners test for ideational apraxia by asking the patient to perform a series of sequential movements such as filling a pipe, lighting it, and then smoking; or putting a letter into an envelope, sealing it, and then affixing a stamp. Ideational apraxia is due to parietal lesions, most often diffuse and degenerative.
2. In ideomotor apraxia, the concept or plan of movement is intact, but the individual motor engrams or programs are defective. Ideomotor apraxia is commonly tested for by asking patients to undertake specific motor acts to verbal or written commands, for example, wave goodbye, salute like a soldier, comb their hair, or use a hammer to fix a nail, etc. The patients with ideomotor apraxia often improve their performance if asked to mimic the action when the examiner shows them what to do or when given the object or tool to use. Ideomotor apraxia usually does not interfere with normal spontaneous motor actions, but requires specific testing for its demonstration. It is usually, but not always, associated with aphasia, and is due mainly to lesions in the dominant hemisphere, particularly in the parietotemporal regions, the arcuate fasciculus, or the frontal lobe; such ideomotor apraxia is bilateral, providing there is not a hemiplegia. Lesions of the corpus callosum can cause apraxia of the nondominant hand.
3. Limb-kinetic apraxia is the least understood type. It refers to a higher order motor deficit in executing motor acts that cannot be explained by simple motor impairments. It has been attributed to lesions of premotor regions in the frontal lobe, such as supplementary motor area.

Blocking (Holding) Tics

Blocking (or holding) is a motor phenomenon that is seen occasionally in patients with tics and is characterized as a brief interference of social discourse and contact. There is no loss of consciousness, and although the patient does not speak during these episodes, he/she is fully aware of what has been spoken. They appear in two situations: (1) as an accompanying feature of some prolonged tics, such as during a protracted dystonic tic or during tic status and (2) as a specific tic phenomenon in the absence of an accompanying obvious motor or vocal tic. The latter occurrences have the abruptness and duration of a dystonic tic or a series of clonic tics, but they do not occur during an episode of an obvious motor tic; it can be considered as a negative motor phenomenon, that is, a 'negative' tic.

Cataplexy and Drop Attacks

Drop attacks can be defined as sudden falls with or without loss of consciousness, due either to collapse of postural muscle tone or to abnormal muscle contractions in the legs. There are many neurological and nonneurological causes of symptomatic drop attacks, but most are of unknown etiology. Neurological disorders include leg weakness, sudden falls in parkinsonian syndromes including those due to freezing, transient ischemic attacks, epilepsy, myoclonus, startle reactions (hyperekplexia), paroxysmal dyskinesias, structural CNS lesions, and hydrocephalus. In some of these, there is a loss of muscle tone in the legs, and in others, there is excessive muscle stiffness with immobility, such as in hyperekplexia. Syncope and cardiovascular disease account for nonneurological causes.

Cataplexy is another cause of symptomatic drop attacks that does not fit the categories listed earlier. Patients with cataplexy fall suddenly without loss of consciousness, but with an inability to speak during an attack. There is a precipitating trigger, usually laughter or a sudden emotional stimulus. The patient's muscle tone is flaccid and remains this way for many seconds. Cataplexy is usually just one feature of the narcolepsy syndrome, which also includes sleep paralysis and hypnagogic hallucinations, in addition to the characteristic feature of uncontrollable falling asleep.

Catatonia, Psychomotor Depression, and Obsessional Slowness

About catatonia:

> "... the patient remains entirely motionless, without speaking, and with a rigid, mask like facies, the eyes focused at a distance; he seems devoid of any will to move or react to any stimuli; there may be fully developed "waxen" flexibility, as in cataleptic states, or only indications, distinct, nevertheless, of this striking phenomenon.

> The general impression conveyed by such patients is one of profound mental anguish. . ."
> Karl Ludwig Kahlbaum, 1874
> from Bush et al., 1996

Catatonia is a syndrome characterized by catalepsy (abnormal maintenance of posture or physical attitudes), waxy flexibility (retention of the limbs for an indefinite period of time the positions in which they are placed), negativism, mutism, and bizarre mannerisms. Patients with catatonia can remain in one position for hours and move exceedingly slowly to commands, usually requiring the examiner to push them along. However, when moving spontaneously, they move quickly, such as when scratching themselves. In contrast to patients with parkinsonism, there is no concomitant cogwheel rigidity, freezing, or loss of postural reflexes. Classically, catatonia is a feature of schizophrenia, but it can occur with severe depression. Gelenberg also stated that catatonia can appear with conversion hysteria, dissociative states, and with organic brain disease.

Depression is commonly associated with a general slowness of movement, as well as of thought, so-called psychomotor retardation, and catatonia can be considered as an extreme case of this problem. Although depressed patients are widely recognized to manifest slowness in movement, some, particularly children, may not have the more classical symptoms of low mood, dysphoria, anorexia, insomnia, somatizations, and tearfulness. In this situation, slowness due to depression can be difficult to distinguish from the bradykinesia of parkinsonism; like catatonia, lack of rigidity and preservation of postural reflexes may help to differentiate psychomotor slowness from parkinsonism.

Some patients with OCD may present with extreme slowness of movement, so-called obsessional slowness. The major differential diagnosis is parkinsonism.

Freezing

Freezing refers to transient periods, usually lasting several seconds, in which the motor act is halted, being stuck in place. It commonly develops in parkinsonism and is one of its six cardinal signs. The freezing phenomenon has also been called motor blocks, 'pure akinesia' and 'gait ignition failure.' In freezing, the voluntary motor activity being attempted is halted, because agonists and antagonist muscles simultaneously and isometrically contract, preventing the normal execution of voluntary movement. The motor blockage, therefore, is not one of lack of muscle tone or flaccidity, but rather is analogous to being glued to a position so that the patient exerts an increased effort to overcome being 'stuck.' The stuck body part attempts to move to overcome the block, and muscle force (isometric) is exerted. Hence, with freezing of gait, by far the most common form of the freezing phenomenon, as the patient attempts to move the feet, short, incomplete steps are attempted, but the feet tend to remain in the same place ('glued to the ground'). After a few seconds, the freezing clears spontaneously, and the patient is able to move at his/her normal pace again, until the next freezing episode develops. Often the patient has learned some trick maneuver to terminate the freezing episode sooner; stepping over an 'inverted cane' when the legs begin to freeze is one method by which patients can manage to ambulate.

Freezing of speech also occurs; speech is 'arrested' with the patient repeating a sound until it finally becomes unstuck, and speech then continues. This can be considered a severe form of parkinsonian palilalia, which usually refers to a repetition of the first syllable of the word trying to be verbally expressed. Parkinsonian palilalia differs from the palilalia seen in patients with Tourette syndrome, in which there is repetition of entire words or a string of words.

Freezing of the arms can affect handwriting, shaving, or teeth-brushing. Difficulty in opening the eyes can be another target of freezing. This eyelid freezing was originally called 'apraxia of eyelid opening,' which is a misnomer, because the problem is not an apraxia. Eyelid freezing has also been called 'levator palpebrae inhibition' and even a form of dystonia.

Freezing of gait can sometimes appear as a disorder without other features of parkinsonism, except for loss of postural reflexes and mild bradykinesia; most commonly as this disorder worsens over time, features of progressive supranuclear palsy become manifest.

Hesitant Gaits

Hesitant gaits or uncertain gaits are seen in a number of syndromes. The cautious gait seen in some elderly people is slow on a wide base with short steps and superficially may resemble that of parkinsonism except there are no other parkinsonian features. Fear of falling, either because of perceived instability or realistic loss of postural righting reflexes, produces an inability to walk independently without holding onto people or objects. Since this abnormal gait disappears when the person walks holding onto someone, it is often considered to be a psychiatric disorder, a phobia of open spaces (i.e., agoraphobia). However, because previous falls usually play a role in patients developing this disorder, it is likely a true fear of falling and should be distinguished from agoraphobia, which is a separate syndrome. Fear of falling should be differentiated from psychogenic gait disorders.

The senile gait disorder (or gait disorder of the elderly) is a poorly understood condition that comprises a number of different syndromes. In gait ignition failure, also called

primary freezing gait, the problem is one of getting started. Once underway, such patients walk fairly briskly, and equilibrium is preserved. In frontal gait disorders, there is also start-hesitation, and walking is with slow, small, shuffling steps, similar to that in PD. However, there are few other signs of parkinsonism, and equilibrium is preserved. Such a gait can occur with frontal lobe tumors, cerebrovascular disease, and hydrocephalus, all causing frontal lobe damage. This pattern has been incorrectly called frontal ataxia or gait apraxia.

Other hesitant gaits are those due to severe dysequilibrium. These types of gait have been associated with frontal cortex and deep white matter lesions (frontal disequilibrium) or thalamic and midbrain lesions (subcortical disequilibrium).

Hypothyroid Slowness

Along with decreased metabolic rate, cool temperature, bradycardia, myxedema, loss of hair, hoarseness, and myotonia, severe hypothyroidism can also feature motor slowness, weakness, and lethargy. These signs could be mistaken for the bradykinesia of parkinsonism, but the combination of the other signs of hypothyroidism, along with lack of rigidity and loss of postural reflexes, should aid the correct diagnosis.

Rigidity

Rigidity is characterized as increased muscle tone in the presence of passive motion. It is distinguished from spasticity in that it is present equally in all directions of the passive movement, equally in flexors and extensors, and throughout the range of motion, and it does not exhibit the clasp-knife phenomenon nor increased tendon reflexes. Rigidity can be smooth (lead-pipe) or jerky (cogwheel). Cogwheeling occurs in the same range of frequencies as action and resting tremor and appears to be due to superimposition of a tremor rhythm. Cogwheel rigidity is more common than the lead-pipe variety in parkinsonism (nigral lesion), and lead-pipe rigidity can be caused by a number of other CNS lesions, including those involving corpus striatum (hypoxia, vascular, neuroleptic malignant syndrome), midbrain (decorticate rigidity), medulla (decerebrate rigidity), and spinal cord (tetanus).

An increase in passive muscle tone can sometimes lead to impaired motor performance or even immobility. Before there was a clear understanding of bradykinesia, rigidity was considered to be responsible for the paucity of movement in parkinsonism, but rigidity is clearly distinct from bradykinesia; the former is more easily treated by levodopa therapy or by stereotactic thalamotomy and can be relieved while bradykinesia with residual paucity of movement persists. When rigidity is extremely severe so that the examiner can barely move the limbs, as in patients with neuroleptic malignant syndrome, the patient is virtually unable to move. The extended neck occasionally seen in progressive supranuclear palsy may be due to rigidity (vs. dystonia); the neck can be immobile in this disorder, and other axial muscles are also rigid.

Stiff-Muscles

Stiff muscles are defined as being due to continuous muscle firing without muscle disease and not due to rigidity or spasticity. There are four major categories of stiff-muscle syndromes: continuous muscle fiber activity or neuromyotonia, encephalomyelitis with rigidity, the stiff-limb syndrome, and the stiff-person syndrome. Neuromyotonia is a syndrome of myotonic failure of muscle relaxation plus myokymia and fasciculations. Clinically, it manifests itself as continuous muscle activity causing stiffness and cramps. The best-known neuromyotonic disorder is Isaacs syndrome.

Encephalomyelitis with rigidity manifests itself with marked rigidity and muscle irritability, with increased response to tapping the muscles, along with myoclonus. It is now recognized as a severe manifestation of stiff-person syndrome and may respond to steroid therapy.

Stiff-person syndrome refers to a rare disorder in which many somatic muscles continuously contract isometrically, resembling 'chronic tetanus,' in contrast to dystonic movements, which produce abnormal twisting and patterned movements, and postures. The contractions of stiff-person syndrome are usually forceful and painful and most frequently involve the trunk and neck musculature. The proximal limb muscles can also be involved, but rarely does the disorder first affect the distal limbs. Benzodiazepines and valproate are usually somewhat effective. Withdrawal of these agents results in an increase of painful spasms. This disorder has now been recognized to be an autoimmune disease, with circulating antibodies against the GABA-synthesizing enzyme glutamic acid decarboxylase and also other type of antibodies, including against insulin. Diabetes is a common accompanying disorder. The diagnosis can now be aided by laboratory testing for these antibodies. The so-called 'stiff-baby' syndrome is actually due to infantile hyperekplexia, in which the muscles continue to fire repeatedly and so frequently that the muscles appear to contract continuously.

See also: Akathisia; Ataxia; Athetosis; Basal Ganglia; Chorea; Dystonia; Huntington's Disease; Parkinson's Disease: Definition, Diagnosis, and Management; Tics; Tremor.

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Movement Time

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Glossary

Movement time – The time to complete a discreet predefined motor task.

Definition and History

Movement time may be defined as the time to complete a discreet predefined motor task. The timing of the task starts at the initiation of movement rather than at the start of a prompt as in reaction time. Movement time is a measure of bradykinesia and has been used as an outcome measure for therapeutic trials of agents designed to improve motor function. Movement time is task specific and, for this reason, care must be taken to control all variables to standardize the test for clinical trials.

A number of instruments have been used to measure movement time. Many of these require the subject to place their hand on a button and then at a prompt move their hand to another button. In this model, the time from the prompt to releasing the first button is simple reaction time, and the time from releasing the button to depressing the second button is movement time. Movement time increases with age, but there is no difference between men and women. In a model using a stopwatch to measure the movement time, there is no significant difference between the nondominant and dominant hands. In another model using other instruments, movement time is slower on the nondominant side than on the dominant side.

Several studies demonstrate that movement time measures, like reaction time measures, are dependent on a number of variables, and great care must be taken to control for these when comparing studies. Movement time has been utilized in a number of studies as a quantifiable measure of bradykinesia. As expected, most of these have been investigations of Parkinson's disease (PD) and related disorders.

Movement Time – PD

Patients with PD are slower to react and to move than the normal subjects, and disease severity more highly correlates with movement time than reaction time. In subjects with PD and asymmetrical signs, both responses were longer on the more affected side and bradykinesia is the clinical symptom that best correlates with the objective measurements. Levodopa significantly improves both the responses, whereas anticholinergic agents are less effective. There is evidence to suggest that movement time may be a more sensitive outcome measure than the motor

examination part of the Unified Parkinson's Disease Rating Scale (UPDRS-III) in predicting the magnitude of long-term dopaminergic responsiveness from a short-term dopaminergic challenge. Interestingly, abnormalities in movement time found in patients with PD more closely correlate with abnormalities in color vision than reaction time. This suggests that movement time and abnormalities in color vision may be more closely tied to dopaminergic dysfunction than reaction time.

Movement time has been successfully used as an outcome measure in surgical trials for PD. These studies typically have limited numbers of subjects making a sensitive outcome measure more attractive. The effectiveness of deep-brain stimulation of the subthalamic nucleus on bradykinesia has been examined by the analysis of movement time. After turning off stimulation, movement time progressively increases, reaching a plateau after ~30 min. Upon pulse generator reactivation, movement time shows a dramatic shortening, already significant after 2 min. In these studies, a significant correlation between movement time and the severity of PD exists. Reaction time and movement time have been used to gauge the change in motor performance in patients with PD who received embryonic tissue implants. The physiological measures detected significant changes in patients undergoing embryonic nigral cell implants and correlated directly with clinical outcome measures. In this model, reaction time and movement time analysis could document subtle changes in motor performance over time, suggesting utility as outcome measures in therapeutic trials of PD.

Movement Time – Other Conditions

Movement time has been studied in essential tremor patients. Using a test paradigm around metacarpophalangeal, wrist, elbow, and shoulder joints, there was no significant difference in movement time between essential tremor and normal controls.

Fast voluntary neck movements have been studied in patients with cervical dystonia before and after therapy with botulinum toxin type-A (BoNT-A). Before receiving BoNT-A, patients perform pro- and antidystonic movements with lower peak angular velocity than control subjects. Prodystonic movements show a reduced angular amplitude, and antidystonic movements show an abnormally long movement time. Flexion and extension movements require longer movement times, but other kinematic variables are normal. After BoNT-A injections, prodystonic movement amplitude and antidystonic movement peak angular velocity increase, whereas flexion and extension movement times remain unchanged.

In Huntington's disease, a series of methods to measure voluntary movement (reaction time, tapping speed, and movement time) have been studied. Despite identifying several abnormalities, none are specific to Huntington's disease.

Conclusion

Movement time is a quantifiable measure of subtle bradykinesia that may have utility both in clinical and research settings. It is a better predictor of dopaminergic responsiveness in PD than the reaction time. Movement time measures are very task specific, and care must be taken to standardize the recording protocol.

See also: Akinetic-Rigid Syndrome; Bradykinesia; Huntington's Disease; Intra-Individual Variability in Movement; Parkinson's Disease: Definition, Diagnosis, and Management; Reaction Time.

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MPTP

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Glossary

Levodopa-induced dyskinesias (LIDs) – Abnormal involuntary movements such as tics, chorea, or spasm or distortion of voluntary movements which are a side effect of L-DOPA therapy.
MPP+ (1-methyl-4-phenylpyridinium) – The positively charged fully oxidized metabolite of MPTP.
MPTP (1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine) – A small molecule neurotoxin that selectively damages nigrostriatal dopamine neurons and induces parkinsonism in humans and nonhuman primates.
Parkinson's disease – A neurodegenerative disease that involves loss of nigrostriatal dopamine neurons and that is characterized clinically by bradykinesa, rigidity, and tremor.

Definition and History

MPTP (1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine) is a small molecule that selectively damages nigrostriatal dopamine neurons and induces parkinsonism in humans and nonhuman primates. Since 1982, when the parkinsonogenic effects of MPTP were first recognized in humans, this simple chemical and the experimental models that it made possible have provided transformative insights into our understanding of the etiology, natural history, and treatment of Parkinson's disease. In this entry, we review the history of MPTP and its impact on PD research and focus on how experimental studies in MPTP-treated monkeys have lead to new treatments for PD. Unlike the development of many models of human disease that exploit the toxicity of a chemical agent in experimental animals, the effects of MPTP were first observed as an outbreak of parkinsonism among relatively young drug-abusers in northern California in 1982. This outbreak was traced to the intravenous use of a street drug produced by a clandestine laboratory. The laboratory operator was synthesizing, 1-methyl-4-phenyl-4-propionoxy-piperidine (MPPP), a synthetic opiate related to the narcotic analgesic meperidine. MPTP is a by-product of the process used in the synthesis of MPPP. Probably as a result of using either too much heat or acid, the clandestine chemist managed to produce a batch of drug that was primarily made up of MPTP. While the target compound, MPPP, had been selling briskly as 'China White' or 'synthetic heroin,' when this 'bad batch' reached the streets, its users rapidly developed a series of untoward effects, the worst of which was enduring and profoundly disabling parkinsonism. On the basis of the analysis of heroin bindles used by these patients, their clinical picture, and an autopsy study of the earlier reported case in which the offending agent had never been clearly identified, we concluded that MPTP was the culprit and that it was selectively toxic to the substantia nigra: a conclusion that has subsequently and repeatedly been confirmed in nonhuman primates, as well as in other species, including mice and even invertebrates. As a result, this discovery opened up an entirely new research era in Parkinson's disease. It is important to note that it did not emerge from a research laboratory, but rather from clinical observation, reminding us of the power of clinical observation when it comes to advancing medical research.

As the effects of MPTP occurred in a human cohort, it was possible to compare directly the clinical, physiological, therapeutic, and eventually the neuropathological features of MPTP-induced parkinsonism in humans with those seen in the idiopathic disease. These rare, if not unprecedented, circumstances provided two important insights. The first was that the key motor features (bradykinesa, rigidity, and tremor) can result solely from a lesion of the substantia nigra. This conclusion is based on two findings: (1) our patients with MPTP-induced parkinsonism exhibited these cardinal motor features of PD, including rest tremor and (2) clear-cut pathologic evidence that MPTP induces a selective lesion of the zona compacta of the substantia nigra in humans. The observation regarding tremor resolved long-standing and considerable controversy over the neuroanatomic origins of rest tremor and whether a purely nigral lesion can induce it. Interestingly, the results of recent physiological studies in a case of MPTP-induced human parkinsonism undergoing deep brain stimulation (DBS) were consistent with recordings from MPTP-treated primates and humans with PD, thus providing further validation for the MPTP model in the study of the neurophysiology of the nigrostriatal dopaminergic deficit in PD. Furthermore, DBS in this patient provided similar clinical benefit as what is usually seen in patients with idiopathic PD. Ironically, much of the preclinical work that led to the development of DBS of the subthalamic nucleus came from the MPTP primate model, which in turn was based on the original observations in these human cases. It is also

interesting to note that our MPTP patients demonstrated mild cognitive deficits seen in nondemented patients with the disease and facial seborrhea, suggesting that these features are dopaminergic as well.

A second observation in patients with MPTP-induced parkinsonism relates to the side effects of therapy. Although the response of our patients to dopaminergic therapy was dramatic, they rapidly experienced all of the side effects typically encountered with chronic levodopa treatment. For example, a short-duration response was seen almost immediately after starting treatment and dyskinesias were encountered within days to weeks of initiating treatment. It is possible that the relative youth of these patients could be responsible for the early onset of dyskinesias, since these are well known to begin earlier in younger idiopathic patients. However, the short-duration response is not known to be age-dependent, suggesting that this phenomenon is related to disease severity: an observation that is consistent with the hypothesis that diminishing storage at the level of the synaptic vesicles may be a key feature underlying this phenomenon.

Neuropathologic studies have been conducted on three of MPTP cases, who subsequently died. The time from exposure to MPTP until death in these three cases ranged from 3 to 14 years. Surprisingly, in each of these individuals, there was neuropathologic evidence of active, ongoing nerve cell death. Specific findings included microglial proliferation and clustering with clear-cut neuronophagia, and in two of the cases, abundant extraneuronal melanin. The mechanism by which a fixed insult might induce and maintain an ongoing active neuropathologic process is presently not clear, but might include enhanced oxidative stress from increased dopamine turnover in remaining dopaminergic neurons, ongoing effects propagated by protein misfolding, or an active inflammatory process that has become self-sustaining. Whatever the underlying cause(s) of these observations, they may be precedent setting, as they provide compelling evidence that a time-limited exposure to an exogenous toxin can induce an active neurodegenerative process that can persist for many years.

MPTP-Induced Parkinsonism in Nonhuman Primates: A Proving Ground for New Therapy

The epidemic of MPTP-induced parkinsonism in humans gave birth to an immediate quest to use this neurotoxicant to create new animal models for PD. Indeed, the drug has been given to organisms ranging from baboons to yeast to study its biological effects and to produce PD models. As would be expected, the first studies were in rats, which at the time was the primary model for neurobiological study. However, this animal turned out to be completely refractory to the effects of the toxin. Since that time, the models that have been most widely used are the mouse and the nonhuman primate, and most of what we know about the mechanism of action of MPTP has come from these studies. Mice and monkeys are quite different in their response to MPTP. While mice develop significant nigrostriatal damage, they do not develop the full-blown parkinsonism, whereas MPTP-lesioned monkeys faithfully reproduce the motoric features of idiopathic PD. For this reason, the development of pharmacological, surgical, and other symptomatic treatments for PD has relied on the MPTP-lesioned monkey.

Dopamine Agonist Therapy

While dopamine agonists of the ergoline class were in use at the time of discovery of MPTP, investigation of dopaminergic receptors in the MPTP-lesioned monkey greatly expanded our insight into the role of receptor subtypes involved in nigrostriatal denervation and behaviorally overt parkinsonism and served as a 'proving ground' for many of the nonergoline dopamine agonists introduced into clinical practice in the past 2 decades. D2 receptors are consistently upregulated in MPTP-treated monkeys, suggesting that the brunt of presynaptic damage is proximal to these receptors. Consistent with these changes in D2 receptors, D2 and D2-like agonists (D2, D3, D4) have been found to reliably reverse parkinsonism in MPTP-monkeys and PD patients. The fate of D1 receptors in MPTP-treated monkeys has been variable, that is, either unchanged, increased, or decreased after nigrostriatal denervation. The anti-parkinsonian effects of selective D1 agonists have been moderate and variable in MPTP-treated primates. These preclincal findings have been predictive of the clinical outcomes of investigational D1 agonists. Thus, the MPTP-treated monkey work has led to the emergent view that the pathophysiology of Parkinson's disease may relate primarily to the D2 like dopamine receptors. The MPTP-lesioned primate has played a key role in the development of most of the dopamine agonists in current use, including ropinerole, rotigotine, and pramipexole.

Levodopa-Induced Dyskinesias (LIDs)

Dopamine replacement (L-DOPA) and agonist therapy are effective at reversing the majority of motoric deficits early in PD. With chronic use, a variety of motor complications occurs, including abnormal involuntary movements (dyskinesias) and these present a challenge to the long-term management of therapy. As expected from the experience with MPTP-exposed humans, MPTP-lesioned monkeys quickly developed classic, levodopa-induced dyskinesias (LIDs) virtually identical to those

seen in humans with PD. This model has become the 'gold standard' for investigating dyskinesias and the ability to faithfully model LIDs has led to an intensive search for agents to treat LIDs. The more severe the lesion, the more likely animals are to develop dyskinesias, lending credence to the hypothesis that the development of dyskinesias in PD is related to severity of disease. Another potentially important observation is that these animals never develop dyskinesias on their first dose of levodopa, thus confirming the need for so-called 'priming.' The availability of this model provides an opportunity to dissect the changes that occur during 'priming,' which may itself lead to an understanding of the cause(s) of dyskinesias.

Dopamine agonists and LIDs

D1- and D2-like agonists both produce dyskinetic movements in MPTP-lesioned monkeys, but D1 and D2 agonists together cause more prominent dyskinesias than either alone. This observation is consistent with the 'mixed' agonism of levodopa, Studies in the MPTP-lesioned primate showing that D2 agonists are less likely than levodopa to produce dyskinesias lead to the widespread clinical practice of starting with agonist therapy in order to forestall the onset of dyskinesias and motor fluctuations.

The greater likelihood that pulsatile rather than continual administration of agonists to MPTP-lesioned monkeys is associated with dyskinesia development has led to the testing of constant delivery forms of dopamine agonists including the percutaneous administration (patch) of rotigotine, subcutaneous administration of apomorphine, and modifications of L-DOPA itself, including extended release formulations or new routes of delivery such as duodenal infusion. A number of new drugs are L-DOPA prodrugs that promise more sustained absorption and stable levels of L-DOPA. Additional approaches have sought pharmacokinetic control over L-DOPA concentrations by modulating L-DOPA metabolism with the catechol-*O*-methyltransferase inhibitor entacapone. Each of these has been pioneered in the preclinical monkey model before introduction to clinical practice.

Serotonergic agonists and LIDs

Further, serotonin terminals have been shown to take up and decarboxylate L-DOPA and potentially store and release the dopamine formed and this process has been implicated in LIDs. Combinations of 5HT1A and 5HT1B agonists have been reported to reduce LIDs without diminishing the antiparkinsonian effects of L-DOPA in the MPTP monkey. A number of other clinical candidates with more complex pharmacological profiles that include 5HT agonism among their properties have been tested in this model as well. While to our knowledge no pure serotonergic agonists have been studied in the clinic, drugs such as sarizotan, quetiepine, and clozapine that possess 5HT activity in their pharmacological profile have all followed this pathway from monkey to man with somewhat mixed results. Clozapine appeared efficacious, while quetiepine and sarizotan failed to show efficacy in the larger clinical trials. While the complex pharmacology of these agents (both clozapine and quetiepine are D2 antagonists and possess 5HT2, histamine, and adrenergic action in their profile) 'muddies the waters' as to the role of serotonin, future trials with more selective agents may shed light on this. ACP-103 (primavanserin), a selective 5HT2A inverse agonist, reduced LIDs in the monkey model and is currently under study in a clinical trial.

Glutamate receptors and LIDs

Recently, there has been increasing interest in the possibility that both NMDA and AMPA subtypes of glutamate receptors might be involved in LIDs. Altered phosphorylation of these receptors and downstream changes in their function might produce enhanced glutamatergic transmission and drive dyskinesias, possibly through increased D1 activity.

Perhaps the most convincing evidence of the antidyskinetic effects of NMDA antagonists and the utility of the MPTP-lesioned monkey comes from the clinical use of amantadine to treat dyskinesias in patients and the observation that amantidine reduces dyskinesias by 40% without increasing motor impairment in MPTP-lesioned monkeys receiving high-dose L-DOPA monkeys. Other nonselective NMDA receptor antagonists, including currently available compounds such as dextromethorphan, attenuate LIDs in the MPTP-lesioned monkeys, and several have been studied with variable success in phase II clinical trials.

Nicotinic receptors and LIDs

Nicotine has long been of interest to those investigating PD, since abundant studies have established that smokers are significantly less likely to develop PD than nonsmokers. One of the most recent and interesting findings that have emerged from the MPTP-monkey model of dyskinesias is the observation that nicotine reduces LIDs in monkeys with MPTP-induced parkinsonism. Several small clinical studies examining the effect of nicotine patch and gum formulations on motor symptoms in PD have been reported. However, the results have been conflicting and none of the studies to date has specifically examined the effect of nicotine on dyskinesias. Clinical trials to examine this indication are in the planning stages.

Deep Brain Stimulation (DBS) and the Subthalamic Nucleus (STN)

The MPTP-lesioned monkey has also opened a window into a better understanding of the basal ganglia circuitry and the neurophysiologic changes that occur in the

presence of parkinsonism induced by a dopaminergic nigrostriatal deficit. One of the seminal observations using the MPTP-primate model is that, in the presence of a nigrostriatal deficiency, there is a decrease in striatal inhibitory output to the STN. As the output of the STN to the internal segment of the pallidum is excitatory, the result appears to be an overstimulation of the globus pallidus, thus altering outflow to the thalamus and cortex. Lesioning the subthalamic nucleus results in the reversal of akinesia, rigidity, and tremor in MPTP-treated primates and the subsequent demonstration that high-frequency stimulation of the STN in MPTP-lesioned monkeys reversed parkinsonism led to the successful introduction of DBS: a procedure that is now widely used to treat patients with PD.

Neurotransplantation

The MPTP-lesioned primate, with its full array of parkinsonian features, has proved to be an excellent testing ground for the effectiveness of this approach. Intraputaminal implantation of fetal mesencephalic tissue in this model provided the feasibility, efficacy, and safety data to translate this approach into human trials. However, while human open label studies have shown some encouraging results, including transplanted neuronal survival and some clinical improvement, randomized, sham-surgery controlled studies have not demonstrated the anticipated benefit. Of note is that the fetal grafting procedure was used on three human cases of MPTP-induced parkinsonism and that all the three subjects experienced substantial improvement. These individuals may have done slightly better than patients with the idiopathic disease because of their young age or because they have more selective lesions of the substantia nigra. Nonetheless, the MPTP-lesioned monkey will remain the standard for developing modifications of the surgical procedures (e.g., nigral delivery of grafts) as well as improvements in substrates for cell therapy such as stem cells.

Gene Therapy

MPTP-lesioned monkeys have provided a rich proving ground for various approaches to in vivo gene therapy. At least 3 separate 'therapeutic genes' (encoding for): (1) aromatic amino acid decarboxlyase (AADC); (2) the growth factor neurturin (CERE120); and (3) glutamic acid decarboxylase (GAD)) have been studied with the goal of greatly increasing the expression of their target proteins in the brain. In each case, the genes are transfected into either the putamen (AADC, CERE120) or STN (GAD) using an adeno-associated viral vector (AAV); in each case the preclinical results in the MPTP-lesioned monkey have provided sufficient proof of concept data to advance to human trials. While it is still too early to predict the ultimate outcomes of these approaches in patients, the successful translation of the approach has provided an avenue to evaluate and deliver candidates for gene therapy.

Mechanism of Action and the Advent of Neuroprotective Therapy

The striking similarities between the effects of MPTP and the idiopathic disease in humans, and the fact that the toxin and the disease both targeted the dopaminergic cells of the substantia nigra raised the possibility that the processes involved in MPTP-induced cell death might mirror, or shed light on, the underlying processes that occur in the disease produced tremendous interest in exploring its mechanism of action. Several of the key steps in a concerted process that is ultimately responsible for selectivity and cell death were quickly elucidated, with MAO-mediated biotransformation of MPTP, the dopamine uptake system, and mitochondrial respiration emerging as central players. This information produced the experimental evaluation of a range of strategies designed to protect against MPTP toxicity that has now been tested at almost every level of biologic complexity, ranging from tissue culture to patients with PD. Indeed, it would not be an overstatement to say that these studies ushered in a new age of research on 'neuroprotection' or disease-modifying strategies aimed at stopping or slowing the progress of PD. While there have been numerous studies of putative neuroprotective agents in the MPTP primate model, we focus on those that have lead to clinical trials for idiopathic PD.

The Biotransformation of MPTP

The first investigations to define the distribution and fate of MPTP in primates revealed that the parent compound was short lived and most of it was converted into the metabolite MPP+ and that high and persistent concentrations of MPP+ were present in the nigrostriatal regions of the brain. Interestingly, although the administration of MPTP to mice also produces high striatal concentrations of MPP+, this metabolite is rapidly cleared from the CNS: an observation that may explain the fact that mice are less sensitive to toxin than primates. Perhaps one of the most surprising and interesting observations was that the conversion of MPTP to MPP+ is mediated by monoamine oxidase B (MAO B). Investigators wasted little time demonstrating that blocking this enzyme with MAO B inhibitors prevented both dopamine depletion in mice and nigral cell degeneration in primates.

These observations had several exciting implications, both practical and theoretical. First, the chemical structure of the metabolite MPP+ was very similar to that of

paraquat, a widely used and highly toxic herbicide, triggering a renaissance of research on possible environmental risk factors for PD. Second, the role of MAO in the bioactivation of MPTP stimulated a renewed interest in MAO and its role in the human nervous system. Generally considered a housekeeping enzyme, these new data raised the possibility that MAO might play a role in the bioactivation of other possible agents and that the inhibition of MAO B might slow or stop the progression of PD: a possibility suggested by previous clinical studies with the MAO B inhibitor selegiline. Testing this hypothesis in a clinical trial was especially attractive, because selegiline had already been approved for human use in Europe. For these reasons, we initiated a prospective controlled trial in patients with PD to assess the effect of selegiline on disease progression. Shortly thereafter, planning for a much larger trial was initiated that included an additional arm to measure the effect of vitamin E on disease progression. Newly diagnosed patients, who did not yet require L-DOPA therapy, were enrolled and the primary endpoint was the need for L-DOPA. In addition, the rate of progression was measured using standard rating scales for PD. As far as we are aware, this was the first prospective trial evaluating a therapeutic intervention to slow or halt disease progression. In 1988, the results of both studies showed that the need for L-DOPA therapy could be delayed nearly twofold with the initiation of early selegiline treatment in de novo patients. Furthermore, based on clinical evaluation, the drug appeared to slow disease progression by about 50% and this effect persisted after a 2 month 'wash out' of selegiline. Subsequent recognition that a small but statistically significant symptomatic benefit was derived from selegiline was seen by some as a confounding factor that might mask disease progression and that the 2 month wash out was inadequate to rule out this possibility.

The recent clinical development of a second generation MAO-B inhibitor for Parkinson's disease, rasagiline has renewed interest in MAO-B inhibitors. While approved for both the early and late treatment of PD, clinical studies are now also evaluating its neuroprotective properties, using a novel 'delayed start' design. This design was chosen to address the two issues that marred the selegiline study as described earlier: (1) the symptomatic benefit masking possible disease modifying effects and (2) the washout period. According to this design, one group of subjects receives active drug from the beginning of the study, while the other group is not exposed to the drug until after several months. If the investigational drug has only symptomatic effects, then the delayed start group should quickly 'catch up' with the first (early start) group. On the other hand, if the drug indeed has neuroprotective properties, then the delayed start group should never completely catch up. Preliminary analyses suggest that this indeed appeared to be the case in the rasagiline study. Importantly, a much larger study has now been completed using this same designed, the results of which should be announced shortly to see whether these results can be replicated.

MPP± and Dopaminergic Uptake

While the MAO-B-mediated conversion of MPTP to MPP+ was the first step and required for toxicity, it did not explain the selectivity for dopaminergic neurons. This would come, at least in part, with the observation that MPP+ (but not MPTP) was a substrate for the dopamine transporter – thus the nerve cells own uptake system proved to be the mechanism for the selective accumulation of the toxin within dopaminergic neurons. It was quickly shown that inhibitors of the dopamine uptake transporter protected against MPTP toxicity in rodents, but protection in primates was more difficult to achieve, probably because of the long half-life of MPP+ in this species and difficulties in maintaining constant uptake inhibition with available agents. Perhaps for this reason there has yet to be an evaluation of dopamine uptake inhibitors in a neuroprotective trial in PD.

If one considers this aspect of MPTP toxicity, it could be argued that it exemplifies an unfortunate 'alignment of the stars,' in which several factors combine to predispose the dopaminergic system to damage. This is particularly true, since we now know that the MAO B generation of MPP+ occurs primarily in glia. Thus, MPTP must enter the brain and gain access to glia, which then convert a nontoxic substance into a toxin that cannot be further metabolized or conjugated, but rather is retained within the brain by virtue of its positive charge (see **Figure 1**). Next, the dopamine

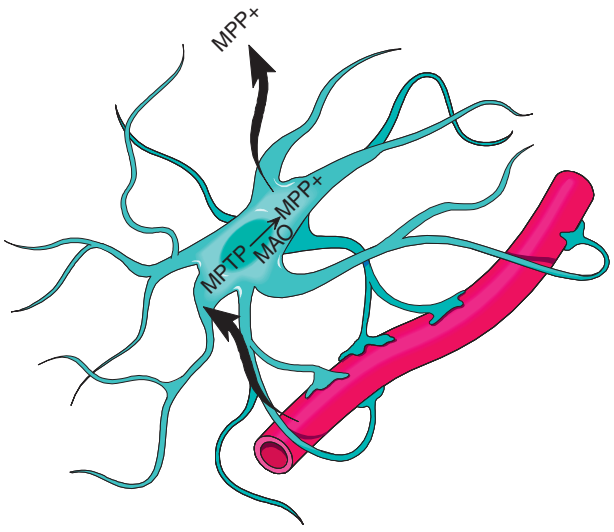

Figure 1 Glial cell: After absorption, circulating MPTP crosses the blood brain barrier by diffusion and enters the glial cell. MPTP is oxidized to MPP+ by monoamine oxidase B within the glia and diffuses into the extracellular space.

uptake carrier mistakes this toxic metabolite for the normal substrate (i.e., dopamine) and transports it intracellularly, where it causes cell death (this has been referred to as a Trojan horse effect). One of the more interesting questions to address is "is this remarkable sequence of events a rare aberration?" or "is it a much more common scenario that plays a role in other human neurodegenerative diseases as well?".

MPP± and Mitochondria

While the multistep mechanism described earlier explains the means by which MPTP selectively delivers high concentrations of a toxic product to dopaminergic neurons, there is still the question of what is the ultimate 'coup de grace' that kills the cell. MPP+ has a number of potentially toxic properties that might be involved but most studies point toward a direct effect on mitochondria. MPP+, by virtue of its positive charge is driven by the energy-dependent gradient across the mitochondrial membrane to accumulate within mitochondria. There, MPP+ inhibits Complex I of the electron transport chain and this derangement leads to the potential production of reactive oxygen species and a rapid loss of cellular energy as a consequence of ATP depletion (see **Figure 2**). These observations led to the search for similar deficits in PD itself, where a complex I deficiency was in fact found. Indeed, the mitochondrial hypothesis of PD, which was largely precipitated by MPTP-related discoveries, continues to be one of the most viable hypotheses regarding potential mechanisms that may underlie cell death in PD.

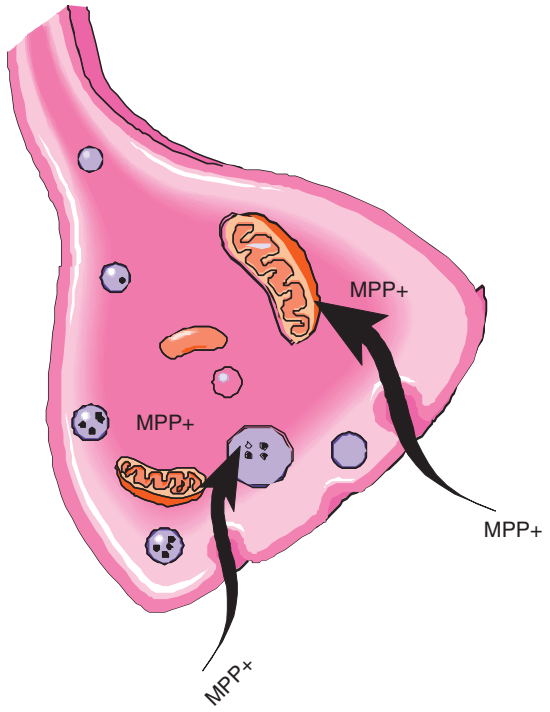

Figure 2 Dopaminergic neuron: MPP+ is actively taken up by dopaminergic neurons. Once inside the cell, it is concentrated by mitochondria where it inhibits complex 1 leading to derangement of electron transport and loss of ATP production.

While much is still unknown, there is near-universal agreement that a complex I deficit is present in the substantia nigra of patients with PD and that the deficit is also present in platelets. This aspect of the MPTP story has again launched a number of experimental studies targeting mitochondrial function and several clinical trials in PD are underway. Perhaps since most of the agents under consideration are nutrients and are expected to have an acceptable safety profile for human use, few studies have been done in primates and most of the preclinical data have been generated in MPTP-treated mice. Nonetheless, there are several large and long-term clinical trials examining agents such as creatine, which may increase phosphocreatine buffering against ATP depletion, and coenzyme Q10, which would be expected to improve or supplement the function of mitochondrial complex I. Both of these agents have shown protection against the effects of MPTP in mice.

Conclusion

Since recognition of the biological effects of MPTP, this small molecule neurotoxin has propelled an extensive array of scientific research in Parkinson's disease. Studies have encompassed the full spectrum of disciplines from molecular biology to epidemiology and have yielded insights into both the disease process and putative agents for its treatment.

See also: Deep Brain stimulation; Dopamine; Dopaminergic Agonists in Parkinson's Disease; Dyskinesias; Dyskinesias: Animal Models; Levodopa; Mitochondrial Dysfunction; Monoamine Oxidase Type B Inhibitors; Transplantation.

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Multiple System Atrophy

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Glossary

Camptocormia – An abnormal flexion of the thoracolumbar spine during standing and walking that abates in the recumbent position.
Dysautonomia – A medical term utilized for a group of complex conditions that are caused by a dysfunction of the autonomic nervous system.
Multiple system atrophy-parkinsonian-type (MSA-P) – Implies parkinsonism with or without some degree of cerebellar dysfunction.
Multiple system atrophy-cerebellar type (MSA-C) – Indicates primarily cerebellar defects with minor degrees of parkinsonism.
Red-flags – Clinical clues that could distinguish between MSA-P and PD in the early differentiation of two entities.

Definition and History

The term multiple system atrophy (MSA) was introduced by Graham and Oppenheimer in 1969 to denote a neurodegenerative disease characterized clinically by any combination of autonomic, parkinsonian, cerebellar, or pyramidal symptoms and signs, and pathologically by cell loss and gliosis in the basal ganglia and olivopontocerebellar system. Previous cases of MSA were reported under the terms of olivopontocerebellar atrophy (OPCA), Shy–Drager syndrome (SDS), and striatonigral degeneration (SND). Recent studies describing the patterns of pathological involvement of gray matter are generally an extension of the original accounts, noting neuronal loss and gliosis in the striatum, substantia nigra, locus ceruleus, inferior olivary nucleus, pontine nuclei, cerebellar Purkinje's cells, intermediolateral cell column in the thoracic spinal cord, and Onuf's nucleus in the sacral cord. Depending upon which part of the central nervous system is affected first, MSA may present in different ways. According to the most recent diagnostic criteria, MSA is divided into two main clinical categories: (1) MSA-parkinsonian type (MSA-P) which implies parkinsonism with or without some degree of cerebellar dysfunction (SND) and (2) MSA-cerebellar type (MSA-C) which indicates primarily cerebellar deficit with minor degrees of parkinsonism (OPCA). In both conditions, autonomic failure is a frequently associated manifestation of the clinical spectrum of the disease.

Pathogenesis

The discovery of glial cytoplasmic inclusions (GCIs) and α-synuclein immunostaining as a sensitive marker of MSA is the major milestone in the definition of MSA as a clinicopathological entity. Concentration of GCIs in MSA in cerebral structures is variable (**Table 1**). How the expression and aggregation of α-synuclein in glial cells affects their biology as well as the glia–neuron interactions, which might be a critical step in the

Table 1 Concentration of glial cytoplasmic inclusions (GCI) in MSA

High concentration	*Low concentration or absence*
Primary motor cortex	Visual pathways
Supplementary motor cotex	Auditory pathways
Putamen: dorsolateral portion	Olfactory system
Caudate: dorsolateral portion	Somatosensorial system
Globus pallidum	Limbic areas
Internal and external capsula	
Substantia nigra	
Basis pons	
Medial cerebellar peduncle	
Cerebellar white matter	

pathogenesis of all α-synucleinopathies, is not yet elucidated. Whether environmental factors influence α-synuclein aggregation, and the survival of glial and neuronal cells remains unknown as well. MSA is a sporadic disease, and no confirmed familial cases of MSA have been described yet; notwithstanding, it is conceivable that genetic factors may play some role in the etiology of the disease.

Clinical Picture

MSA-P

MSA patients may present with parkinsonism that often responds poorly to levodopa. This has been identified as the most important early clinical discriminator of MSA and PD, although a subgroup of MSA patients may show a good, but usually short-lived, response to levodopa. Bradykinesia, rigidity, postural tremor as well as disequilibrium, and gait unsteadiness characterize parkinsonism associated with MSA. Jerky postural tremor, and less commonly tremor at rest may be superimposed and, frequently, patients exhibit a characteristic quivering high-pitched mixed dysarthria. It has been suggested that a symmetrical atremulous picture might distinguish MSA-P from PD. However, motor disturbance was asymmetrical in 74% of patients in a clinical series, and unilateral at onset in 47% of the literature cases. Also, some sort of tremor is present in 64–80% of cases and, tremor present at rest is observed in 29–40% of cases. Even so, a classical pill-rolling resting tremor may be observed in only 7–9% of subjects. Therefore, the differential diagnosis of MSA-P and PD may be quite difficult in the early stages due to a number of overlapping features such as rest tremor or asymmetrical akinesia and rigidity. Levodopa-induced dyskinesia affecting orofacial and neck muscles occurs in 50% of MSA-P patients, sometimes in the absence of motor benefit. This feature seems typical of MSA.

MSA-C

Progressive ataxia may also be a presenting feature of MSA, and this variant of MSA appears to be more common than the parkinsonian variant in Japan compared to Western countries.

The cerebellar disorder comprises gait ataxia, limb kinetic ataxia, and scanning dysarthria as well as cerebellar oculomotor disturbances. Quite common is a wide-based ataxic gait; however, a subgroup of patients present with narrow-based unsteady gait due to more marked impairment of the postural reflexes. The finding of a mixed dysarthria with combinations of hypokinetic, ataxic, and spastic components is consistent with both the overall clinical and the neuropathologic changes of MSA.

Dysautonomia

Dysautonomia is a characteristic of both MSA subtypes, primarily including urogenital and orthostatic dysfunction. Urogenital dysfunction manifesting with urinary incontinence (71%) or retention (27%), often early in the course or as presenting symptoms, is very frequent. In men, the urological symptoms of pollakiuria, urgency, nicturia, and incontinence together with hesitancy and incomplete emptying or chronic retention may simulate those of prostatic outflow obstruction. Early impotence is virtually universal in men with MSA. In a series of 62 MSA patients, impotence occurred in 96% of the men and was the first symptom alone in 37%. In addition, MSA patients may note severe constipation and hypo or anhydrosis.

Orthostatic dysfunction characterized by recurrent syncopal attacks is commonly regarded as a typical feature of MSA. However, severe orthostatic hypotension with recurrent (more than three) syncopes was only reported in 15% of subjects whereas postural faintness was present, but only to a mild or moderate degree, in up to 53% of cases. The analysis of a detailed questionnaire and autonomic function tests in a series of 121 patients with clinically diagnosed MSA showed that urinary symptoms (96%) were more common than orthostatic symptoms (43%). Orthostatic hypotension is frequently associated with impaired or absent reflex tachycardia upon standing and, dopaminergic drugs may provoke or worsen its manifestation.

Pyramidal Signs

Although pyramidal signs may be elicited in up to 61% of MSA patients, obvious spastic paraparetic gait or significant pyramidal weakness should cast doubt upon the clinical diagnosis of MSA.

Other Clinical Features

MSA-P can be difficult to differentiate from idiopathic PD because of the lack of clear pathognomic features between the two disease states. Besides the poor response to levodopa, and the additional presence of pyramidal or cerebellar signs or severe autonomic failure as major diagnostic clues, certain other features may either raise suspicion of MSA, or at least suggest that one might not be dealing with PD. Diagnostic clues that distinguish between the two entities could assist in the early differentiation of MSA-P from PD in a clinical setting. A recent multicenter study by the European MSA Study Group (EMSA-SG) evaluated the diagnostic role of potential 'red flags' in MSA-P versus PD in order to better raise clinical suspicions of MSA-P. The initial list of potential

'red-flags' included the following items: instability and early falls, rapid progression of the disease, camptocormia (prolonged episodes of forward trunk flexion), Pisa syndrome (prolonged episodes of lateral trunk flexion), orofacial dystonia, disproportionate antecollis, contractures of joints, jerky tremor, diurnal and nocturnal inspiratory stridor, severe dysphonia, severe dysarthria, severe dysphagia, sleep dysfunction (including REM sleep behavior disorder and sleep apnea), emotional incontinence, and history of hypertension. Red-flags signs were then further grouped into six categories: early instability, rapid progression, abnormal postures, bulbar dysfunction, respiratory dysfunction, and emotional incontinence. All these categories were significantly found to occur more frequently in MSA than in PD. Larger studies of the identified red flags in patients with possible MSA-P would be useful to further establish the predictive value of this system.

Progression

MSA is a chronically progressive disease characterized by the gradual onset of neurological symptoms and rapid accumulation of disability reflecting involvement of the systems initially unaffected. Thus, patients who present initially with extrapyramidal features commonly progress to develop autonomic disturbances, cerebellar disorders, or both. Conversely, patients who begin with symptoms of cerebellar dysfunction often progress to develop extrapyramidal or autonomic disorders, or both. Patients whose symptoms initially are autonomic may later develop other neurological disorders. In a study looking at the progression of Hoehn and Yahr (HY) stages in different parkinsonian disorders, patients with PD showed significantly longer latencies to each HY stage than patients with atypical parkinsonian disorders such as MSA. In fact, development of a HY-III within 1 year of motor onset accurately predicted MSA. Once patients with PD and MSA became wheelchair-bound, both had equally short survival times. Although therapeutic options are limited at present, there is a real hope for a radical change of our approach to this devastating illness. A few trials with possible neuroprotective agents are already ongoing.

See also: Autonomic Dysfunction; Camptocormia; Glial Cytoplasmic Inclusions; Olivopontocerebellar Atrophy; Shy–Drager Syndrome; Striatonigral Degeneration.

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Multiple System Atrophy: Animal Models

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Glossary

3-NP (3-nitropropionic acid) – A mycotoxin and an inhibitor of succinate dehydrogenase that induces selective neurodegeneration of striatal GABAergic medium spiny neurons.

6-OHDA (6-hydroxydopamine) – A neurotoxin that is closely related to dopamine and is readily taken into dopaminergic and noradrenergic neurons via their normal reuptake mechanism, whereupon it destroys the neuron terminals, causing loss of function.

MPTP (1-methyl 4-phenyl 1,2,3,6-tetahydropyridine) – A neurotoxin that causes permanent symptoms of Parkinson's disease by killing dopaminergic neurons in the substantia nigra pars compacta.
Multiple system atrophy – An adult onset neurodegenerative disorder with features of levodopa resistant parkinsonism, cerebellar ataxia, pyramidal signs, and autonomic failure.
Quinolinic acid (QA) – An *N*-methyl-D-aspartate receptor agonist that may cause selective excitotoxic cell death of striatal GABAergic medium spiny neurons.
Spinocerebellar ataxias – A group of autosomal dominant ataxic disorders caused by degeneration of the cerebellum and its afferent and efferent connections.

Neurotoxin Models of MSA

The first effort to model multiple system atrophy (MSA) in rodents occurred in 1996 with the unilateral double lesion rat model. Wenning et al. based the idea of reproducing striatonigral degeneration (SND) in rats by applying selective nigral and striatal neurotoxins. To do this, 6-hydroxydopamine (6-OHDA) is administered into the medial forebrain bundle to induce an almost complete lesion of the substantia nigra pars compacta (SNc), and is followed by intrastriatal injection of quinolinic acid (QA) into the ipsilateral striatum to target GABAergic medium spiny neurons of the striatum. The unilateral 6-OHDA lesion results in ipsilateral rotation to amphetamine-induced dopamine release and contralateral rotation to apomorphine (dopamine receptor agonist). Following the subsequent striatal lesion, amphetamine-induced ipsilateral rotation persists, but apomorphine-induced contralateral rotation is reduced or abolished. The unilateral double lesion rat model has demonstrated a complex interaction of nigral and striatal lesions depending on the lesion sequence. Further, it has reproduced the typical levodopa-unresponsive motor disability accompanied by levodopa-induced dyskinesia correlating with striatal FosB/ΔFosB upregulation in the remaining striatum.

The unilateral double lesion rat model has been widely used to test the neuroprotective and neurorestorative strategies for the parkinsonian variant of MSA (MSA-P). Riluzole, an antiglutamatergic drug, demonstrated striatal, but no nigral protection in the double-lesion rat model of MSA-P. Minocycline, which has been demonstrated to have a significant neuroprotective effect in Parkinson's disease (PD) and Huntington's disease (HD) models, was ineffective in the MSA-P rat model in terms of sparing neurons in the striatum and SNc; nevertheless, there was efficient suppression of microglial and astroglial activation. Finally, caspase inhibition failed to exert neuroprotection in the MSA-P rat model. Grafting in the double-lesion rat model has demonstrated that embryonic allografts of mesencephalic and striatal origin survive transplantation in SND with, however, poor dopaminergic reinnervation of the lesioned striatum. Yet, striatal grafts could restore the apomorphine-induced contralateral rotation suggesting a possibility to restore the dopamine response in the lesioned striatum of SND.

In an attempt to better reproduce the symmetric lesion pattern in MSA-P, selective neurotoxins have been used to develop systemic models of MSA-P with bilateral striatal and nigral lesions. 3-Nitropropionic acid (3-NP) and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) have been intraperitoneally injected in mice and primates in various sequence- and dose-paradigms. The studies confirm the complex integrative mechanisms that likely regulate the vulnerability of the striatum and SNc to cell death in MSA-P. Again, neuroprotective studies with riluzole provided limited 'neuronal rescue' with subtle motor improvement in the systemic MSA-P mouse model.

In conclusion, all neurotoxin models, whether stereotaxic or systemic, reproduce the neuronal cell loss in the striatum and SNc, and thus model the SND pathology of MSA-P. These models are useful to study the neuronal circuitry interactions with possible pathogenic contribution in the striatonigral system as well as to explore therapeutic approaches for neuroprotection. The neurotoxin double lesion rodent models prove to be valuable preclinical tools for testing neurotransplantation with restoration of dopamine response as a possible strategy in MSA treatment.

Transgenic Models of MSA

In 2000, Zuscik et al. suggested that overexpression of α_{1B}-adrenergic receptors might cause MSA. Overexpression of α_{1B}-adrenergic receptors in transgenic mice induced apoptotic neurodegeneration of SNc with a levodopa responsive Parkinson-like motor disorder, autonomic dysfunction, and α-synuclein inclusion formation. However, the authors also observed recurrent grand mal seizures, which are atypical for MSA. In addition, the pattern of brain lesions, beginning in cortex, hypothalamus, and cerebellum, and then progressing with age to encompass all brain areas, was only partially consistent with the neuropathology of MSA. For all these reasons as well as the limited information on the expression of adrenergic receptors in MSA, it has been difficult to correlate the disease

pathogenesis with the mouse model overexpressing α_{1B}-adrenergic receptors.

Further, after detecting specific oligodendroglial α-synuclein pathology in MSA, efforts have focused on reproducing glial cytoplasmic inclusions (GCIs) in transgenic mice with targeted overexpression of human α-synuclein in oligodendrocytes. The proteolipid protein (PLP) promotor was first used to express human α-synuclein in mouse oligodendrocytes. The transgenic α-synuclein demonstrated high insolubility and hyperphosphorylation at serine 129, like in human MSA. Behavioral studies indicated stride length shortening in these animals associated with mild loss of dopaminergic neurons in SNc and extensive region-specific and age-related microglial activation that at least partly mediates neurodegeneration. Later on, two other transgenic mouse models applied either the 2′, 3′-cyclic nucleotide 3′-phosphodiesterase (CNP) promotor or the myelin basic protein (MBP) promotor for oligodendroglial overexpression of α-synuclein; these models suggested that GCI-like pathology may initiate neurodegeneration associated with secondary axonal degeneration and mitochondrial dysfunction, yet without achieving the selective neurodegeneration pattern of MSA.

Further, transgenic mice with oligodendroglial α-synuclein pathology showed increased susceptibility to exogenous oxidative stress. When systemically applied, 3-NP led to severe SND with striatal shrinkage, loss of striatal GABAergic medium spiny neurons, loss of dopaminergic neurons in the substantia nigra pars compacta, and loss of dopaminergic nigrostriatal fibers. Additionally, 3-NP exposure of (PLP)-α-synuclein transgenic mice affected the cerebellar cortex, pons, and inferior olives, thereby reproducing human olivopontocerebellar atrophy (OPCA) with cerebellar shrinkage and loss of Purkinje cells, neuronal loss in pons and inferior olives. In addition to the transgenic oligodendroglial pathology with insoluble and hyperphosphorylated α-synuclein-positive inclusions, the degenerating areas included prominent astrogliosis and microglial activation. This has been the first complete phenotypic animal model of MSA which completely reproduces the selective neurodegeneration of the human disease by a combination of genetic predisposition (oligodendroglial α-synuclein expression) and induction of exogenous oxidative stress. It has recently proven to be successfully applicable in preclinical neuroprotection studies. High doses of rasagiline, a selective monoaminoxidase-B (MAO-B) inhibitor used in the symptomatic therapy of PD, achieved significant motor improvement in MSA mice. This correlated with neuroprotection at a striatonigral and olivopontocerebellar level, thereby suggesting rasagiline as a potent neuroprotective candidate for MSA. Furthermore, this combined MSA mouse model has proven to be a valuable tool for studying the role of oligodendroglial α-synuclein pathology, embryonic striatal graft survival, and functional activity as these will be important determinants in potential clinical trials of neurotransplantation in MSA patients.

In conclusion, despite their imperfection, the transgenic mouse models with oligodendroglial α-synuclein expression are useful tools that reveal pathogenic mechanisms related to GCI-like pathology. The combined α-synuclein+3-NP mouse model provides an excellent phenotypic system with both behavioral and neuropathological outcome parameters that may serve to evaluate novel therapeutic strategies for MSA.

Animal Models of SCAs

Spinocerebellar ataxias (SCAs) are a group of genetically determined neurodegenerative disorders. The experimental animal models typically target the affected gene either by transgenic or knockin approaches. SCA 1, SCA 2, SCA 6, SCA 7, and SCA 17 are members of the group of the polyglutamine (polyQ) diseases. However, excluding the CAG repeat, the gene products associated with these SCAs share no significant homology and in most cases, have partly unknown function. The use of animal models has been crucial to understand the disease pathogenesis in SCA 1 and the affected protein, ataxin-1. Numerous SCA 1 models have emphasized the importance of the subcellular localization of the mutated protein, the role of the nuclear inclusions, protein folding, as well as the clearance and posttranslational modification in the disease. SCA 2 is a neurodegenerative disorder caused by the expansion of an unstable CAG repeat in the ataxin-2 gene with a phenotype of progressive ataxia accompanied by slow saccadic eye movements. Transgenic mice expressing mutant ataxin-2 show progressive functional and pathological deficits, namely shortened stride length and abnormal rotarod performance combined with loss of Purkinje cells. SCA 7 is caused by CAG trinucleotide expansion within the coding region of the gene coding ataxin-7. All SCA 7 mouse models express full-length ataxin-7 with different sizes of polyQ expansion in different targeted neuronal types. In knockin and transgenic mice, widespread expression of mutant ataxin-7 in the CNS causes adult onset and progressive neurological phenotype usually with gait ataxia, motor incoordination, and premature death regardless of the phenotypic differences.

In summary, the animal models of SCAs allow insights into the regional susceptibility and main pathogenic mechanisms related to the various genetic mutations associated with SCA. Therapeutic strategies have now been addressed in animal models of SCA by overexpression of chaperones, such as HSP70, HSP40/HDJ1, DNAJ1, and HSP104, or reduction of acetylation through histone deacetylase inhibitors.

Acknowledgment

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See also: Multiple System Atrophy; Olivopontocerebellar Atrophy; SCA1; SCA2; SCA3, Machado–Joseph Disease; SCA4; SCA5; SCA6; SCA7, Spinocerebellar Ataxia with Macular Dystrophy; SCA8; SCA10; SCA11; SCA12; SCA13, 14, 15, and 16; SCA17; Spinocerebellar Ataxia Type 19, 20, 21, 22, 23, 26; Spinocerebellar Ataxias Genetics; Striatonigral Degeneration.

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Myoclonic Epilepsy with Ragged Red Fibers (MERRF)

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Glossary

Cytochrome *c* oxidase (COX) – Complex IV of the mitochondrial respiratory chain.
Cybrids – Cytoplasmic hybrid cells usually generated by fusing cytoplasm from patient cells harboring a mtDNA mutation with cells lacking mtDNA (rho-zero cells).
Heteroplasmy – A mixture of different forms of multicopy DNA molecules (e.g., mtDNA).
Homoplasmy – A uniform population of multicopy DNA molecules.
Maternal inheritance – Vertical transmission of DNA from mother to progeny.
Mitochondrial DNA (mtDNA) – A small (16 569 base pair) circular DNA molecule within mitochondria and encoding 37 genes.
Ragged-red fibers – Abnormal muscle fibers with subsarcolemmal reddish appearance by modified Gomori trichrome stain.
Respiratory chain – A set of four multisubunit enzymes (complexes I–IV) embedded in the mitochondrial inner membrane that transfers reducing equivalents (electrons) to generate a transmembrane proton gradient.
Succinate dehydrogenase (SDH) – Complex II of the mitochondrial respiratory chain, and a component of the tricarboxylic acid cycle.
Transfer RNA – A small RNA molecule that transfers an amino acid to a growing polypeptide.

Definition and History

Myoclonus epilepsy with ragged-red fibers (MERRF) is a multisystem mitochondrial disorder defined by myoclonus, generalized epilepsy, ataxia, and ragged-red fibers (RRFs) in muscle biopsies. In 1921, Ramsay Hunt described six patients with a disorder resembling Friedreich ataxia characterized by ataxia, myoclonus, and epilepsy, which he called 'dyssynergia cerebellaris myoclonica.' Several different disorders have been associated with this clinical triad, but nearly 60 years passed before Fukuhara and colleagues

reported two patients with a syndrome that they named 'myoclonus epilepsy associated with ragged-red fibers,' but has also been called Fukuhara disease.

Pathogenesis and Pathophysiology

In 1990, Shoffner and colleagues identified a mitochondrial DNA (mtDNA) point mutation, m.8344A > G, in a large pedigree with maternally inherited MERRF. This mutation in the tRNA-Lys (MTTK) gene has been found in about 80% of patients with MERRF. Three additional MTTK gene mutations (m.8356T > C, m.8361G > A, and m.8363G > A) have been identified in MERRF patients as well as a tRNA-Phe (MTTD) mutation (m.611G > A). It is unclear why the MTTK gene is a hot-spot of MERRF mutations.

Studies of cultured myoblasts from patients and cybrid cells (cytoplasmic hybrid cells containing different mtDNA species against a uniform nuclear DNA background) have demonstrated that the m.8344A > G mutation impairs molecular modification (addition of a 5-taurinomethyl-2-thiouridine to the anticodon wobble base) of $tRNA^{Lys}$, and leads to reduced levels of the native and aminoacylated $tRNA^{Lys}$. At high levels (>85%) of the m.8344A > G or m.8356T > C mutant $tRNA^{Lys}$ cause reduction of mitochondrial protein synthesis and mtDNA-encoded proteins leading to respiratory chain defects, particularly cytochrome *c* oxidase (COX) deficiency and decreased oxygen consumption.

Clinical expression of the mutation depends on three factors: (1) mtDNA heteroplasmy, (2) mtDNA tissue distribution, and (3) tissue threshold. Skeletal muscle biopsies typically demonstrate mitochondrial abnormalities; by histochemistry a mosaic pattern of RRFs and COX and by biochemistry, respiratory chain defects, particularly COX deficiency, are often detected. The RRF and COX-deficient fibers harbor higher levels of mtDNA mutations supporting pathogenicity and accounting for the mosaic pattern. Pathological studies of brain have revealed neuronal loss in the dentate nucleus, inferior olivary nucleus, degeneration of the posterior columns of the spinal cord, and diffuse gliosis of the cerebellar white matter and of the brain.

Epidemiology/Risk Factors

MERRF patients have been found worldwide. The disorder has no known ethnic predilection. Three epidemiological studies in northern European countries have estimated prevalence of the A8344G mutation to be 0–1.5 out of 100 000.

Clinical Features and Diagnostic Criteria

MERRF is defined clinically by: (1) myoclonus, (2) generalized epilepsy, (3) ataxia, and (4) RRFs in the muscle biopsy. Onset of the disease is usually in childhood, but adult onset has been described. Besides the defining criteria, other common clinical manifestations include impaired hearing, dementia, peripheral neuropathy, short stature, exercise intolerance, optic atrophy, and lactic acidosis. Other less frequent manifestations include optic nerve atrophy, cardiomyopathy, electrocardiographic preexcitation syndrome, pigmentary retinopathy, pyramidal tract signs, ophthalmoparesis, pes cavus, and multiple lipomatosis. Most patients have a family history of mitochondrial encephalomyopathy, although not always the full MERRF syndrome. Occasional patients that fulfill the clinical criteria for MERRF also have had strokes similar to mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes (MELAS). Maternally inherited spinocerebellar degeneration, atypical Charcot–Marie-Tooth disease, and Leigh disease have been reported as unusual manifestations in a MERRF pedigree while one patient presented with parkinsonism without myoclonus, epilepsy, or ataxia.

Differential Diagnosis

The differential diagnosis of syndromes characterized by myoclonus epilepsy and ataxia includes Unverricht–Lundborg disease, Lafora body disease, neuronal ceroid lipofuscinosis, and sialidosis. When no etiology is found, the diagnosis of Ramsay Hunt syndrome is made.

Diagnostic Work-up/Tests

Screening patients for MERRF should begin with routine blood tests including complete blood count, serum electrolytes, liver function tests, blood urea nitrogen, creatinine, lactate, and pyruvate. These tests may reveal kidney or liver dysfunction. Lactate and pyruvate at rest are commonly elevated in MERRF patients and may increase dramatically after moderate exercise. Blood leukocyte or urinary sediment DNA should be screened for an mtDNA point mutation because identification of an mtDNA mutation will obviate the need for a costly and invasive muscle biopsy.

Electrocardiograms may reveal preexcitation. Lumbar puncture may show elevated cerebrospinal fluid protein, but generally $<100\,mg\,dl^{-1}$. Electromyography and nerve conduction studies are typically consistent with a myogenic process, although a neuropathy may also be present. Typically, there are decreased amplitudes of compound muscle or nerve action potentials indicating axonal degeneration. Electroencephalography may show atypical generalized spike and wave discharges, with abnormal background slowing; focal epileptiform discharges may also be seen. Somatosensory-evoked responses often reveal giant cortical-evoked responses. Brain imaging with CT or MRI may show basal ganglia calcification and generalized atrophy.

Finally, muscle biopsy can be performed to confirm the diagnosis. RRFs on modified Gomori trichrome stain are the hallmark histological feature and a defining criterion. In addition, a mosaic pattern of COX-deficient fibers is typically seen; however, some MERRF patients with the A8344G mutation lack RRFs and COX-deficient fibers. Mitochondrial enzyme activities can be measured in whole muscle homogenate or in isolated mitochondria and usually demonstrate multiple respiratory chain defects, particularly in complex IV. When the clinical and muscle histological abnormalities indicate MERRF, mtDNA should be screened for the mutations.

Management

The seizures of MERRF can be treated with conventional anticonvulsant therapy. There are no controlled studies to compare efficacy of different antiepilepsy regimens. Aerobic exercise can reverse deconditioning in MERRF and other mitochondrial diseases.

No treatment for the genetic defect is currently available. Coenzyme Q10 (50–200 mg tid) and L-carnitine (300 mg qd) have been used to improve mitochondrial function.

Prognosis

The disease gradually progresses over years. The age of death has ranged from 7 to 79 years. The major complications are seizures and, less commonly, blindness and cardiac failure.

See also: Ataxia; Ataxia (Familial Cerebellar) with Muscle CoQ_{10} Deficiency; Co-enzyme Q_{10}; Leigh Syndrome.

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Myoclonus

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Glossary

Cortical myoclonus – Myoclonus arising from a hyperexcitable focus within the sensory-motor cortex.

Essential myoclonus – A syndrome of isolated myoclonus or a syndrome accompanying dystonia and no other neurologic abnormalities.

Lance–Adams syndrome – Myoclonus following hypoxic encephalopathy.

Negative myoclonus – Brief losses of muscle tone in the agonist muscles followed by a compensatory jerk of antagonist muscles.

Palatal myoclonus – Myoclonus that presents as rhythmic movements of the palate at a frequency of

2 Hz. This form of myoclonus may be primary or secondary.
Propriospinal myoclonus – Myoclonus resulting from a thoracic cord generator that is notable for the relatively slow spread of impulses up and down the cord.
Reticular reflex myoclonus – A form of brainstem myoclonus that causes flexor jerks of the proximal limbs and trunk and is stimulus sensitive.
Spinal segmental myoclonus – A form of spinal myoclonus derived from several adjacent segments of the spinal cord, usually the cervical or thoracic cord.
Subcortical myoclonus – Myoclonus not associated with a cortical discharge. An example is thalamic myoclonus.

Definition and History

Myoclonus is defined as brief, involuntary lightning-like muscle jerks that arise from the central or peripheral nervous system. These movements correlate with brief electromyographic discharges lasting for 10–100 ms in duration. Positive myoclonic jerks are contractions of a muscle or group of muscles which are most noticeable during voluntary movements such writing, using utensils, or walking. Negative myoclonic jerks are brief losses of muscle tone in the agonist muscles followed by a compensatory jerk of antagonist muscles. Examples of negative myoclonus include asterixis seen in hepatic encephalopathy, and loss of postural tone seen in posthypoxic myoclonus and stiff person syndrome. Myoclonus was first defined by Friedrich in 1881, through a case report of a patient with essential myoclonus.

Pathogenesis and Pathophysiology

Myoclonus can originate from the cerebral cortex, subcortical structures, brainstem, spinal cord, or peripheral nerve. Determining the origin of myoclonus is important in guiding the treatment. Cortical myoclonus arises from a hyperexcitable focus within the sensory-motor cortex. Thalamic myoclonus, an example of subcortical myoclonus, is not associated with a cortical discharge. There are three types of myoclonus that arise from the brainstem – startle, palatal myoclonus, and reticular reflex myoclonus. Palatal myoclonus may be primary or secondary. The secondary form is caused by a lesion within the Guillain–Mollaret triangle which includes the dentate, red, and inferior olivary nuclei. Such a lesion interrupts the dentato-olivary pathway, leading to olivary denervation and hypertrophy. Spinal myoclonus can be further subdivided into two types, segmental and propriospinal. Spinal segmental myoclonus is derived from several adjacent segments of the spinal cord, usually the cervical or thoracic cord. Propriospinal myoclonus usually results from a thoracic cord generator and is notable for the relatively slow spread of impulses up and down the cord. Myoclonus resulting from peripheral nerve injury, for example hemifacial spasm, is limited to the involved motor unit.

Epidemiology and Risk Factors

Myoclonus is one of the most common movement disorders that neurologists encounter in the hospital and outpatient setting. However, myoclonus has received less attention than other hyperkinetic disorders such as dystonia, tremor, chorea, and tics. This may be in part due to the fact that myoclonus is typically transient in the hospital setting, and often overshadowed by other associated medical problems. Myoclonus is also seen in the outpatient setting. In the community, chronic myoclonus has a prevalence rate of 8.6 per 100 000. Negative myoclonus is more common in the inpatient setting, while positive myoclonus is more prevalent in the outpatient clinic.

The causes of myoclonus are varied and include physiologic phenomena, epileptic syndromes, and metabolic disturbances. Physiologic myoclonus is a normal phenomenon exemplified by hiccups (myoclonus of the diaphragm) and hypnic jerks upon falling asleep. Essential myoclonus or myoclonus-dystonia is a syndrome of isolated myoclonus or with accompanying dystonia and no other neurologic abnormalities. This is a rare disorder and is inherited in autosomal dominant fashion with maternal imprinting. Most cases of inherited myoclonus-dystonia are exquisitely sensitive to alcohol, and the disorder has been linked to mutations in the ε-sarcoglycan gene located on chromosome 7, and in other families to chromosome 18. There is probably a higher incidence of obsessive–compulsive disorder in patients with myoclonus-dystonia. Myoclonus may be associated with epileptic syndromes such as juvenile myoclonic epilepsy and Lennox–Gastaut syndrome. Progressive myoclonic epilepsy is a term used to describe a group of degenerative disorders characterized by epilepsy, myoclonus, and progressive neurologic deterioration. Examples of progressive myoclonic epilepsy are neuronal ceroid lipofuscinosis, Lafora body disease, MERRF, MELAS, sialidoses, and Unverricht–Lundborg disease. Symptomatic myoclonus can occur in the setting of metabolic encephalopathy such as renal, hepatic, or pulmonary dysfunction; these movements are generally negative myoclonus such as asterixis. Posthypoxic myoclonus is classically described post cardiac arrest but can be seen after asthmatic attacks, obstructed airways, or accidental intubation of the esophagus.

The latter is less common now with end-tidal CO_2 monitoring. Drug toxicity, such as the serotonin syndrome, is another cause of myoclonus. Myoclonus is associated with a variety of degenerative diseases such as Huntington's disease, Alzheimer's disease, Creutzfeldt–Jakob disease, corticobasal ganglionic degeneration, multiple system atrophy, and subacute sclerosing panencephalitis. Common causes of secondary palatal myoclonus are multiple sclerosis and cerebrovascular disease. The infectious encephalopathy of Whipple's disease features facial myoclonus referred to as oculofacial-masticatory myorhythmia; other common features include supranuclear vertical gaze palsy and cognitive changes. Encephalomyelitis with rigidity is a severe, sudden-onset variant of the stiff-person syndrome, denoted by stiffness, excessive startle, and stimulus-triggered myoclonic jerks; it often responds to steroid therapy. An uncommon form of myoclonus is polymini-myoclonus, in which the jerks are of small amplitude, resembling irregular tremor that is continuous, and generalized. The term opsoclonus is applied when the eyes are involved with spontaneous, irregular, chaotic saccades. First described as part of an encephalopathic picture in infants, particularly in association with neuroblastoma, it also has been found in adults, usually as a paraneoplastic or postviral syndrome. The latter disorder is self-limiting after months or years. The paraneoplastic syndrome is associated with antineuronal antibodies and may remit with removal of the tumor.

Clinical Features and Diagnostic Criteria

Myoclonic jerks may occur singly or repetitively, and they may be focal, segmental, or generalized. Their amplitude ranges from mild contractions that do not move a joint, to gross contractions that move limbs, the head, or the trunk. Myoclonic jerks range in frequency from rare isolated events to many events each minute; they may occur at rest, with action or with intention. Commonly myoclonic jerks are stimulus sensitive; they can be induced by sudden noise, movement, light, visual threat, or pinprick. Most often myoclonic jerks occur irregularly and unpredictably, but some occur in bursts of oscillations and may even be rhythmic, as in palatal myoclonus. Rhythmical myoclonus almost always denotes a segmental origin, either brainstem or spinal cord. An uncommon rhythmical form, cortical tremor, originates in the cerebral cortex.

Cortical myoclonus is triggered by action or intention and is typically stimulus sensitive. Examples of stimuli include sound, touch, or startle. It is classically arrhythmic and involves an arm, leg, or face; however, in the case of epilepsia partialis continua, myoclonic jerks may be rhythmic. Thalamic myoclonus, an example of subcortical myoclonus often presents as asterixis. Myoclonus originating from the brainstem can be either generalized (reticular myoclonus) or segmental (e.g., ocular-palatal-pharyngeal myoclonus).

Palatal myoclonus presents as rhythmic movements of the palate at a frequency of 2 Hz. Primary palatal myoclonus disappears during sleep, while secondary myoclonus may persist. Primary palatal myoclonus is of unknown etiology and is often associated with annoying constant clicking sounds in the ear caused by contractions of the tensor veli palatini muscles which open the eustachian tubes. Secondary palatal myoclonus is often associated with rhythmic vertical ocular movements, also occurring at 2 Hz, called ocular myoclonus.

Reticular reflex myoclonus causes flexor jerks of the proximal limbs and trunk, and is stimulus-sensitive. Spinal segmental myoclonus is rhythmic and stimulus-insensitive and persists during sleep. Propriospinal myoclonus causes flexor jerks of the trunk and is sensitive to stimuli such as when eliciting the knee jerk. The muscles in the torso are commonly activated first and then spread rostrally and caudally. Myoclonus resulting from peripheral nerve injury, such as hemifacial spasm, is irregular and typically stimulus-insensitive.

Myoclonus following hypoxic encephalopathy is known as the Lance–Adams syndrome and was first observed by Dr. James Lance in survivors of cardiac arrest in the 1960s. Most patients with this syndrome are between the ages of 15 and 60. This probably reflects the relative resistance of the young brain to hypoxia and the poor survival of older adults after cardiac arrest. Myoclonus in this syndrome may be cortical, subcortical, or both. Similarly, it may be action and intention myoclonus, negative myoclonus with postural lapses, or both. The myoclonus may be stimulus-sensitive and have a distal predominance. Myoclonic jerks are triggered by voluntary movements such as reaching for an object, drinking from a glass, or feeding oneself. Affected patients have a tendency to fall due to failed sustained contraction of antigravity muscles. Negative myoclonus may involve the hamstring and quadricep muscles, producing a characteristic "bouncing" gait that may be misinterpreted as psychogenic by an untrained observer. Another peculiar tendency of these patients is their susceptibility to startle. One misstep or stumble could result in myoclonic jerks or loss of postural tone resulting in a fall. Other associated neurological features include dysarthria, dysmetria, and ataxia. Patients also suffer from difficulties with attention, memory, and executive function which are recognized with formal neuropsychological testing. Patients with posthypoxic myoclonus are usually in a coma for up to 7 days and seizures are common during this stage. These patients may be noted to startle easily to sounds. Of patients who emerge from coma and enter the chronic phase of this disorder, at least one third will have dysarthria and ataxia and more than two thirds have difficulty walking. Seizures are frequent but are usually well controlled by anti-epileptic medications. Many patients who develop the Lance–Adams syndrome are left with significant permanent disability.

Differential Diagnosis

Myoclonus is usually easily distinguished from other hyperkinetic movement disorders. In contrast to dystonia, tics, chorea, and tremor, myoclonus is one of the few movement disorders that persists during sleep. Dystonia is slower, sustained, and results in twisting postures. Tics are brief, stereotyped movements, which are suppressible – a distinguishing feature from myoclonus. Chorea is fragmentary, flowing, and associated with motor impersistence; however, patients with chorea of the distal extremities may occasionally mimic myoclonus. Tremor is rhythmic and oscillatory, present at rest, posture, or action, and is slower than myoclonus.

Diagnostic Work-Up/Tests

Surface EMG

The principal diagnostic test of myoclonus is surface EMG recording of myoclonic movements. Recording simultaneously from as many muscles as possible allows one to determine the distribution and spread of myoclonus. Band pass filters of 30–1000 Hz are adequate. Cortical myoclonus is associated with an EMG discharge of abrupt onset and short duration, lasting less than 50 ms. In most cases, agonist and antagonist muscles contract simultaneously. It may spread from proximal to distal muscles at the speed of about $50\,m\,s^{-1}$, which approximately corresponds to the conduction velocity of α-motor fibers.

EEG–EMG Polygraph

Simultaneous recording of EEG with the surface EMG is especially useful for the confirmation of cortical myoclonus. The EEG is recorded by placing electrodes according to the International 10–20 System. The referential derivation with ipsilateral earlobe reference or bipolar derivation is used. Band pass filter of 1–500 Hz is usually used. The demonstration of spikes or multiple spikes on EEG highly suggests a cortical origin of myoclonus. The spikes may be associated with myoclonic jerks, or they may not. Absence of EEG spikes, however, does not exclude cortical myoclonus, because small spikes may not be detected by scalp recording because of attenuation of the electric potential by the skull.

Jerk-Locked Back Averaging of EEG

The technique of jerk-locked back averaging can be used for detecting spikes associated with myoclonus that are otherwise not detectable on the conventional EEG–EMG polygraph. It can also be used for investigating the time and spatial relationship between the EEG spikes and myoclonus. EEGs and EMGs are simultaneously recorded just like the conventional polygraph, and the onset of EMG discharges associated with myoclonus is used as a fiducial point for back-averaging the EEG. The EMG may be rectified to avoid the canceling effect by averaging, integrated, and then its onset used as a fiducial point for back averaging. In order to obtain a record of good quality, it is important to choose the most appropriate muscle for obtaining the fiducial point, to distinguish the myoclonic discharges from the background EMG activities, and to avoid artifacts such as head movements. In the case of hand myoclonus, the positive peak or the onset of the negative peak of the EEG spike leads the myoclonus by 20 ms on average, and is localized to the central region of the contralateral head.

Somatosensory Evoked Potential (SEP)

The SEP is recorded by delivering electric shocks to the median nerve at wrist with the pulse duration of 0.2–0.3 ms and the stimulus intensity of 10% above the motor threshold. The initial peak of the cortical SEP, N20/P20, is not significantly enlarged, but the subsequent peaks (P25, N30/P30, N35) are extremely enlarged in patients with cortical reflex myoclonus.

Long-Loop Reflex

It is convenient to record the long-loop reflex at the time of SEP recording. While the median nerve is electrically stimulated for recording SEP, the surface EMG can be simultaneously recorded from the thenar muscle of that hand by a pair of surface electrodes. In cortical reflex myoclonus, the transcortical reflex (C reflex) at the latency of about 45 ms is enhanced, while in normal subjects it is not detectable under the resting condition. In the case of severe cortical reflex myoclonus, the reflex EMG response is seen not only in the thenar muscle, but also from other muscles of the same limb and also from the thenar muscle of the contralateral hand. In this case, the C reflex of the contralateral hand occurs 10–15 ms later than that of the stimulated hand.

Management

Several general principles apply to the selection of antimyoclonic therapy. There are few placebo-controled trials of antimyoclonic treatments, and even fewer double-blind trials. As a result therapy is empiric. The choice of agents is dictated by the underlying diagnosis, the likely origin of the myoclonus, and the side effect profile of the antimyoclonic agents. Positive myoclonus is more likely to respond to treatment, while negative myoclonus has more limited treatment options. In practice, after precipitants of

myoclonus are identified and corrected, one treats the positive myoclonus and hopes that negative myoclonus will respond partially as well, or resolve spontaneously.

Unlike the treatment of epilepsy, antimyoclonic agents are usually used in combination, and it is rare for one agent to achieve complete control of myoclonus. It is important to begin one drug at a time, starting slowly and titrating to tolerance or efficacy. The choice of agents is dictated by the underlying diagnosis, the likely origin of the myoclonus, and the side effect profile of the antimyoclonic agents.

There are nine drugs that are used to treat myoclonus: clonazepam, valproic acid, acetazolamide, primidone, L-5-hydroxytryptophan, piracetam, levetiracetam, zonisamide and sodium oxybate. L-5-Hydroxytryptophan is rarely used due to the risk of eosinophilia–myalgia syndrome, and piracetam is not available in the United States. Primidone and acetazolamide are not widely used for the treatment of myoclonus, but in occasional patients these drugs are useful. Sodium oxybate is approved in the United States for the treatment of narcolepsy – while there is preliminary evidence to support its use in select myoclonus patients, it should be considered investigational. This leaves clonazepam, valproic acid, levetiracetam, and zonisamide as the major four drugs used to treat patients with myoclonus in clinical practice.

Clonazepam is used in cortical, subcortical, and spinal myoclonus, and is probably the drug of choice for spinal myoclonus. Clonazepam is available in 0.5, 1, and 2 mg tablets, and is usually prescribed three times per day. It is wise to begin with a small dose, typically 0.5 mg, and to titrate until there is control of symptoms or side effects appear. Most patients require doses of at least 2 mg day^{-1}. Clonazepam is contraindicated in patients with hepatic dysfunction or narrow angle glaucoma. Drug interactions between clonazepam and other drugs are not significant. Clonazepam may potentiate the sedative effect of other medications. The most common side effect is drowsiness, although occasional patients experience ataxia or personality changes. After prolonged use, the dose should be tapered off if discontinuation is required in order to avoid withdrawal symptoms.

Valproic acid was the first drug specifically used for the treatment of myoclonus. It has been shown to be effective in cortical and subcortical myoclonus. A recent open-label study of valproic acid in myoclonic Huntington's disease showed significant improvement in myoclonus with good tolerability. Valproic acid is available in 125, 250, and 500-mg tablets, and is also available in 125-mg capsules. Valproic acid is usually begun at 125 mg BID, and titrated to clinical response. Doses of 750–1000 mg day^{-1} are usually required to achieve antimyoclonic effect. Valproic acid blood level monitoring is available, but is usually not necessary unless patient compliance is at issue. Valproic acid should not be administered to patients with hepatic disease or significant hepatic dysfunction. The drug is also contraindicated in patients with urea cycle disorders. Valproic acid may cause neural tube defects, craniofacial defects and cardiovascular malformations if taken during pregnancy. Drugs that increase levels of hepatic enzymes may decrease serum levels of valproic acid. Phenytoin, carbamazepine, and phenobarbital may decrease levels of valproic acid. Valproic acid may increase levels of warfarin, lamotrigine, phenobarbital, and phenytoin. Fatal hepatic failure may occur in patients taking valproic acid, usually within the first 6 months of treatment. This may occur in individuals who have no history of hepatic impairment. Liver function tests should be monitored frequently in patients taking valproic acid. Valproic acid may also trigger potentially life-threatening pancreatitis in adults and children. Dose-related thrombocytopenia is also possible. Action tremor, alopecia, and reversible parkinsonism are not uncommon. Valproate's extensive side effect profile and potential life-threatening adverse events have relegated this drug to second-line status in our opinion.

Piracetam is a nootropic agent that is available in Europe. It is not FDA-approved and is unlikely to be made available in the United States. Piracetam has been shown to be effective in patients with cortical myoclonus. Tablets are formulated by pharmacies, usually in 400 or 800 mg strength, and it is generally prescribed three times a day. The usual target dose is 16–24 g day^{-1}. Piracetam is contraindicated in patients with renal insufficiency or hepatic dysfunction. Piracetam is excreted unchanged and is not protein bound. There are no major drug interactions. Piracetam is generally well tolerated. There have been case reports of reversible thrombocytopenia and leukopenia. Piracetam should not be abruptly discontinued, as this may precipitate withdrawal seizures.

Levetiracetam is a novel antiepileptic agent, introduced into the United States in early 2000. Levetiracetam has been reported in several studies to be effective in patients with cortical myoclonus, including patients with posthypoxic myoclonus and progressive myoclonic epilepsy. Levetiracetam is probably ineffective in subcortical myoclonus. It is available in 250, 500, and 750 mg tablets. The standard initial dose for epilepsy is 500 mg twice daily, and this dose typically provides adequate seizure control. In contrast, patients with chronic myoclonic disorders may experience side effects from an initial dose of 1000 mg daily, and it is wise to begin initially with 250 or 500 mg day^{-1}, with gradual titration by 500 mg $week^{-1}$. The maximum recommended dose is 3000 mg day^{-1}, although doses as high as 4000 mg day^{-1} have been used. Pediatric doses are 20–40 mg kg^{-1} day^{-1}. Levetiracetam should be used cautiously in elderly patients and in those with decreased renal function. Levetiracetam's great advantage is its pharmacokinetics. It is minimally protein bound and excreted in the urine. There are virtually no interactions with other drugs. Levetiracetam is

exceptionally well tolerated. In placebo-controlled trials, the most commonly reported side effects were dizziness, somnolence, and asthenia. The most troublesome side effects, which occur uncommonly, are psychosis and ataxia.

Sodium oxybate (Xyrem) is used in certain European countries for the treatment for of alcohol withdrawal and in maintaining abstinence from alcohol. It is a schedule III agent in the United States, strictly regulated and approved for the treatment of cataplexy and excess daytime sleepiness in patients with narcolepsy. In one report, alcohol-sensitive myoclonus-dystonia was successfully treated with $6.125\,g\,day^{-1}$. Sodium oxybate has recently been shown to be effective in several patients with posthypoxic myoclonus and myoclonus-dystonia. Sodium oxybate may cause respiratory depression when used along with other CNS depressants. High doses (more than $10\,mg\,kg^{-1}$) may produce CNS depression. Patients with sodium oxybate toxicity may be agitated and combative despite profound CNS depression. Use of sodium oxybate should be considered experimental.

Rarely a first-line antimyoclonic drug, primidone is sometimes used in patients with cortical or subcortical myoclonus. Primidone is available in 50, 125, and 250 mg tablets. Unlike patients with epilepsy, patients with myoclonus do not tolerate rapid titration of primidone. It is wise to start with $25\,mg\,day^{-1}$, gradually increasing no faster than 25 or $50\,mg\,week^{-1}$. The dose is usually increased to tolerance, with a target of $500–750\,mg\,day^{-1}$. Primidone should be used with caution in the elderly, because of the risks of sedation, depression, and mental slowness. Primidone is contraindicated in patients with porphyria. Primidone is metabolized to phenobarbital and phenylethylmalonamide (PEMA). Phenobarbital induces hepatic enzymes and may decrease the levels of drugs metabolized in the liver. Primidone lowers the levels of warfarin and steroids, and may either decrease or increase levels of phenytoin. Sodium valproate decreases phenobarbital metabolism. The most common adverse reaction is drowsiness although tolerance to this side effect usually develops. Primidone may cause significant neurobehavioral and subtle cognitive side effects. It may exacerbate existing behavioral problems and trigger irritability. It may also impair memory and tasks requiring prolonged periods of attention.

Treatment of Specific Myoclonic Syndromes

Posthypoxic myoclonus

A review of posthypoxic myoclonus from 2000 summarized the effects of various agents on myoclonus. Clonazepam significantly improved posthypoxic myoclonus in 24 of 47 patients in whom it was prescribed, and valproate was similarly effective in 10 of 22 patients. L-5-Hydroxytryptophan was effective in only 17 of 43 patients, often with intolerable side effects. Piracetam was effective in three of six patients. Drugs that did not produce significant benefit in even one patient include nitrazepam, primidone, phenobarbital, phenytoin, and tetrabenazine. In March of 2000, the novel antiepileptic agent levetiracetam was released in the United States. Several case reports and series have reported good to dramatic benefit in patients with posthypoxic myoclonus treated with levetiracetam in doses of $1000–1500\,mg\,day^{-1}$. A pilot study to test the tolerability and efficacy of levetiracetam in patients with chronic myoclonus, including four patients with posthypoxic myoclonus, showed that levetiracetam was well tolerated and beneficial in at least two patients. A significant number of patients with posthypoxic myoclonus demonstrate dramatic benefit with alcohol, although benefits are short-lived. Some of these patients may benefit from treatment with sodium oxybate. As patients emerge from coma, myoclonic jerks are probably best managed with clonazepam. This drug has a short half-life, and its sedative properties may be welcome in an encephalopathic, agitated patient. Piracetam is available in Europe and Canada, is well tolerated and is effective in many patients with cortical myoclonus. Side effects are minimal, although patients must be able to swallow pills as the effective dose ranges from 16.8 to $24\,g\,day^{-1}$ (a liquid formulation is available). It is unknown whether piracetam or levetiracetam is more effective in treating cortical myoclonus. Therefore it seems reasonable to choose either drug for patients with proven or suspected cortical posthypoxic myoclonus. If a patient does not respond to one drug, the other should be tried as there have been anecdotal reports of patients responding to only one agent. Once treatment with levetiracetam or piracetam has begun, patients should be weaned off clonazepam in order to minimize its potential side effects (sedation, depression, personality change, and impotence). For patients who do not obtain adequate relief from these drugs, valproic acid is another option. However, its side effect profile and its potential effects on hematologic and liver function parameters make this a less desirable drug.

Posthypoxic myoclonus patients who are afflicted with reticular reflex myoclonus pose a particular challenge. Clonazepam is often helpful; however, drugs that are effective in cortical myoclonus are generally of little benefit. In these patients, and in patients with cortical myoclonus who do not respond to any of the drugs mentioned before, consider using L-5-Hydroxytryptophan. This agent requires pretreatment with carbidopa, and even then nausea and gastrointestinal upset is a major nuisance. The drug can be found in many health food stores, although the purity of the preparation is unknown. In the past, an impurity in one lot of L-5-Hydroxytryptophan triggered a potentially lethal eosinophilia myalgia syndrome, raising concern about the source of the agent. At present, few patients take the drug, and ideally it should be used only with an institutional review board-approved protocol that includes written informed consent.

Progressive myoclonic epilepsy (PME)

Zonisamide has been reported to be particularly effective in PME at doses of 400–600 mg day^{-1}. Other medications that have been used are sodium valproate, topiramate, levetiracetam, baclofen, L-5-hydroxytryptophan, clonazepam, piracetam, and primidone. Phenytoin and carbamazepine should be avoided because of their tendency to worsen cerebellar signs. In a series of four patients with PME, seizures were reported to improve with *N*-acetylcysteine (NAC), without change in myoclonus or ataxia. In the reported cases NAC was used at doses of 3.0–3.6 g day^{-1}. Higher doses may cause neutropenia. One recent series demonstrated the use of chloral hydrate to control daytime myoclonic exacerbations in three patients with PME. Patients were treated with doses ranging from 500–1500 mg day^{-1}. The liquid formulation was found to be more effective and better tolerated that the capsule form. Several open-label trials have shown levetiracetam to be effective in forms of progressive myoclonic epilepsy, including MERRF, Unverricht-Lundborg, Lafora body disease, and in benign adult familial myoclonic epilepsy.

Myoclonus-dystonia

Although alcohol suppresses myoclonus in these patients, it should be avoided because of the risk of abuse and dependence. Repetitive transcranial magnetic stimulation has been tried with empiric benefit in patients with myoclonus-dystonia. One case improved with high frequency deep brain stimulation of the ventral intermediate thalamic nucleus (VIM). Clonazepam, benztropine, anticholinergics, valproic acid, and piracetam have also been reported to be effective in selected patients. Recently, sodium oxybate has been shown to be effective in several patients with ε-sarcoglycan-linked myoclonus-dystonia.

Intractable hiccups

Hiccups require treatment only if they do not remit with conventional treatments. Baclofen, amitryptiline, and valproic acid remain the most commonly used medications. Neuroleptics should be avoided because of the risk of tardive dyskinesia.

Palatal myoclonus

Asymptomatic palatal myoclonus does not require treatment. In a case report from 2002, lamotrigine improved ear clicking from palatal myoclonus. Carbamazepine, L-5-hydroxytryptphan, phenytoin, barbiturates, diazepam, and trihexyphenidyl have been used in selected patients. In one report, injection of botulinum toxin into the levator veli palatini and tensor veli palatini muscle was beneficial. A second study of five patients showed resolution of symptoms in four patients, with transient velopharyngeal insufficiency in one patient.

Opsoclonus-myoclonus

This paraneoplastic or parainfectious disorder may spontaneously resolve, especially when it follows a viral infection. Various immunomodulatory approaches have been used in patients with persistent debilitating opsoclonus-myoclonus. High-dose intravenous immunoglobulin has been reported to be effective as has high-dose methylprednisone, but a recent randomized clinical trial of Piracetam in pediatric opsoclonus-myoclonus found it ineffective. Plasmapheresis has also been found to be beneficial. There have been isolated case reports of response to thiamine and clonazepam.

Spinal myoclonus

Keshwani described three patients with symptomatic spinal myoclonus who improved with levetiracetam. One report mentioned a good response of spinal myoclonus to apomorphine. Botulinum toxin injections have also been used to treat stimulus-sensitive spinal segmental myoclonus. Clonazepam, tetrabenazine, trihexyphenidyl, baclofen, carbidopa/levodopa, valproic acid, and L-5-HTP are the most commonly used medications.

Prognosis

The prognosis of myoclonus is dependent on the underlying cause. For example, drug-induced myoclonus tends to be transitory. Posthypoxic myoclonus, as well, improves with time. Myoclonus in progressive myoclonic epilepsy and degenerative disorders, on the other hand, is typically progressive.

See also: Benzodiazepines and Movement Disorders; Brainstem Reticular Myoclonus; Cortical Myoclonus; Juvenile Myoclonic Epilepsy; Lance–Adams Syndrome; Myoclonus, Animal Models; Myoclonus, Epileptic; Myoclonus-Dystonia/Essential Myoclonus; Opsoclonus-Myoclonus Syndrome; Palatal Myoclonus; Propriospinal Myoclonus; Spinal Segmental Myoclonus.

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Relevant Websites

http://www.ninds.nih.gov/disorders/myoclonus/detail_myoclonus.htm – National Institute of Health.

Myoclonus, Animal Models

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Glossary

Myoclonus – Myoclonus is defined as a brief, sudden, shock-like, involuntary movement caused by muscular contractions or inhibitions.
Posthypoxic myoclonus – Myoclonus induced after cardiac or pulmonary arrest or after anesthesia accidents during surgery.

Introduction

Myoclonus is defined as a brief, sudden, shock-like, involuntary movement caused by muscular contractions or inhibitions. Myoclonus can be caused by many pathological conditions affecting the central nervous system. For example, neurodegenerative disorders involving the basal ganglia, dementias, cerebral hypoxia, and drug intoxications can cause myoclonus. Posthypoxic myoclonus (PHM) is the most severe form of myoclonus and was first well-described in 1963 by Lance and Adams. PHM is caused by brain injury that results from lack of oxygen as the blood flow is interrupted during cardiac or pulmonary arrest or during anesthesia accidents related to surgery. PHM is characterized by action-triggered jerking, myoclonic movements affecting the normal daily activities of patients. Although the mechanism underlying PHM is not fully understood, the development of medications to manage this movement disorder has been challenging. An animal model of PHM is thus a valuable tool to elucidate the mechanism underlying this movement disorder.

A Rat Model of Cardiac Arrest-Induced PHM

Early attempts to develop animal models of PHM were mostly induced by chemicals instead of transient hypoxic insults. Because the method of myoclonus induction in these animal models is toxic rather than hypoxic, the results from these animal models may have limited direct relevance to PHM in humans. Truong and colleagues have developed an animal model of PHM by mechanical obstruction of the major cardiac vessels for 8.5 min. This method was first introduced by Kawai and colleagues. Cerebral ischemic insult is induced as a result of low arterial blood pressure. Resuscitation is initiated by mechanical ventilation and an injection of an intravenous bolus of epinephrine ($20\,\mu g\,kg^{-1}$) and sodium bicarbonate ($4\,mEq\,kg^{-1}$), followed by manual thoracic compression until the systemic arterial blood pressure returns to the preoperative level. Mechanical ventilation continues until the animal is capable of initiating spontaneous breathing. This mechanical method of inducing PHM mimics the events that occur during anesthesia accidents, allowing the biochemical and pharmacological findings from this animal model to be directly relevant to PHM in humans.

Movement Behavior in the Animal Model

Subjects with severe cardiac arrest-induced cerebral ischemic insults usually go through a deep coma phase before action-induced myoclonus develops. These animals are most susceptible to auditory stimuli, but myoclonic jerks can also be triggered by other stimuli such as

flashing lights. In this animal model, rats are in a coma for 2–3 h after cardiac arrest surgery, and after awakening, they are prone to seizures that may be spontaneous but are more often preceded by running movements. Seizures can also be evoked by external stimuli such as noise. Two days after cardiac arrest, the seizures subside and myoclonic jerks become the predominant movement disorder. The severity of myoclonic jerks reaches its peak on the fourth day after cardiac arrest and thereafter, they gradually subsides over ~1 month.

Evaluation of Myoclonic Jerks in the Animal Model

For evaluating myoclonic jerks, rats are given auditory stimulation of 45 clicks from a metronome recorded on audiotape. The involuntary muscle jerks of rats in response to each click are scored with the following rating scale: 0, no reaction; 1, ear twitch; 2, ear and head jerk; 3, ear, head, and shoulder jerk; 4, whole animal jerk, and 5, whole body jerk causing the animal jump. The sum of the cumulative scores in response to the 45 clicks yields a total myoclonus score for the animal, and this score is the primary outcome measure for most studies. The severity of myoclonus is age-dependent, and older rats consistently show higher myoclonus scores than younger rats. Further, younger animals have a faster recovery from hypoxia so that the number of days they have myoclonus is shorter than that of older animals. However, the mortality rates from the surgery increase with the age.

Pharmacology of the Animal Model of PHM

Early clinical studies showed that an array of antiepileptic agents can reduce myoclonic jerks in humans. In this animal model, antimyoclonic activity of these antiepileptics has been evaluated, and valproate, clonazepam, 5-hydroxytrytophan (5-HTP), and felbamate dose-dependently reduce auditory-induced myoclonic jerks of the posthypoxic animals when compared with animals treated with vehicle alone. Newer generation antiepileptic drugs such as levetiracetam and brivaracetam are also effective in this model. In addition, ketogenic diets, a nutritional treatment used in humans for controlling seizure resistant to antiepileptic drugs, are also effective in reducing seizure and audiogenic myoclonic jerks in this animal model. The antimyoclonic activity of other antiepileptic agents, which work by interfering with excitatory synaptic glutamatergic neurotransmission, has also been evaluated. Lamotrigine, which inhibits voltage-gated sodium channels in the deactivated state and thus reduces presynaptic release of the excitatory transmitter, glutamate, has antimyoclonic activity in the animal model. Similarly, riluzole, another antiepileptic agent with a similar mechanism of action to lamotrigine, reduces myoclonic activity in this animal model.

Histological Features of the Animal Model

Fluoro-jade staining in coronal brain sections from posthypoxic rats with myoclonus reveals that the cerebral hypoxia-induced neurodegeneration is confined to the hippocampal CA1 region, the cerebellum, and the thalamic reticular nucleus (TRN) (**Figure 1**). Using specific neuron phenotype markers, researchers have identified injuries in regions of the brain involved in normal functioning of motor coordination. Specifically, excitatory amino acid carrier expression in the Purkinje cell layer of the cerebellum is reduced. Glutamate decarboxylase, a marker for GABAergic neurons, is also significantly reduced in the TRN of the posthypoxic rats, indicating injury of the GABAergic neurons. These findings are consistent with a study in which fos protein expression, an immediate early gene product, was detected in the TRN and in specific areas in the brainstem of the

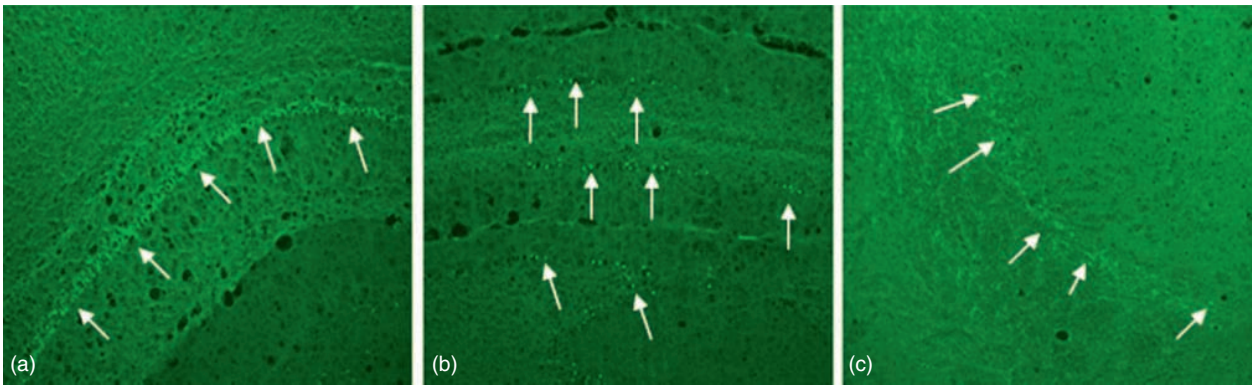

Figure 1 Neurodegeneration of a rat subjected to cardiac arrest-induced cerebral hypoxia for 8.5 min. (a) Hippocampus CA1, (b) cerebellum, and (c) thalamic reticular nucleus. The arrows indicate fluoro-jade-positive degenerating neurons.

posthypoxic myoclonic rats, suggesting that activity of this nucleus is associated with PHM. This hypothesis was verified by the finding that electrolytic lesion of the TRN reduced PHM in this animal model.

Serotonin (5-HT) Neurotransmission Dysfunctions in the Animal Model of PHM

Early clinical observations suggested that chemical imbalances in the serotonin (5-HT) neurotransmitter system could be the underlying cause of PHM. Studies detected low levels of the 5-HT metabolite, 5-hydroxyindol acetic acid (5-HIAA), in the cerebrospinal fluid of patients with PHM. This notion is further supported by the observation that 5-HTP in combination with an oral aromatic amino acid decarboxylase inhibitor such as carbidopa, which increases plasma 5-HTP significantly, abated myoclonus in humans with PHM. Myoclonic jerks in this animal model also improve with 5-HTP treatment. Further, the level of 5-HT metabolites in different areas of the brains of posthypoxic rats with myoclonus including the cortex, cerebellum, striatum, and hippocampus are significantly reduced when compared with nonhypoxic rats. The reduction in striatal 5-HT, cortical 5-HIAA, and mesencephalic 5-HIAA appears to most relevant to the development of PMH, as the correlation between myoclonus scores and the levels of indoles in these brain regions are particularly high. These results suggest that dysfunctions in serotonergic transmission in the cortical and the extrapyramidal ascending pathways are involved in the pathophysiology of PHM. Given the complexity of the 5-HT system and the existence of many types of 5-HT receptors, the animal model has tested the antimyoclonic efficacy of different 5-HT receptor agonists and antagonists. Myoclonus can be attenuated by a 5-HT1B/1C/2 agonist, a 5-HT2 agonist, and a 5-HT3 agonist. In contrast, 5-HT1A agonists, 5-HT1B agonists, and 5-HT2 antagonists are ineffective. These results suggest that enhancement of the serotonergic transmission in particular via the 5-HT2 and 5-HT3 receptors can reduce PHM in this animal model. This conclusion is consistent with observations in human PHM. A study by Pappert et al. (1999) using the same animal model of PHM showed that a 5-HT1B/1D/2 receptor antagonist and a 5-HT2A/2B antagonist dose-dependently reduced myoclonic jerks. Results from their study suggested that 5-HT1B, 5-HT2A/2B, and 5-HT1D receptor subtypes are likely to play a role in PHM.

Future Research Directions

Myoclonus is a common movement disorder but is difficult to manage clinically due to the lack of understanding of the pathophysiological basis of this movement disorder. The animal model of PHM replicates the essential features seen in patients with PHM. The model has been proven experimentally to be a valuable tool for evaluation of new antimyoclonic agents and to study the mechanism underlying this movement disorder. With the advent of new pharmacological products, preclinical testing with this model offers an inexpensive screening tool for the development of agents to be studied in prospective double-blind randomized clinical trials of new treatments for humans with PHM.

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See also: Brainstem Reticular Myoclonus; Cortical Myoclonus; Myoclonus; Propriospinal Myoclonus; Spinal Segmental Myoclonus.

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Myoclonus, Epileptic

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Glossary

Electroencephalogram (EEG) – A noninvasive test for epilepsy during which electrodes are placed on a patient's scalp to record electrical impulses from the brain.
Electromyogram (EMG) – Recording of electric currents associated with muscle contractions; it is done by placing a small needle into the muscle.
Epileptic syndrome – A seizure disorder characterized by a pattern of findings, such as the age of onset, cause, EEG data, family history, precipitating factors, and prognosis.
Myoclonus – A sudden brief involuntary muscle jerk.
Progressive myoclonic epilepsy (PME) – A rare form of epilepsy, often hereditary, characterized by myoclonic and other types of seizures and progressive neurological impairment.
Somatosensory-evoked potentials (SSEP) – Recording of electrical signals along the somatosensory pathways after stimulation of peripheral nerves.

Definition and History

Myoclonus is a quick involuntary movement that can be seen in a large variety of disorders. The term myoclonus comes from two Greek words: myo meaning muscle and clonus meaning turmoil. It was used by Nikolaus Friedreich in 1881 to describe a movement known today as essential myoclonus. Throughout the years, the term myoclonus was used by different authors with different meanings, leading to nosological confusion. Uverrich, Lundborg, Herpin, and Rabor contributed to a further definition of myoclonus by adding their own descriptive terms, most of which are still used. In the 1980s, there was a notion that the term myoclonus must be used only in the context of CNS disorders and not to describe muscle jerks due to peripheral nerve and plexus lesion or fasciculations due to motor neuron disease. Today, the term myoclonus is used to describe a sudden, involuntary, shock like muscle contraction, and anatomic or etiological considerations help to define the subclasses of myoclonus.

Epileptic myoclonus is a form of myoclonus that occurs as an ictal phenomenon related to several epilepsy syndromes. The epileptic myoclonic movements can be unilateral or bilateral, symmetric or asymmetric, or single or repetitive. They can be violent, leading to large amplitude movements of the arms and legs or very small in amplitude and not noticeable to an observer. Based on the area involved, the myoclonus can be further subdivided into generalized (generalized epilepsies), focal or regional (partial seizures), and isolated (epilepsia partialis continua). Myoclonus can also be defined as positive, caused by muscle contractions and negative, caused by muscle inhibitions. The brief lapses of muscle tone during an atonic seizure caused by an epileptic discharge in the brain is an example of negative myoclonus.

Epidemiology/Risk Factors

The only epidemiological study of myoclonus in a defined population was done in Olmstead County, Minnesota and published in 1999. The study reported the lifetime prevalence of myoclonus to be 8.6 cases per 100 000 population. Symptomatic myoclonus was most commonly seen (72%), followed by epileptic myoclonus (17%) and essential myoclonus (11%). It appears that postanoxic insults, neurogenerative disorders, and epileptic syndromes are the most common causes of myoclonus, frequencies that concur with observation based on day-to-day practice.

Pathogenesis/Pathophysiology

The pathophisiology of myoclonus is best studied by using the correlation between cortical discharges as recorded by EEG and the actual muscle movement as recorded by EMG. Based on this methodology, Halliday described three types of myoclonus:

1. *Pyramidal myoclonus* – originates from a stimulus in the cerebral cortex that is transmitted to the muscle trough the pyramidal tract. There is a definite correlate between the EEG discharge and the myoclonic movement, in which the action potential seen on EMG follows the EEG discharge by a few milliseconds.
2. *Extrapyramdal myoclonus* – originates from the subcortical regions. There is no correlation between the EEG discharge and the EMG action potential.
3. *Segmental myoclonus* – occurs due to hyperactive apha motor neurons in the spinal cord or brain stem that have lost their normal inhibitory inputs.

Epileptic myoclonus is a pyramidal myoclonus that can be further subdivided into

1. *Cortical reflex myoclonus* – originates from hyperexitable cerebral sensory-motor cortex and each jerk represents a discharge from that area. These types of movements are particularly seen in focal seizures involving the facial muscles.
2. *Reticular reflex myoclonus* – originates from the hyperexcitable caudal brain reticular formation. The EEG shows a generalized spike and wave discharge that follows the EMG signs of myoclonus, suggesting that the stimulus travels from the brain stem to the cortex.
3. *Primary generalized epileptic myoclonus* – originates diffusely from the cerebral cortex. The impulses travel down the brain stem and induce muscle movements. The movements are usually bilateral, involving primarily the muscles of the upper extremities and the face. The myoclonic jerks are locked in with the EEG discharges of generalized polyspike, spike-wave and polyspike-wave activity.

Clinical Features/Diagnostic Criteria

Epileptic myoclonus is usually seen as a part of an epileptic syndrome. Myoclonus can be only one component of a seizure, the only seizure manifestation (myoclonic seizure), or as one of multiple seizure types within an epileptic syndrome. The cause may be idiopathic, genetic, or a static encephalopathy.

Epileptic myoclonus can also be seen as a result of defined pathologic process, and in this case, falls into the category of symptomatic myoclonus. Focal cortical myoclonus can be seen to be associated with many cortical lesions such as tumors, angiomas, hemorrhage, and infections.

In this article, we describe several epileptic syndromes that have the common feature of having myoclonic movements as part of their semiology. While doing that, our primary goal is to emphasize the clinical features of the myoclonic seizures.

Juvenile Myoclonic Epilepsy (JME)

This is one of the most commonly seen epileptic syndromes associated with myoclonus. It consists of a combination of absence seizures, myoclonic seizures, and generalized tonic–clonic seizures (GTCS) in the absence of any neurological deficits. The myoclonic seizures of JME are the true presentation of pure myoclonic seizures. Myoclonic seizures usually occur early in the morning, soon after awakening. They involve most commonly the upper extremities, extensor muscles more than flexors, leading to the patient's dropping utensils during breakfast or for 'the cereal to fly.' The myoclonic jerks frequently involve the muscles of the face and shoulders and less commonly the muscles of the legs. The jerks can be single or repetitive. When repetitive, a generalized tonic–clonic convulsion can follow. The myoclonic seizures are very sensitive to sleep deprivation or alcohol use the night before. They can be precipitated by photic stimulation in some cases. The EEG pattern is very characteristic and shows generalized polyspike discharge, which is synchronous to the myoclonic jerks. Interictal EEG has a normal background with fast (4–6 Hz) generalized spike and wave, polyspike, and wave activity. The seizures are usually easy to control with antiepileptic drugs (AED), but life-long treatment is needed in most cases.

Benign Myoclonic Epilepsy of Infancy

This is a rare condition characterized by generalized myoclonic seizures occurring in otherwise normal children during the first or second year of life. No other seizure types are seen. The myoclonic jerks are characterized by head drops and sudden movements of upper extremities upwards, while the legs are flexed. The

amplitude of the movements varies and may cause a fall if severe enough. The myoclonic jerks usually last one to three seconds. Consciousness does not appear to be affected. No precipitant factors have been identified. The EEG shows generalized irregular 3-Hz, spike wave, or polyspike wave discharges, synchronous with the muscle activity on the EMG. The seizures are easy to control with AED, and the prognosis is good if treatment is started early, which is important in order to prevent deterioration of intellectual development.

Severe Myoclonic Epilepsy of Infancy (SMEI)

This is a rare syndrome, first described by Charlotte Dravet in 1978. It starts during the first year of life with febrile generalized or focal seizures. Soon after, myoclonic seizures appear in addition to complex partial and simple partial motor seizures. The myoclonic seizure can be violent leading to a fall, but they can also be subtle. EEG during the myoclonic seizures shows generalized fast spike-wave and polyspike-wave discharges. Cognitive impairment, psychomotor delay, and ataxia develop gradually after the onset of the seizures.

Doose and colleagues described an epileptic syndrome with myoclonic astatic seizures and strong genetic predisposition. The onset is between 1 and 5 years of age, usually with a generalized febrile seizure. Characteristically, boys are affected twice as often as girls. The patients can have multiple types of seizures, including absence, generalized tonic, generalized tonic–clonic in addition to myoclonic and myoclonic–astatic and astatic seizures. Myoclonic seizures consist of symmetric jerking of the arms, head, and shoulders. Some myoclonic seizures can be violent and lead to falls, other may not be evident to the observer. In myoclonic–astatic seizure, myoclonic jerks of arms and face precede the loss of tone. EEG during the myoclonic seizures shows generalized polyspike wave discharges. The prognosis differs from being favorable with spontaneous remission, to being poor with severe mental deterioration and medically intractable seizures.

Progressive Myoclonic Epilepsies (PME)

The syndrome of PME consists of myoclonic seizures, tonic–clonic seizures and progressive neurological dysfunction, particularly ataxia and dementia, which leads to severe mental impairment and death in many cases. PME is rare and usually genetic in etiology. The syndrome of PME is clearly heterogeneous. The onset is usually in late childhood or adolescence, but it can be at any age. Unverricht–Lundborg syndrome, Baltic myoclonus, Lafora body disease, and Myoclonic Epilepsy with Ragged Red Fibers (MERRF), among others, are representative of PME.

Myoclonus in PME is very characteristic, being multifocal and usually precipitated by posture, action, or external stimuli such as light, touch, or sound. Facial and distal limb muscles are typically involved. However, massive myoclonic jerks involving arms and legs leading to falls can also be seen. The origin and generators of myoclonus in PME is one confusing and still controversial issue. Neurophysiological studies document that most, but not all, myoclonic jerks are cortical in origin. When the myoclonic jerks are cortical in origin, they are accompanied by obvious discharges on EEG such as burst of spikes, polispikes, and spike wave complexes. Some of the myoclonic jerks are bilateral, which means that they are either generated in the cortex unilaterally and then spread contralaterally via the corpus callosum, or they are generated in a source in the brain stem, therefore representing a reticular reflex myoclonus. Clearly, however, some myoclonic jerks are not accompanied by any EEG changes, leading to the conclusion that those are 'nonepileptic' in etiology. From a pragmatic point of view, in this particular disorder, the patients are diagnosed with epileptic myoclonus when most, even if not all, of the myoclonic jerks are accompanied by EEG discharges. In PME, the prognosis is poor, with seizures that are difficult to control and cognitive deterioration in most patients.

Diagnostic Work-up/Tests

Assessment of patients with epileptic myoclonus should start with obtaining a good clinical history: age of onset, presence of other seizure types or neurological problems, family history, toxin or drug exposure, etc. Physical examination should concentrate on the myoclonic movement-distribution as well as the temporal and activation profile. These steps are followed by basic ancillary testing, brain imaging, and clinical neurophysiological testing, including EEG–EMG correlation studies, SSEP, and CSF examination in selected cases. Genetic testing and mitochondria function studies, lactate levels, and muscle biopsy are needed for inherited disorders. Neuropsychological testing is used to detect cognitive deterioration. Recognition of the epileptic syndrome may be delayed for a while due to the fact that some of its clinical features can develop slowly over time.

Management

The best strategy in treating epileptic myoclonus is to treat the underlying epileptic disorder. The treatment

usually targets the deficient cortical inhibition, which is thought to be at least one of the mechanisms behind the seizures. Studies done on CSF from patients with PME have shown 25–40% reduction of GABA concentration. Sodium valproate is considered to be the drug of choice due to its capacity to increase cortical GABA concentration and to potentate GABA postsynaptic inhibitory activity. Valproate can be given in IV load when needed at a dose of $20\,mg\,kg^{-1}$ or can be started gradually orally. Benzodiazepines also facilitate GABAergic transmission by effects on GABA receptor complex. Clonazepam is usually effective in the treatment of myoclonus; however, tolerance can develop over time. While effective in the treatment of myoclonic seizures, clonazepam is not effective in preventing other types of seizures such as generalized tonic–clonic seizures that can be part of the same epileptic syndrome. Levetiracetam is an AED with unknown exact mechanisms of action that has been very effective in the treatment of myoclonus. Levetiracetam can be used up to $3–4000\,mg\,day^{-1}$. It can also be used in IV load when needed. Zonisamide was also reported to help with myoclonic seizures. Depending on the epileptic syndrome, myoclonic seizures can be very refractory to medical treatment and using a combination of AED is sometimes needed. Some polytherapy regiments such as valproate and clonazepam, while effective in the treatment of the myoclonus, can lead to severe sedation and encephalopathy. Vagal nerve stimulation and ketogenic diet have been reported to be useful as adjunctive treatment in some patients. The medical treatment of atonic seizures is often unsatisfactory. Corpus callosotomy may be effective in well-selected cases, especially after a trial of VNS treatment had failed.

It is important to note that commonly used AEDs such as carbamazepine, phenytoin, lamotrigine, vigabatrin, and even gabapentin have been associated with the worsening of myoclonic seizures. In addition, drugs commonly used in patients with epilepsy to treat comorbid conditions such as SSRIs or tricyclic antidepressants can cause myoclonus. Quinolone antibiotics can cause myoclonus in the presence or absence of seizure disorder. In most cases, withdrawal of the drug precipitating the myoclonus is enough to resolve the disorder.

Prognosis

The prognosis of the myoclonic seizures depends on the 'company they keep.' Patients with myoclonic seizures due to benign epileptic syndromes such as JME have a normal life span, intelligence, and good seizure control as long as they are compliant with the treatment. It is essential to sensitize patients to the fact that JME is a life-long condition with a highly favorable prognosis, but there is a very high recurrence of seizures (including myoclonic) when treatment is withdrawn. In contrast to JME, patients with progressive myoclonic epilepsies, in general, have poor prognosis. When symptomatic, the prognosis of the epileptic myoclonus depends on the cause.

See also: Mitochondrial Encephalopathies; Myoclonic Epilepsy with Ragged Red Fibers (MERRF); Myoclonus.

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Myoclonus-Dystonia/Essential Myoclonus

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Glossary

***DYT11* MC** – *DYT11* mutation carriers: carriers of a mutation in the *SGCE* gene, causing M–D.
Myoclonus–dystonia (M–D) – Autosomal dominantly inherited movement disorder characterized by myoclonic jerks and dystonic movements/postures.
SGCE – ε-sarcoglycan gene, on chromosome 7q21, causing M–D.

Definition and History

Myoclonus–dystonia (M–D) is a movement disorder characterized by myoclonic jerks and dystonic movements or postures. Myoclonus is a rapid, brief contraction ('fast lightning jerk') of one muscle or a group of muscles. Dystonia is characterized by sustained twisting and repetitive movements that may result in abnormal postures. The abnormal movements most often affect the neck, trunk, and the upper limbs. M–D has an autosomal dominant inheritance with reduced penetrance because of maternal imprinting and is caused by mutations in the ε-sarcoglycan gene (*SGCE*) on chromosome 7q21.

M–D was described by Friedreich in 1881 as 'paramyoclonus multiplex' but since then, a large variety of terms have been used to describe the movement disorder: 'hereditary essential myoclonus,' 'essential familial myoclonus,' 'familial essential myoclonus,' 'dominantly inherited myoclonic dystonia with dramatic response to alcohol,' hereditary myoclonic dystonia, and M–D and inherited M–D syndrome. The hyphenated combination of the two terms 'myoclonus' and 'dystonia' with the specific order of presentation is now considered to be the appropriate term for M–D. However, it should be noted that myoclonus, or rarely, dystonia is the sole symptom of the disorder. Although M–D is a predominantly myoclonic syndrome associated with often mild dystonia, M–D has been classified as *DYT11* among the hereditary forms of dystonia since the detection of the *SGCE* on chromosome 7q21 in several M–D families, and it is considered as a dystonia-plus syndrome.

A patient with clinically typical M–D is shown in Video 1.

Pathogenesis and Pathophysiology

Pathogenesis: Function of the *SGCE* Protein

SGCE is a member of the sarcoglycan family of transmembrane proteins that are part of the dystrophin-associated glycoprotein complex. This complex links the cytoskeleton to the extracellular matrix in skeletal and cardiac muscle. α-, β-, γ-, and δ-sarcglycan are predominantly expressed in muscles, and mutations cause different forms of autosomal recessive limb girdle muscular dystrophies. *SGCE* is highly homologous to the α-sarcoglycan. However, expression of *SGCE* in the membrane of skeletal muscles in M–D patients is normal, which is reflected by the normal morphological and immunohistological investigations of muscle tissue and the normal muscle strength at neurological examination. Unlike the other sarcoglycans, *SGCE* is widely expressed in different tissues including the brain. *SGCE* is found in neurons of the cerebral cortex, basal ganglia, cerebellum, hypocampus, and the olfactory bulb, but the molecular function of the protein in human neurons is still elusive.

In *SGCE* knock-out mice with a deletion of exon 4, impaired motor skills and anxiety-like behavior have been observed. These mice exhibited an altered monoamine metabolism in the striatum with an increase in dopamine, 3,4-dihydroxy-phenlacetic acid (DOPAC) and 3-methoxy-4-hydroxyphenylacetic acid (HVA) levels in the striatum. These findings suggest that increased endogenous dopamine levels may be involved in the pathophysiology of M–D. This is further supported by a recent IBZM (iodobenzamide) SPECT imaging study that showed reduced dopamine receptor availability in the striatum of *DYT11* MC.

Mutations in the *SGCE* gene are thought to result in loss of function of the *SGCE* protein. Loss of *SGCE* function at the plasma membrane of neurons may lead to changes in the excitability of the neuronal membrane. This loss of function may be due to the mechanism of nonsense-mediated decay, which is a mRNA surveillance mechanism that detects premature stopcodons on mutant mRNA and prevents expression of a truncated protein. Lack of expression of the *SGCE* protein is then believed to be the disease-causing mechanism. Another possible mechanism is the altered intracellular trafficking of mutant *SGCE* to the plasma membrane. Recently, torsin A, mutated in *DYT1* dystonia, has been implicated in promoting degradation of intracellular mutant *SGCE* by the proteasome when both proteins are coexpressed.

Pathophysiology

The pathophysiology of M–D is largely elusive. Myoclonus in M–D is considered to be of subcortical origin due to the usual lack of stimulus-sensitivity of the myoclonus, the absence of giant somato-sensory-evoked potentials, the negative C-reflex and the absence of a cortical potential on EEG jerk-locked back averaging. The mean duration of myoclonic burst is 90–100 ms and is in line with these findings. Several functional studies point to a primary dysfunction of the basal ganglia. Study of the local field potentials (LFP) of the internal globus pallidus (GPi) in *DYT11* MC who underwent deep brain stimulation because of invalidating motor symptoms showed significantly increased coherence in the low (3–15 Hz) frequency band between GPi activity and the muscles, with the LFP leading the muscles. In addition, an EEG–EMG coherence study demonstrated that the normal cortical drive to the muscles in the beta band during weak isometric contraction is replaced by a similar low-frequency drive which correlates with dystonic muscle activity. These findings suggest that the basal ganglia, most specifically, GPi, are involved in the pathophysiology of M–D, which is supported by the dramatic effect of GPi stimulation on the symptoms of myoclonus and dystonia. Suppression of increased oscillatory activity in the low-frequency band is believed to be the mechanism responsible for the clinical effect of GPi stimulation.

A recent fMRI study detected hyperactivity of different cortical structures in symptomatic and nonsymptomatic *DYT11* MC which is likely to be secondary to dysfunction of the basal ganglia. However, short- and long-interval cortical inhibition was normal in different transcranial magnetic stimulation (TMS) studies, suggesting normal cortical inhibition in M–D.

Epidemiology

M–D is considered rare, although no clear prevalence data are available. Nonetheless, M–D may be much more common than previously thought for different reasons: the clinical picture of M–D is often mild and many patients do not come under medical attention; the disorder is not very well known among pediatricians nor neurologists, leading to likely underdiagnosis; although known to be hereditary, because of reduced penetrance, M–D may appear sporadically and therefore not be considered by many clinicians.

Phenotype–Genotype Characteristics

Phenotypical Characteristics

The myoclonic jerks in M–D are brief, lightning-like jerks usually affecting the neck, trunk, and the proximal upper limbs. The legs and distal upper limbs are less commonly involved. However, characterization of the motor symptoms in a Dutch M–D family revealed that slight jerky movements of the fingers may be the only presentation of myoclonus in M–D. Myoclonus is often the presenting symptom, but in 20% of the patients, dystonia may be the first symptom.

The myoclonic jerks are frequently elicited or worsened by active movements of the affected or a remote body part. Other factors negatively influencing the myoclonic jerks are fatigue, emotional stress, anxiety, nervousness, sound, touch, startle, and caffeine. Myoclonus and dystonia disappear during sleep.

A positive effect of alcohol on the symptoms of myoclonus, and to a lesser extent, dystonia is commonly reported but not invariably present. Some patients experience a rebound phenomenon after alcohol withdrawal.

Focal or segmental dystonia is present in half of the affected patients and often consists of cervical dystonia and/or writer's cramp. Involvement of the legs is rare in contrast to primary generalized dystonia. Dystonia in M–D does not tend to generalize. Rarely, dystonia is the only manifestation of the disease.

The onset is usually in childhood or adolescence (mean age of 6 years). Late age of onset, up to the eighth decade, can occur. Gender may influence the age of onset: the onset occurs earlier in girls than in boys in 42 *DYT11* MC from 11 families.

Psychiatric comorbidity is common in M–D patients but so far, it remains unclear whether psychiatric symptoms are part of the phenotypic spectrum of M–D or are secondary to the debilitating motor symptoms. Psychiatric symptoms include obsessive compulsive disorder, alcohol dependence, depression, anxiety, and panic attacks. Uniform standardized assessment of a larger number of symptomatic and asymptomatic *DYT11* MC may give more conclusive insights on whether such signs are implicit to the disorder or secondary social adjustment effects.

Unusual features have been described in selected families with a mutation in the *SGCE* gene and include postural or other forms of tremor. Alcohol withdrawal seizures may occur because of the relieving effect of alcohol on the motor symptoms but epileptic seizures in the absence of alcohol abuse have been observed in a few families.

Cognitive function is considered normal in M–D patients. An extensive neuropsychological test battery in a large Dutch M–D family showed no differences between *DYT11* MC and controls on any of the examined cognitive domains. However, mild cognitive abnormalities, including impaired verbal learning and memory, have been reported in a limited number of patients. In one M–D report, mental retardation has been observed. Mutation analysis showed an interstitial deletion of chromosome 7q21 completely removing

the *SGCE* and surrounding genes. It has been hypothesized that the mental retardation is due to the absence of surrounding genes.

Genotypical Characteristics

The SGCE *gene on chromosome 7q*

Linkage to chromosome 7q was observed in several M–D families in the late 1990s. In 2001, the *SGCE* gene encoding the ε-sarcoglycan protein was identified on chromosome 7q23. Subsequently, *SGCE* gene mutations have been identified in many individuals with familial M–D and occasionally in sporadic M–D cases. The mutations that have been described in literature up to the present can be found on *http://www.dmd.nl/sgce_seqvar.html*. In only one-third of the total number of genetically investigated M–D, a *SGCE* mutation can be demonstrated. This suggests genetic heterogeneity.

Recently, exonic deletions, not detected with direct sequence analysis, have been identified in several M–D families, indicating that *SGCE* mutations may account for a larger amount of the genetic cases of M–D than was previously thought and stresses the importance of performing gene dosage analysis.

De novo mutations in apparently sporadic M–D have been reported indicating that *SGCE* mutations must be considered in M–D patients with a negative family history.

Mutations in two other genes have been associated with M–D, that is, a missense mutation in the dopamine receptor 2 gene in a single family and an 18-bp deletion in the *DYT1* gene usually associated with early-onset primary torsion dystonia, in another single family. In both the families, however, an additional mutation in the *SGCE* gene was subsequently identified, which makes the pathological involvement of these genes in M–D uncertain. A large Canadian M–D family shows linkage to chromosome 18p (*DYT15*), but the contribution of this locus to the genetic heterogeneity of M–D remains unclear until the gene is identified.

Reduced penetrance due to maternal imprinting

The reduced penetrance in *DYT11* positive M–D patients is due to the mechanism of maternal imprinting. This implies that when inheriting the mutation from your mother the mutated maternal allele is silenced and the wild-type paternal allele is expressed leading to clinically unaffected mutation carriers. Silencing of the mutated maternal allele is probably due to differential methylation of CpG nucleotides which have been demonstrated in the *SGCE* gene. However, about 5–10% of affected individuals inherit the mutation from their mother, indicating an escape from maternal imprinting. The underlying mechanism for the loss of imprinting is unclear. Coexpression of the mutated and the wild-type allele or a different level of imprinting in brain compared to peripheral blood leucocytes (imprinting mosaicism) has been suggested as possible mechanisms.

Genotype–Phenotype Correlation

Considerable inter- and intrafamilial heterogeneity has been observed. However, no genotype–phenotype correlations have been found. An association between the localization or the type of the reported mutations and the described phenotype is not obvious, since *SGCE* mutations are likely to result in a loss of function of the *SGCE* gene.

Because mutational testing of the *SGCE* gene is expensive and laborious, several *SGCE* mutational screening studies have tried to identify distinct phenotypic features that could predict the presence of a *SGCE* mutation in M–D patients. Except for onset before the age of 20 years and truncal myoclonus, no other predictive factors could be identified.

Diagnostic Criteria

Several descriptions of M–D were reported in the literature before 1967, but Mahloudji and Pikielny were the first to formulate diagnostic criteria for M–D, which they called 'hereditary essential myoclonus.' These criteria have been modified by Gasser and recently by Klein on the basis of the findings in genetically proven *DYT11* M–D patients.

Since epileptic seizures and/or EEG changes have been found in mutation-positive M–D families, presence of seizures and an abnormal EEG are no longer considered as exclusionary criteria for M–D. In **Table 1**, the modified diagnostic criteria are displayed.

Differential Diagnosis

The clinical picture with myoclonus, dystonia, or both is quite distinct in M–D. Most other conditions in which myoclonus is a prominent feature are characterized by a variety of other neurological symptoms making a diagnosis of M–D unlikely. Genetically confined conditions with myoclonus as a major component include progressive myoclonus epilepsy and myoclonus epilepsy associated with ragged-red fibers. In rare cases, myoclonus can be a prominent feature of primary dystonia syndromes,

Table 1 Diagnostic criteria of M–D

Diagnostic criteria
Onset of myoclonus usually in the first or second decade of life; dystonic features are observed in more than half of the affected in addition to myoclonus and may rarely be the only manifestation of the disorder
Males and females about equally affected
A relatively benign course, often variable but compatible with an active life of normal span in most cases
Autosomal dominant mode of inheritance with variable severity, and incomplete pentrance, which is dependent on the parental origin of the disease allele; affected individuals usually inherit the disease from their father
Absence of dementia, ataxia and other neurological deficits
Normal SSEP, normal results of neuroimaging studies (CT or MRI)
Optional diagnostic criteria
Alleviation of symptoms (particularly of the myoclonus and to a lesser degree of the dystonia) with alcohol use
Various psychiatric symptoms

including *DYT1* and *DYT5* dystonia. It should be noted that myoclonus in these syndromes is often restricted to the body part affected by dystonia and the typical lightning-like character is usually absent. Benign hereditary chorea may be sometimes difficult to distinguish from M–D, especially when choreic movements are jerky.

Diagnostic Workup

The diagnosis of M–D is established on clinical grounds and can be confirmed by genetic analysis of the *SGCE* gene. By definition, additional tests are normal.

Laboratory tests (including lactate, pyruvate, serum copper, ceruloplasmin, and red cells) and neuroimaging studies (including brain CT and MRI) should be performed to exclude secondary causes of myoclonus(–dystonia).

Management

There is no etiological therapy for M–D. Pharmacological therapy is often ineffective. Various drugs have been tried including benzodiazepines (clonazepam), anticholinergics (trihexyphenidyl), antiepileptics (valproate, levetiracitam), L-dopa, dopamine agonists, neuroleptics, serotonergic agents, and β-blockers. Trihexiphenydyl may improve the dystonia, whereas clonazepam is sometimes effective to treat the myoclonus. Botulinum toxin can be used to treat focal dystonia, especially cervical dystonia. Alcohol often induces a dramatic relief of the symptoms of myoclonus and dystonia, but due to the risk of addiction to alcohol, this appears an unacceptable treatment option. Motor symptoms in some patients are severe and may lead to considerable disability. In selected patients deep brain stimulation of the internal GPi or the ventral intermediate thalamic nucleus has shown to substantially improve the motor symptoms. The effect of deep brain stimulation on the commonly associated psychiatric symptoms is unknown.

Prognosis

The course of the disease is usually benign with a normal lifespan of active life. Very often, stabilization of the condition is reached in adulthood, with most patients functioning independently in the activities of daily life. In selected cases, spontaneous remissions of myoclonus (and dystonia) have been reported. In contrast, some patients worsen progressively during the course of the disease, also at older age. Increase in frequency and intensity of the myoclonus or dystonia and the involvement of body parts that had been previously unaffected have been reported. This may lead to considerable functional disability.

See also: Dystonia; DYT11, DYT15, Myoclonus-dystonia; Myoclonus.

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Myokymia

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Glossary

Ephaptic transmission – Transmembrane spread of an action potential from motor axon to motor axon (as is suspected in myokymia), or sensory axon to sensory axon or muscle cell to muscle cell.
Entrapment neuropathies – Compression of individual named nerves, such as median mononeuropathy at the carpal tunnel.
Motor unit – The anterior horn cell, its lower motor neuron axon, its surrounding myelin, terminal axon sprouts, neuromuscular junction, and the respective skeletal muscle fibers.
Myokymia – An involuntary movement disorder characterized by continuous, undulating skin movements.
Myokymic discharges – Spontaneous grouped motor unit action potentials, generated at the level of motor units, with suspected ephaptic spread to other motor units, down to their respective muscles cells, causing continuous wormlike movements of the skin.

Definition

Myokymia is an involuntary movement disorder with a distinctive appearance best described as earthworms moving continuously under the skin.

Pathophysiology

The source of these vermicular (wormlike) movements originate somewhere along the course of the motor units, usually distally or proximally in the anterior horn cells, depending on the cause of the myokymia. Pathophysiologically, spontaneous depolarization of axons or anterior horn cells occur – perhaps via ephaptic transmission – thereby sending an action potential down the various motor units to their respective skeletal muscles fibers. And since each motor unit innervates several hundred muscle fibers (fewer in the face), there is a visible movement of skin overlying the contracting muscle cells.

Clinical Presentation

There is a clinical value in recognizing myokymia, as it results from a limited number of pathological conditions, and fewer physiological conditions.

Moreover, myokymia may be generalized or localized, which further assists in determining its cause.

One of the typical examples of physiological myokymia is something most of us have experienced: eyelid twitching. But because the eyelids are so thin, myokymia has the appearance of an eyelid twitch rather than the undulating skin movements common to facial or limb myokymia.

Myokymia may be observed in both peripheral nervous system and central nervous system disorders.

Clinical myokymia may appear in several patterns of distribution:

1. Focal myokymia limited to the face (generally observed in the chin) occurs in conditions such as multiple sclerosis, brainstem neoplasm, Bell's palsy, Guillain–Barre syndrome, or in individuals with no abnormalities (physiological).
2. Limb (segmental) myokymia may be seen in syringomyelia, cervical or lumbar radiculopathies, chronic entrapment neuropathies such as median neuropathy at the wrist, or in the classic condition associated with myokymia: postirradiation brachial plexopathy.
3. Generalized myokymia has been seen in acute inflammatory neuropathies such as Guillain–Barre (which as stated above can present with facial myokymia) or chronic inflammatory neuropathies such as Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). Other conditions causing myokymia include uremia, thyrotoxicosis, Isaac's syndrome, postexercise induced myokymia, timber rattlesnake venom, gold therapy, or hereditary episodic ataxia.

Diagnosis

When a needle electromyogram (EMG) is inserted into muscles demonstrating clinical myokymia, the potentials generated are referred to as myokymic discharges. These are spontaneous discharges of grouped motor unit potentials, with an average of 2–10 motor unit potentials per burst, and an intraburst frequency of 20–150 Hz. The frequency of burst discharges ranges from 0.1 to 10 Hz, and these bursts discharge with a periodicity that is often referred to as marching shoulders (on the auditory portion of the EMG exam).

In the author's opinion, the diagnosis of myokymia should be made in conjunction with a needle EMG test, since other conditions may potentially mimic generalized myokymia. These conditions include blepharospasm, facial myoclonus, myotonia, or spasticity.

Treatment

Treatment of myokymia includes eliminating the source of the causative factor. Reducing the symptoms may be improved with medicines such as anticonvulsants.

See also: Electromyography (EMG).

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Myorhythmia

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Glossary

Guillain–Mollaret triangle – A triangular neural circuit from the cerebellum (dentate nucleus), through the superior cerebellar peduncle to the contralateral red nucleus and inferior olive, and back to the cerebellum via the inferior cerebellar peduncle.
Holmes tremor – A combined rest, postural, and intention tremor at 2–5 Hz, which is produced by lesions in the vicinity of the red nucleus or neighboring ventrolateral thalamic and subthalamic area.
Myorhythmia – An unusually slow 1–3 Hz tremor that affects various combinations of the face, jaw, throat, tongue, head, eyes, torso, and extremities.
Oculomasticatory myorhythmia – A synchronous myorhythmia of the face and eyes, which is regarded by many as a pathognomonic sign of Whipple disease.
Olivary hypertrophy – A degenerative enlargement of the inferior olive that occurs in response to lesions in the dentatorubro–olivary pathway.
Palatal tremor – A rhythmic 1–3 Hz movement of the soft palate caused by lesions in the dentatorubro–olivary pathway.
Whipple disease – A rare systemic infectious disease caused by *Tropheryma whipplei.*

Definition and History

Myorhythmia is an unusually slow 1–3 Hz tremor that affects various combinations of the face, jaw, throat, tongue, head, eyes, torso, and extremities. It is present at rest and during voluntary muscle contraction. Van Bogaert and coworkers described oculomasticatory myorhythmia in 1963, and Masucci and coworkers provided the first detailed description of extremity myorhythmia in 1982.

Pathogenesis/Pathophysiology

Virtually all patients have pathology in the brainstem or cerebellum, produced by a long list of diseases including stroke, demyelinating disease, Whipple disease, celiac disease, Hashimoto encephalopathy, paraneoplastic disease, Wernicke disease, olivopontocerebellar degeneration, viral encephalitis, and collagen vascular disease.

Clinical Features and Diagnostic Criteria

Myorhythmia may affect one body part or multiple body parts, unilaterally or bilaterally. Contiguous body parts are often affected. The 1–3 Hz oscillations appear to be time-locked or synchronous in some patients, but this apparent synchrony is not the rule and has rarely been documented electrophysiologically.

Myorhythmia typically begins months or years after a posterior fossa stroke. In this regard, myorhythmia is similar to palatal tremor and Holmes (rubral) tremor, which may be related disorders. The delayed onset of these conditions suggests that secondary neuroplastic changes enhance or produce rhythmic brainstem and bulbospinal activity.

Oculomasticatory myorhythmia and oculofacioskeletal myorhythmia are classic signs of Whipple disease affecting the central nervous system (CNS). There is a characteristic pendular convergent–divergent movement of the eyes that is synchronous with movements of the face.

The classic clinical triad of Whipple disease is the combination of gastrointestinal malabsorption, supranuclear gaze palsy, and oculomasticatory myorhythmia, but isolated CNS signs and symptoms may occur. Furthermore, Rajput and McHattie reported a patient with vertical gaze palsy and lower limb myorhythmia.

Differential Diagnosis

Damage to the Guillain–Mollaret triangle is present in most patients. Consequently, some patients have olivary hypertrophy and palatal tremor (also known as palatal myoclonus). Palatal tremor has a frequency of 1–3 Hz and could be considered a form of myorhythmia. However, palatal tremor persists during sleep and is nearly always associated with olivary hypertrophy. Myorhythmia stops in sleep and is frequently present in patients who do not have olivary hypertrophy.

Extremity myorhythmia and Holmes tremor may coexist. Both occur at rest and during voluntary muscle contraction. Holmes tremor has a higher frequency (2–5 Hz), but there is an overlap, and some experts regard extremity myorhythmia and Holmes tremor as the same condition. Therefore, the proper nosology of these conditions is unclear. Additional electrophysiologic studies and clinicopathological correlations are needed.

Management

There are no controlled trials for the treatment of myorhythmia. Primary treatment should address the underlying disease whenever possible. Symptomatic treatment with valproate has helped in some patients with Whipple disease. Whipple disease is treatable with trimethoprim–sulfamethoxazole or with ceftriaxone in patients allergic to sulfa.

Prognosis

Prognosis is generally poor but depends on the underlying etiology. Myorhythmia should alert clinicians to pathology in the brainstem or cerebellum. The most common etiology is stroke, but myorhythmia occasionally occurs in treatable progressive conditions such as Whipple disease, paraneoplastic disease, and other immunologic disorders.

See also: Oculomasticatory Myorhythmia; Palatal Myoclonus; Palatal Tremor; Tremor; Tremor, Essential (Syndromes); Tremor, Holmes; Whipple's Disease.

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Myriachit

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Glossary

Coprolalia – Pathological use of foul language.
Culture-specific syndrome – Forms of abnormal behavior restricted in distribution to defined racial or social groups, discrete areas of the world, or particular historical periods.
Echolalia – Pathological repetition of words just spoken.
Echopraxia – Pathological repetition of the acts of other people.
Koryak, Yukaghir, Chuckchee, Yakut, Samoyed – Tribal groups living in Siberia.
Tungus – Russian settlers in Siberia.

Definition and History

The term Myriachit (meriachen'e, meriachit', or emiriachen'e in Russian, sometimes translated also as myryachit, meriachit, etc.) is derived from the Siberian Tungus word meaning 'doing something stupid and useless because of sudden fear.' It is also known as 'arctic hysteria' or 'olonism.' However, 'arctic hysteria' originally refers to a broader category of far-northern psychological disturbances.

The reports on incidents of Myriachit tend to be folkloric in nature. William Hammond, a surgeon/neurologist, collected stories from American soldiers who had been stationed in Siberia, and he tried to describe the syndrome on the basis of the soldiers' recollections. Hammond wrote: ". . .To annoy him [the patient, a steward of the boat], some of the passengers imitated pigs grunting, or called out absurd names; others clapped their hands and shouted, jumped, or threw their hats on the deck suddenly, and the poor steward, suddenly startled, would echo them all precisely, and sometimes several consecutively." As Hammond did not see the cases himself, the article was severely criticized. Shirokogoroff and Jackson also described the syndrome in about the same period, the beginning of the twentieth century. Shirokogoroff wrote: "One day he [the subject] was sitting alone, with his small son, in the wigwam. A knife fell down in front of him (evidently, the knife had been in the hanging hunting belt). He seized it and thrust it into his son's body."

Clinically, Myriachit is a Siberian syndrome consisting of excessive startle reactions, matching behavior (echolalia, echopraxia), and forced obedience (involuntary, immediate obedience to commands). Compared to other culture-specific movement disorders like Latah (Indonesia/Malaysia) and Jumping Frenchmen of Maine (US/Canada), the reports concerning Myriachit in Siberia are the least extensive.

Epidemiology

There is no information on the prevalence of Myriachit other than it was described to be well known to the Russians. In one account half of the Yukaghir women of age 30 or 40 and older were described to suffer from a mild or more severe form of Myriachit.

Pathophysiology

See 'Jumping Frenchmen of Maine.' Specifically for Myriachit, the symptoms have been attributed to difficulties adjusting to the far-northern environment. Shirokogoroff did not regard Myriachit as a disease but as a normal phenomenon. He further states that it has a social function 'without the *Tungus* life would be impoverished.' He thought it should not be considered hysteria.

Clinical Features and Diagnostic Criteria

As the response of the patients were never recorded, there are no clear diagnostic criteria other than that the responses are stimulus-induced. Several clinical features will be discussed. The most prominent is the matching or copying behaviour. When provoked, the individual with Myriachit imitates the actions of others against his will. According to Hammond's article, Myriachit appeared to involve *echolalia* and *echopraxia* only (*coprolalia* is not reported as part of the syndrome, like it is for Latah patients in Indonesia/Malaysia). However, a famous historical report describes a group of soldiers who repeated both the commands and swearing of a colonel. Shirokogoroff stated that "during a parade of this regiment, the soldiers began to repeat the words of command. The colonel grew angry and swore volubly at the men; but the more he swore, the livelier was the chorus of the soldiers repeating his curses after him." This is an account of a group of persons becoming infected simultaneously, something which has not been described for Latah or the Jumping Frenchmen of Maine. Reports of group Myriachit led some authors to conclude that Myriachit can be endemic in groups trained to obey, like the soldiers described by Shirokogoroff. Another consequence of mass Myriachit descriptions was that the occurrence of Myriachit was linked to the consumption of a drug. One story describes 14 soldiers who became liable to fits of echolalia following the consumption of hemp oil given by a sufferer from Myriachit in a settlement in Novokievsky. However, other reports of mass affects do not mention substances. The subjects are mostly female inhabitants of far eastern Siberia, especially Yakutsk. The *Koryak*, *Yukaghir*, *Chuckchee*, and the *Tungus* could all be affected (in other reports *Yakut* and *Samoyed* are included), but the latter were more prone as they were less acclimatized to the Siberian circumstances. Similar to Latah, milder and more severe forms were described. The mild form consisted of an obscenity exclaimed after a sudden fright and the more severe form consisted of a hypnotic-like state in which the person would mimic sounds and actions and follow orders. Shirokogoroff noticed that "Myriachit is liable to diffusion, fashions, and variations, both individual and ethnical, and is rooted in the normal psychomental complex." The behavior was said to be common in areas 'where the winter was harsh.' Further, the pattern is described to become more acute during periods of famine.

Prognosis

See 'Jumping Frenchmen of Maine.'

Differential Diagnosis and Diagnostic Work-Up Tests

See 'Jumping Frenchmen of Maine.'

Management

See 'Jumping Frenchmen of Maine.'

See also: H-reflex; Hyperekplexia; Jumping Frenchmen of Maine; Latah.

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N

Neural Networks

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Glossary

(Artificial) neural network – Mathematical models that use learning algorithms to store information.
Back propagation – A common method of teaching artificial neural networks how to perform a given task.
Multilayer perceptron – The most successful and used neural network.
Training – The process of teaching/learning the network by way of presenting the network with a training set composed of input patterns together with their corresponding desired output pattern.

Definition and History

Neural networks are mathematical models that use learning algorithms inspired by the brain to store information. Since neural networks are used in machines, they are collectively called an 'artificial neural network.' Nowadays, the term machine learning is often used in this field and is the scientific discipline that is concerned with the design and development of algorithms that allow computers to learn, based on data, such as from sensor data or databases. A major focus of machine-learning research is to automatically learn to recognize complex patterns and make intelligent decisions based on data. Hence, machine learning is closely related to fields such as statistics, data mining, pattern recognition, and artificial intelligence. Neural networks are a popular framework to perform machine learning, but there are many other machine-learning methods, such as logistic regression, and support vector machines.

Similar to the brain, neural networks are built up of many neurons with many connections between them. Neural networks have been used in many applications to model the unknown relations between various parameters based on large numbers of examples. Examples of successful applications of neural networks are classifications of handwritten digits, speech recognition, and the prediction of stock prices. Moreover, neural networks are more and more used in medical applications. Many different types of neural networks exist. Examples of various types of neural networks are Hopfield network, the multilayer perceptron, the Boltzmann machine, and the Kohonen network. The most commonly used and successful neural network is the multilayer perceptron and will be discussed in detail.

The first step toward artificial neural networks came in 1943, when Warren McCulloch, a neurophysiologist, and a young mathematician, Walter Pitts, wrote a paper on how neurons might work. They modeled a simple neural network with electrical circuits. In the 1950s, Rosenblatt's work resulted in a two-layer network, the perceptron, which was capable of learning certain classifications by adjusting connection weights but also had some limitations. In the early 1980s, researchers showed renewed interest in neural networks.

Multilayer Perceptron

A multilayer perceptron consists of a number of layers containing one or more neurons (see **Figure 1** for an example). The role of the input neurons (input layer) is to feed input patterns into the rest of the network. After this layer, there are one or more intermediate layers of units, which are called hidden layers. Subsequently, the hidden layers are followed by a final output layer where the results of the computation are read off. Each unit is connected to all units in the subsequent layer and each unit receives input from all units in the previous layer. Each connection has a certain weight, and this weight illustrates the influence of the unit to the response of the unit in the subsequent layer. The output of a multilayer perceptron depends on the input and on the strength of the connections of the units. When information is offered to a

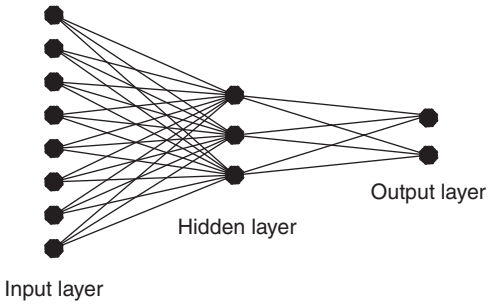

Figure 1 A multilayer perceptron with eight neurons in the input layer, three neurons in the hidden layer, and two neurons in the output layer.

multilayer perceptron by activating the neurons in the input layer, this information is processed layer by layer until finally the output layer is activated. Given enough hidden units and enough data, it has been shown that multilayer perceptrons can approximate virtually any function to any desired accuracy. In other words, multilayer perceptrons are universal approximators. However, these results are valid if and only if there is a sufficiently large number of training data in the series. If there are not enough data to 'train' the neural network, the network will not be able to learn the required input–output relationship accurately. Therefore, multilayer perceptrons are valuable tools to solve complex problems when sufficient data are available to train them.

In many respects, the learning process (training) of a neural network is rather similar to the way the brain learns to distinguish certain patterns from others. The learning process of a neural network proceeds by way of presenting the network with a training set composed of input patterns together with their corresponding desired output pattern. By presenting we mean that a certain pattern is fed into the input layer of the network. We start off with a network with random connections between the neurons, which gives a random output for a given input. We then train the network by presenting it with successive patterns drawn from an example set, which is typical of the problem we want the network to work on. For each of these patterns, we look at the output pattern the network gives us and compare it with the output we would ideally like to see. By comparing the output of the network with the target output for that pattern, we can measure the error the network is making. This error can then be used to alter the connection strengths between layers in order that the network's response to the same input pattern will be better the next time. In other words, the purpose of the training process is to minimize the error between the desired output and the neural network output by adjusting the weights between units of subsequent layers. The training of a network is commonly done by a procedure called backpropagation. Backpropagation modifies the strengths of the connections between a layer and the previous layer starting with the output layer based on the error between desired and actual output of the network. The network processes the records in the training data one at a time, using the weights and functions in the hidden layers, and then compares the resulting outputs against the desired outputs. Errors are then propagated back through the system, causing the system to adjust the weights for application to the next record to be processed. This process occurs over and over as the weights are continually tweaked. During the training of a network, the same set of data is processed many times as the connection weights are refined.

The architecture of a neural network plays a critical role in whether or not it can be trained to learn a particular set of data. The question of how many nodes and connections are ideal in a neural network cannot be answered easily. Clearly, the simpler the architecture, the simpler a function the neural network is computing. Too simple an architecture will result in a network that cannot learn to approximate a complex function. Too complex an architecture has been shown to result in a network losing its generalization capability. The generalization capability is the performance of a network to give a proper classification for new input pattern, which the network has not encountered before. Generalization is an important feature to maintain in order to avoid overfitting. Overfitting happens in case of a small training set, in which case the network cannot distinguish between information in the patterns and the noise. The consequence is that the network learns noise, rather than the general characteristics in the database. The generalization performance of a network can be evaluated by training the network with a part of the whole data set (e.g., 80% of the data, called the training set) and testing the trained network with the remaining data that was not used for training the network (e.g., 20% of the data, called the test set).

Ambulatory Assessment of Dyskinesia

An example of the benefit of neural networks in neurology is the ambulatory assessment of dyskinesia in patients with Parkinson's disease. Dyskinesias are a major problem in the long-term management of Parkinson's disease and add substantially to the patient's disability. Common methods to detect dyskinesia like clinical methods and self-reports have their limitations. Standard clinical detection and rating methods of dyskinesia can only be applied in a hospital setting under supervision of a trained clinical observer. These rating methods, provide only a momentary assessment of the clinical condition and cannot be applied for long-term measurements. Self-report of

the motor state in diaries has several limitations and can be troublesome, subjective or even unreliable. Therefore, patients will greatly benefit from quantitative objective assessment of their motor state in daily life.

New developments in micro-electronics have led to small and cheap miniature movement sensors such as accelerometers, which can be attached to the body and can measure human motion in daily life. These accelerometers appeared to be useful to assess dyskinesia in Parkinson's disease patients when the patients were instructed to abstain from voluntary movements. However, assessing dyskinesia when voluntary movements were present appeared to be problematic indicating that it is difficult to distinguish voluntary movements from dyskinesia in daily life. A more sophisticated approach using sensors on multiple body segments and neural networks resulted in a successful assessment of dyskinesia in daily life. The neural network received parameters of the accelerometer signals of multiple body segments as input pattern and the severity of dyskinesia rated by a neurologist was used as output. After training the neural network, the neural network could correctly classify the severity of dsykinesia for new patients. This study showed that movement parameters of multiple segments and their nonlinear relationships are important to assess dyskinesia in dialy life.

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Neuroacanthocytosis Syndromes

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Glossary

Acanthocytes – Contracted erythrocytes with thorny protrusions.

Chorea-acanthocytosis – An autosomal recessive neurodegenerative disease characterized by involuntary movements (chorea) and acanthocytosis.

Huntington disease-like 2 – An autosomal dominantly-inherited disorder due to expansion of trinucleotide repeats in the gene coding for the protein junctophilin 3.

McLeod syndrome – An X-linked recessive neurodegenerative disease characterized by involuntary movements (chorea) and acanthocytosis, in which there is reduced expression of XK and Kell antigens on erythrocytes.

Neuroacanthocytosis – A term for the group of neurological conditions in which there are abnormalities of red blood cell membranes resulting in thorny protrusions.

Definition

The neuroacanthocytosis (NA) syndromes are those in which there are abnormalities of red blood cell (RBC) membranes, resulting in thorny protrusions, in addition to neurological symptoms (**Figure 1**). The term has been used for inherited disorders of lipoproteins such as abetalipoproteinemia and hypobetalipoproteinemia, which result in deficiency of vitamin E due to malabsorption, with the neurological consequences of degeneration of the posterior columns of the spinal cord and peripheral neuropathy. However, the term NA is more generally used at present, and is used in this article to refer to the syndromes in which the basal ganglia are affected and patients typically develop movement disorders and psychiatric symptoms.

The two core NA syndromes are autosomal recessive chorea-acanthocytosis (ChAc) and X-linked McLeod syndrome. These syndromes are similar in many aspects, and distinguishable from other choreatic disorders by the presence of specific other neurological and nonneurological features. There are two conditions in which acanthocytes are found in a minority of patients: Huntington's disease-like 2 (HDL2) and pantothenate kinase-associated

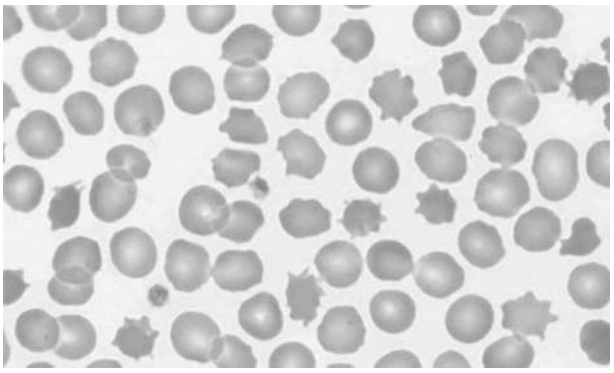

Figure 1 Acanthocytosis on peripheral blood smear. Courtesy of Dr. Hans H. Jung. Reprinted from Danek and Walker, Neuroacanthocytosis. *Current Opinion in Neurology* 18(4): 386–392. Lippincott Williams & Wilkins, Philadelphia, PA, with permission from Lippincott Williams & Wilkins.

neurodegeneration (PKAN). A condition initially known as hypoprebetalipoproteinemia, acanthocytosis, retinal pigmentation, and pallidal degeneration (HARPP) syndrome was subsequently identified as being allelic with PKAN.

A small number of single families with other neurologic syndromes and acanthocytosis have been reported. These include a familial syndrome due to a mitochondrial mutation and a patient with a paroxysmal exertional syndrome. A family with paroxysmal exertional dyskinesia, recently found to be due to mutation of the glucose transporter, GLUT1, was initially reported to have acanthocytosis; however, on electron microscopy, these were found to be echinocytes. This RBC membrane abnormality was likely due to electrolyte abnormalities from the cation leak caused by the transporter mutation.

The presence of acanthocytosis is not invariably present, even in the two core syndromes, and is not required to make the diagnosis. The basis for this abnormality of RBC membrane structure in most of these syndromes is not well-understood.

Pathogenesis

All NA syndromes are monogenic. The functions of the genes responsible for ChAc and McLeod syndrome are not yet understood, nor is it known how their dysfunction leads to neurodegeneration or acanthocytosis. The significance of the abnormality of RBC membranes and its relationship to neurodegeneration, predominantly affecting the basal ganglia, remain obscure.

The exception to this is PKAN, where absence, or reduced functioning, of pantothenate kinase results in reduced coenzyme A. Vulnerable brain areas may be those with the highest energy demands. Impaired lipid synthesis due to coenzyme A deficiency is likely to be the cause of acanthocytosis; however, it is not known why this is seen only in ~10% of patients.

Neurodegeneration, in cases which have come to autopsy, is found predominantly in the basal ganglia. Neuropathological findings consist of neuronal loss and gliosis of these regions, but no inclusion bodies of any nature have been detected.

Epidemiology

These disorders are very rare. The most common and widely-recognized of these syndromes is PKAN, which has been estimated to occur at a rate of 1–3 per 1 000 000.

Both ChAc and McLeod syndrome are exceedingly rare, and identified cases number in the hundreds worldwide. Both have been reported in most ethnic populations. ChAc has a higher incidence in Japan, apparently due to a founder effect.

HDL2 has been reported to date only in families of African ancestry, with the exception of one patient from the Middle East.

Clinical Features and Diagnostic Criteria

As is typical of neurodegenerative disorders involving the basal ganglia, this group of disorders may present with a variety of movement disorders and psychiatric features. In particular, ChAc, McLeod syndrome, and HDL2 may present in young adulthood initially with psychiatric findings. It is not uncommon for the development of the movement disorder and cognitive impairment to be attributed to neuroleptic administration, thus masking and delaying diagnosis.

Childhood onset of generalized chorea and dystonia, with additional features of pigmentary retinal degeneration, suggests PKAN. Dystonic tongue protrusion can be seen both in this disorder and ChAc, but in ChAc it is specifically induced by eating.

The neurological features of ChAc typically develop in the 20s–30s, but may present in adolescence with obsessive–compulsive spectrum symptoms, including tic disorders. Severe, self-mutilating lip- and tongue-biting is typical of ChAc.

McLeod syndrome develops in middle-aged men, and also may present with psychiatric or cognitive deterioration. Hepatosplenomegaly, seizures, peripheral sensorimotor neuropathy, and areflexia suggest either McLeod syndrome or ChAc. Cardiomyopathy is found only in McLeod syndrome.

Patients with HDL2 typically have a family history indicative of autosomal dominant inheritance, with a clinical phenotype also strongly suggestive of HD. Similar

to Huntington's disease (HD), the age of onset is inversely related to the size of the trinucleotide repeat expansion.

Diagnosis of McLeod syndrome and ChAc is made by detection of the absence of their protein marker in peripheral blood. Diagnosis of both these, and PKAN and HDL2, is confirmed by the detection of mutations in the respective genes.

Differential Diagnosis

The differential diagnosis of each of these diseases depends upon the presentation, and may include the possible etiologies of chorea, dystonia, parkinsonism, psychopathology, peripheral neuropathy, myopathy, and tics. The family history, additional clinical features, and laboratory and neuroimaging findings are often informative.

Diagnostic Work-up

Work-up of any patient with a movement disorder should include evaluation of liver enzymes, and if these enzymes are elevated, Wilson's disease should be excluded, which at present is the only treatable neurodegenerative disorder. Once Wilson's disease has been excluded, elevation of liver enzymes suggests ChAc or McLeod syndrome, as does elevation of creatine kinase, which is often increased many times the upper limit of normal.

Sensitivity for acanthocytosis on peripheral blood smear can be increased by incubating the RBCs with an equal volume of normal saline containing 10 IU ml^{-1} heparin for 30 min on a shaker. Electron microscopy of glutaraldehyde-fixed RBCs is also confirmatory. However, the presence of acanthocytes in the NA syndromes is not constant, for reasons which are not well understood, and their absence does not preclude the diagnosis.

Neuroimaging in ChAc, McLeod syndrome, and HDL2 is often reported as being consistent with HD, with bilateral atrophy of the caudate nuclei. In PKAN, iron deposition in the globus pallidus gives the 'eye-of-the-tiger' appearance.

Management

Management of all these neurodegenerative conditions is at present purely symptomatic. Dopamine-depleting and -blocking agents may be useful in the treatment of chorea; however, the involuntary movements may not impair function as much as other aspects of the disease such as psychopathology or peripheral neuromuscular abnormalities. Psychiatric and cognitive symptoms should be treated appropriately.

Results of deep brain stimulation (DBS) have been variable, and the optimal site and stimulation parameters remain to be determined; however, 40 Hz stimulation of the globus pallidus pars interna may be beneficial in ChAc. The largest experience with DBS is in patients with PKAN in which a number of positive responses to high-frequency pallidal stimulation have been reported.

Seizures in ChAc and McLeod syndrome usually respond to standard anticonvulsants, although lamotrigine and carbamazepine have been reported to worsen the involuntary movements.

A multidisciplinary approach with the involvement of paramedical therapists is essential for long-term care. Evaluation by a speech therapist is invaluable to minimize problems due to dysphagia and nutritional compromise. Physical and occupational therapists should be involved to assist difficulties like gait, balance, and activities of daily living.

Prognosis

These disorders are in general slowly progressive over several decades. Sudden death may be due to seizure, or possibly autonomic dysfunction, or there may be gradually progressive, generalized debility, as seen in Huntington's or Parkinson's diseases, with patients succumbing to aspiration pneumonia or to other systemic infection.

See also: Chorea; Chorea–acanthocytosis; Hallervorden–Spatz Syndrome (PKAN); Huntington's Disease; McLeod Syndrome.

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Neuroferritinopathy

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Glossary

Autosomal dominant – Mendelian pattern of inheritance associated with a risk of up to 50% of inheritance from affected persons to children.
Disinhibition – Impaired ability of patients to deal with their immediate impulsive response to a situation.
Ferritin – Protein, of which the light chain is encoded by the FTL gene, is responsible for iron detoxification and iron storage.
Ferritin inclusion bodies – Neuropathological finding of neuroferritinopathy mainly located in the nucleus and cytoplasma of glia and neurons.
Frameshift mutation – Sequence insertion or deletion causing a shift of the translational reading frame.
Neurodegeneration with brain iron accumulation (NBIA) – Group of disorders characterized by deposition of iron in the brain.

Definition and History

Neuroferritinopathy (adult-onset basal ganglia disease, hereditary ferritinopathy (HF), MIM 606159) is a rare autosomal dominant disorder belonging to a group of hereditary neurodegenerative disorders named neurodegeneration with brain iron accumulation (NBIA). Disorders of this group share deposition of iron in the brain as a common feature. It was not until 2001 that the genetic cause of neuroferritinopathy was identified. The causal mutation in the *FTL* gene was detected in a family that was originally believed to be affected by Huntington's disease, a common misdiagnosis of patients with neuroferritinopathy.

The different mutations in this gene had already been attributed to another disorder named hyperferritinemia–cataract syndrome.

Pathogenesis/Pathophysiology

The *FTL* gene is located on the chromosome 19q13.3 and encodes the light chain of ferritin. The mammalian ferritins are expressed in most cells. They are composed of 24 polypeptide subunits with variable proportions of the light (FTL) and the heavy (FTH1) chains. The protein structure is a dodecahedron, a 12-sided hollow ball. The function of ferritin includes iron detoxification and iron storage of up to 4500 iron atoms per ferritin. Iron plays a role in many physiological processes, for instance, in neuronal development, myelination, and synthesis of neurotransmitters. Its toxicity is believed to be based on the generation of reactive oxygen species (ROS) causing lipid peroxidation, DNA strand breaks, and protein modifications.

The first mutation described in the *FTL* gene was an insertional mutation of an additional adenine at positions 460 to 461 causing a frameshift. Reports of six other mutations in the *FTL* gene associated with neuroferritinopathy followed (**Table 1**). All but one mutation are frameshift mutations located in exon 4 leading to elongation of the 175 amino acids long ferritin protein. According to protein modeling, the terminal part of FTL is predicted to form the pores through which the iron molecules must pass when entering the ferritin complex. Uncontroled release of iron could be the underlying pathomechanism of the *FTL* mutations.

Postmortem neuropathological findings in patients with neuroferritinopathy are ferritin nuclear and cytoplasmic inclusion bodies and iron accumulation in glia and neurons throughout the CNS.

Epidemiology/Risk Factors

Neuroferritinopathy is a very rare disorder with about 50 cases reported worldwide until now. Both males and females are equally affected. The majority of patients carry the c.460dupA mutation, which probably represents a founder mutation. All other mutations have been reported in single families.

Clinical Features and Diagnostic Criteria

Diagnostic criteria of neuroferritinopathy include (1) clinical phenotype and progression, (2) family history consistent with autosomal dominant inheritance, (3) inappropriate low serum ferritin, and (4) evidence for iron deposits in the basal ganglia detected by magnetic resonance imaging (MRI).

Clinical Findings

The variability of age of onset and clinical manifestations represents a major problem when diagnosing neuroferritinopathy. The age of onset may vary from 13 to 63 years

Table 1 Clinical findings and mutation status in patients with neuroferritinopathy

Mutation	*Type of mutation*	*Family*	*Onset of disease*	*Clinical symptoms*	*Reference*
474G>A* (p.Ala96Thr)	MS	1	13	Mild non-progressive mental retardation, gait disturbance, psychosis, akinetic-rigid syndrome, ataxia, pyramidal signs	Maciel et al.
641_644dup4* (p.Leu149ProfsX33)	FS	1	Middle age	Chorea	Kubota et al.
646_647insC* (p.Thr150HisfsX43)	FS	1	63	Chorea, limb ataxia, areflexia, bilateral extensor plantar responses	Mancuso et al.
c.458dupA (p.His153GlnfsX28)	FS	1	24–44	Dystonia, anarthria, dysphagia, cerebellar symptoms, subcorticofrontal dementia, parkinsonism	Devos et al.
c.460dupA (p.Arg154LysfsX27)	FS	41 patients	39.4 (13–63)	Dystonia (83%), chorea (70%), oromandibular dyskinesia (65%), characteristic speech with dysarthrophonia and action-specific dystonia 63%), dysphagia (40%), mild cognitive decline (44%), severe dystonic hypophonia and aphonia (11%), facial hypomimia and bradykinesia (35%)	Curtis et al. Chinnery et al.
c.469_484dup16 (p.Leu162ArgfsX24)	FS	1	Middle teens	Hand tremor, generalized hypotonia, hyperextensibility, cognitive impairment, hyperreflexia	Ohta et al.
c.498_499insTC (p.Phe167LeufsX26)	FS	1	20	Tremor, frontal/sub-cortical cognitive impairment, dyskinesia brisk tendon reflexes, Babinski signs	Vidal et al.

*Numbering includes 199 nucleotides from the 5′UTR region.
MS, missense mutation; FS, frameshift mutation.

with a mean onset of about 40 years. The most frequently reported presenting symptoms are focal onset chorea (50%), focal dystonia (43%), and Parkinsonism (7.5%). Less common presenting symptoms include blepharospasm, writer's cramp, and ballistic movements. These symptoms usually progress slowly with ambulation, remaining possibly for up to two decades after disease onset. Some of the patients carrying mutations other than the common c.460dupA mutation were manifested with different symptoms such as hypotonia, tremor, and ataxia, and sometimes these patients showed faster disease progression. The distribution of symptoms is often asymmetric. During the course of disease, nearly all patients develop dystonia and chorea. Additional features patients may suffer from include oromandibular dyskinesia, dysphagia, and a typical speech characterized by a dysarthrophonia and action-specific dystonia. Cognitive impairment is a frequent finding (44% in the first decade of disease progression), but when present, tends to be mild in the form of minor defects of verbal fluency. Only rare cases of frontal/subcortical dementia have been reported. Disinhibition and emotional liability are a frequent finding even in the early stages of disease. Detection of more mutations could further broaden the clinical spectrum of neuroferritinopathy.

Clinical Chemistry

Detection of very low levels of ferritin supports the diagnosis neuroferritinopathy. It is usually combined with normal haemoglobin and serum iron levels. This clinical feature is seen in the majority of affected males and postmenopausal women but only in a quarter of premenopausal females. Other routinely analyzed blood parameters have not been shown to be altered specifically. Muscle biopsy reveals deficiency in the mitochondrial respiratory chain complex in some patients.

Neuroimaging

MRI of patients with neuroferritinopathy is characterized by the evidence of iron deposition in the brain and tissue destruction.

T2 sequence*

About half of the patients have a widespread hypointensity in the cerebral cortex and the basal ganglia (globus pallidus, putamen, caudate nuclei, thalamus, substantia nigra, dentate nuclei). In the remaining patients a confluent area of hyperintensity (cavitation) is found in the

globus pallidus and the putamen surrounded by a rim of hypointensity. In addition, a hypointensity of substantia nigra and dentate nuclei is detected. Rarely, the 'eye of the tiger' sign is seen as in patients with pantothenate kinase-associated neurodegeneration (PKAN) patients.

FSE (fast spin echo) scans

In about half of the patients FSE scans reveal small areas of hyperintensity within pallida, putamen, and caudates combined with hypointensity of substantia nigra and dentates. Remaining patients show confluent hyperintensity (probable cavitation) of pallida and putamen in addition to hypointensity of substantia nigra and dentate nuclei.

Differential Diagnosis

Other progressive neurological diseases with onset in adulthood need to be considered in the differential diagnosis (**Table 2**), especially disorders manifesting with symptoms like dystonia and chorea. Pantothenate kinase-associated neurodegeneration with brain iron accumulation (PKAN) and aceruloplasminemia are further disorder characterized by iron depositions in the brain.

Diagnostic Work-up/Tests

In patients with an adult-onset progressive neurodegenerative disease combined with evidence for an autosomal dominant pattern of inheritance or an inappropriately low serum ferritin, MR T2* imaging should be performed. In the case of evidence for iron deposition in the basal ganglia, diagnosis of neuroferritinopathy should be confirmed by molecular genetic testing. The *FTL* gene is the only gene described for neuroferritinopathy. Sequence analysis identifies mutations in the *FTL* gene in about 80% of affected individuals, in simplex cases the detection rate decreases.

Management

Guidelines for therapy are issued by Chinnery et al. based on their clinical data.

Treatment

No effective treatment exists so far. Therapies under investigation include iron chelation, phlebotomy and coenzyme Q10.

Symptomatic treatments exist in the form of levodopa, tetrabenzine, benzhexol, diazepam, clonazepam, and deanol in standard doses. Botulinum toxin is used to relieve the distress of dystonia. Supportive therapies such as physiotherapy and dietary measures are recommended.

Genetic Counseling

Neuroferritinopathy is inherited in an autosomal dominant manner. Each child of an individual with neuroferritinopathy has a chance of 50% to inherit the *FTL* mutation. Penetrance is age dependent and probably close to 100% at old age. Exact data on the age dependency of the penetrance are not available.

Prognosis

The course of disease is progressive albeit slowly in most cases. It may eventually lead to significant restrictions in form of aphonia, dysphagia, severe motor disability, and cognitive impairment.

Table 2 Differential diagnosis of neuroferritinopathy

Disorder	*Gene*	*MI*	*Difference to neuroferritinopathy*
Huntington's disease	HD	AD	More severe cognitive decline, normal ferritin
Huntington-like disease 2	JPH3	AD	More severe cognitive decline, normal ferritin
Idiopathic torsion dystonia	DYT1	AD	Age of onset is earlier in most cases, normal ferritin
Spinocerebellar Ataxia 17	SCA17	AD	Ataxia is the predominant feature, normal ferritin
AD dopa-responsive dystonia	GCH1	AD	Responsiveness to L-dopa, normal ferritin
Nieman-Pick disease type C	NPC1, NPC2	AD	Abnormal eye movements, normal ferritin
X-linked (McLeod's) neuroacanthocytosis	XK	XR	Elevated CK, compensated haemolysis, seizures, normal ferritin
Recessive choreoacanthocytosis	VPS13A	AR	Elevated CK, seizures, sensory axonopathy, normal ferritin
Pantothenate kinase-associated neurodegeneration (PKAN)	PANK2	AR	Spasticity in most patients, normal ferritin
Aceruloplasminemia	CP	AR	Not confined to neurological symptoms (diabetes mellitus, retinal degeneration) reduced serum copper, reduced serum iron and reduced plasma ceruloplasmin ferroxidase activity, increased serum ferritin

MI, Mode of inheritance; AD, autosomal dominant; XR, X-linked recessive; AR, autosomal recessive; CK, creatine phosphokinase.

See also: Chorea; Dystonia; Dystonia, Secondary; Eye-of-the-Tiger Sign; Hallervorden–Spatz Syndrome (PKAN).

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Neurofibrillary Tangles

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Glossary

Bielschowsky silver stain – A histological silver technique developed by the neuropathologist Max Bielschowsky (*c.*1900), with which it was possible, for the first time, to visualize light microscopically not only nerve cells but also the so-called 'senile plaques' and intraneuronal neurofibrillary tau protein deposits (tangles) that characterize Alzheimer's disease.

Cytoskeleton – A kind of scaffolding found within the cellular cytoplasm consisting of intermediate filaments, actin microfilaments, and microtubules, which lend the cell shape and facilitate intracellular transport.

Gallyas silver stain – A histological silver technique developed by the still active Hungarian neurochemist Ferenc Gallyas, which uses silver ions plus a reducing agent and stabilizer to visualize light microscopically, among other entities, the neurofibrillary lesions associated with Alzheimer's disease.

Microtubule-associated proteins – A family of proteins, including the protein tau (MAPT), that binds to the microtubules of the cytoskeleton.

Tauopathies – Neurodegenerative diseases of the human brain involving aggregations of the protein tau and including Alzheimer's disease, argyrophilic grains disease, corticobasal degeneration, Pick's disease, progressive supranuclear palsy, and frontotemporal dementias (FTD).

Definition and History

A major criterion – and one that is mandatory for the neuropathological confirmation of the clinical diagnosis of Alzheimer's disease (AD) – is assessment of intraneuronal protein inclusions that appear as neurofibrillary tangles (NFTs) and neuropil threads (NTs) in vulnerable types of nerve cells. NFTs were detected and first described by Alois Alzheimer, who employed Max Bielschowsky's silver impregnation. These neurofibrillary lesions result from the pathological aggregation of the misfolded and abnormally phosphorylated protein tau. In healthy individuals, normal tau stabilizes the microtubules of the neuronal cytoskeleton. Among their diverse functions, microtubules facilitate the transport of substances between nerve cell compartments. Aggregated tau filaments cannot be degraded by host neurons and gradually accumulate within the cytoplasm.

Select Projection Neurons Especially Prone to the Neurofibrillary Pathology

NFTs and NTs develop in only a few of the many neuronal types within the human nervous system. Most of the vulnerable cells are projection neurons with a long and thin axon. By contrast, short-axoned cells generally are resistant. Exceptions include chandelier cells, which can develop a soluble material that contains abnormally

phosphorylated tau, but these rapidly disappear before NFTs/NTs can form; large cholinergic interneurons in the striatum can develop globose NFTs early in AD.

Susceptible projection cells not only have a long axon but also one that is unmyelinated or poorly myelinated. In addition, vulnerable cells contain lipofuscin or neuromelanin. Heavily myelinated projection neurons resist the pathological process as do those lacking pigment granules. On the other hand, cells with a long, sparsely myelinated axon and containing large amounts of pigment are not necessarily prone to become involved.

Pretangle Phase

Specific antibodies (e.g., AT8) that react with abnormally phosphorylated tau permit visualization of the very earliest pathogenic stage (pretangle phase) that marks the onset of the neurodegenerative process. Abnormally phosphorylated tau forfeits its binding capacity on the microtubules. It is still soluble and nonargyrophilic in cytosol, filling both the cell body and its cellular processes – an aspect closely resembling a Golgi impregnation (**Figure 1(a)**). The axon is homogeneously immunoreactive and can be followed for a considerable distance in the tissue, including its terminal ramifications (**Figure 2**). Initially, the cellular processes display no deviations from their normal shapes. It is unknown how long the cells remain in this 'pretangle' phase, but it is the forerunner of the argyrophilic NFT/NT stages that follow. Theoretically, the potential for reversing the intraneuronal disease process is at its peak during this phase.

NFT Formation

After the pretangle phase, the abnormal tau protein inclusions undergo crosslinkage (aggregation). The axon is no longer AT8-immunoreactive: distal dendritic segments appear twisted and dilated with shortened appendages, and dendrites become partially detached from their stems (**Figure 1(b)**). Traces of silver-stained fibrillary material occur near lipofuscin or neuromelanin granules (**Figure 1(c)**), and eventually the central portions of larger NFTs become concentrated around pigment deposits. It is even possible that pigment granules serve as initiation sites and support oxidative crosslinking reactions. Slender NTs appear in altered dendrites, and, thereafter, a NFT is visible within the cell body. NFTs are argyrophilic, insoluble, cannot be degraded by the host neurons, and occupy large portions of the cytoplasm (**Figure 1(d)**). In some neuronal types, such NFTs extend into the proximal dendrites (flame-shaped NFTs), whereas globose NFTs remain confined to the cell body. NFTs do not extend into the axon hillock or initial axonal segment. The earliest pretangles and NFTs/NTs denote the beginning of a process which, unless interrupted by death, inevitably progresses to clinically manifest AD (**Figure 1**).

Survival and Death of Tangle-Bearing Neurons

Projection neurons are remarkably sturdy and can survive for decades despite the presence of marked tau protein alterations. Because cell death does not occur immediately, the question arises whether NFTs/NTs are harmful to host nerve cells or whether, instead, the aggregation process represents an attempt to eliminate nonbiodegradable but otherwise benign material. Available evidence indicates that an absence of neuronal loss does not mean that the functional capabilities of involved neurons remain intact; the axonal and dendritic changes take years and are accompanied by a gradual decrease in basophilia. Moreover, microtubule destabilization and impaired axonal transport probably result in deficient protein metabolism, synaptic dysfunction, and impaired signaling by retrograde neurotrophic factors. In other words, functional decline may contribute to neuronal death, but we do not yet understand the exact circumstances of all of the biological mechanisms that are involved at each step along the way to cell loss. Tangle-bearing neurons display mechanisms of dying that most probably differ from apoptosis or necrosis. Neither blebbing, nor chromatin condensations, nor macrophagic activity are observable.

Ghost Tangles

After cell death extraneuronal lesions are visible in the tissue as so-called 'ghost' or 'tombstone' tangles. At this point, the fibrillary material shows markedly reduced immunoreactivity. Ghost tangles have a less tightly twisted, much less argyrophilic aspect than NFTs (**Figure 1(e)**) and are surrounded by local astrocytes. To the extent that ghost tangles are subject to so little change (e.g., disintegration or degradation) for many years, it is highly questionable whether they ever disappear from the tissue entirely. Just how the enormous amount of abnormal material in NTs is processed or metabolized following the deaths of NT-bearing neuronal processes is also unclear.

Evolution and Staging of the Pathological Process

The AD-related pathological process evolves slowly and nearly symmetrically throughout specific cortical areas and subcortical nuclei (**Figure 2**). Beginning in

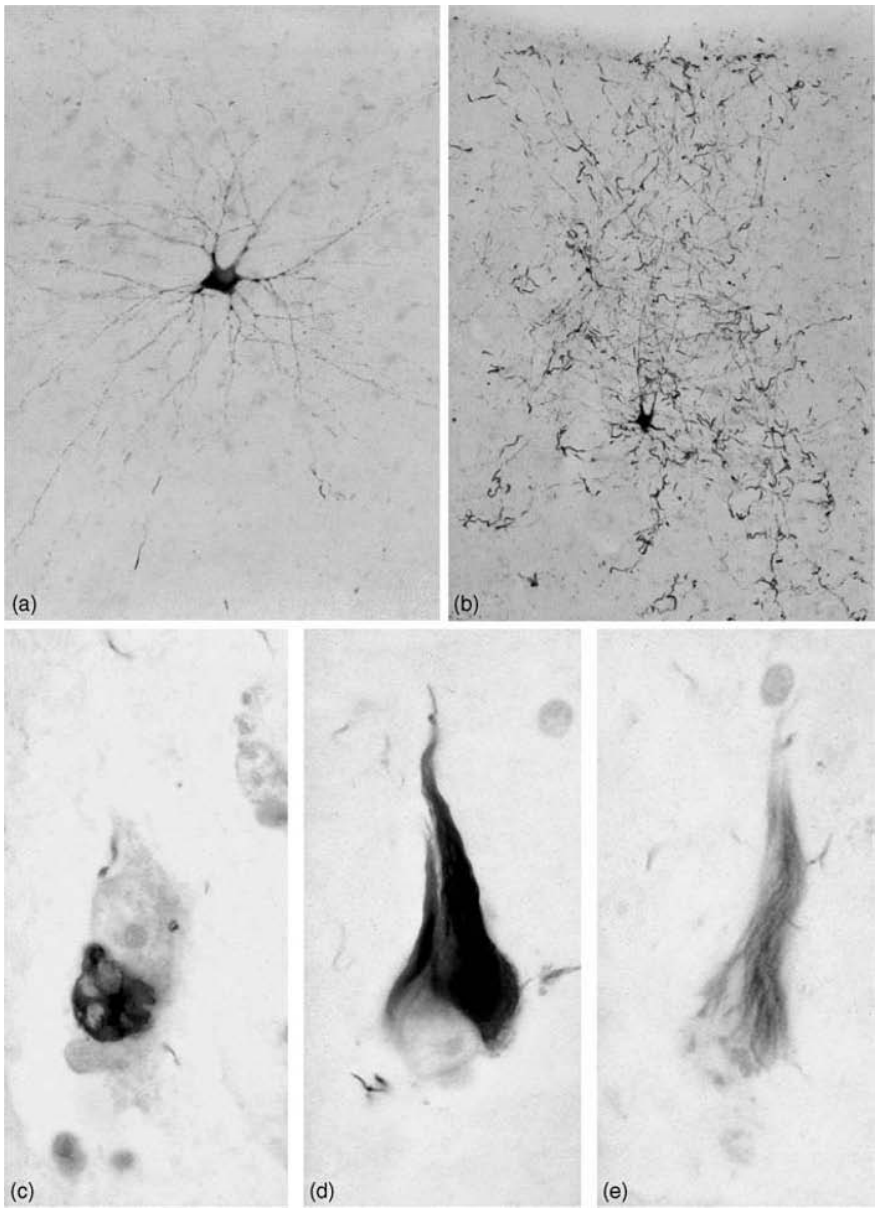

Figure 1 Formation of intraneuronal pretangles, tangles, and ghost tangles. (a) Initial hyperphosphorylation of tau defines the pretangle phase. Soluble tau fills the entire neuron. (b) In a second step, crosslinkage of this abnormal material occurs and distal dendritic segments become twisted (AT8 immunoreactions for abnormally phosphorylated tau protein in 100 μm polyethylene glycol-embedded tissue sections). (c) The now fibrillary material becomes argyrophilic, insoluble, and is nonbiodegradable (inert). Central portions of the NFT are concentrated around lipofuscin granules. (d) The material fills large portions of the soma and may extend into proximal dendrites. (e) After deterioration of the host cell, the NFT remains visible as an extraneuronal ghost tangle (Gallyas silver stain for neurofibrillary changes of the Alzheimer type plus aldehyde fuchsin–Darrow red staining for basophilic material and lipofuscin granules).

predisposed subcortical and cortical induction sites, it then progresses into other portions of the cerebral cortex and specific sets of subcortical nuclei according to a predictable topographic sequence with little interpatient variation. The distribution pattern of the neurofibrillary lesions has provided the conceptual basis for distinguishing six neuropathological stages. These comprise clinically 'silent' or preclinical cases in transentorhinal stages I and II, cases of incipient AD or mild cognitive impairment in limbic stages III and IV, and cases with fully developed AD in neocortical stages V and VI. Staging procedures are imperfect constructs because the lesions develop continually as part of a larger biological process rather than in artificially defined steps.

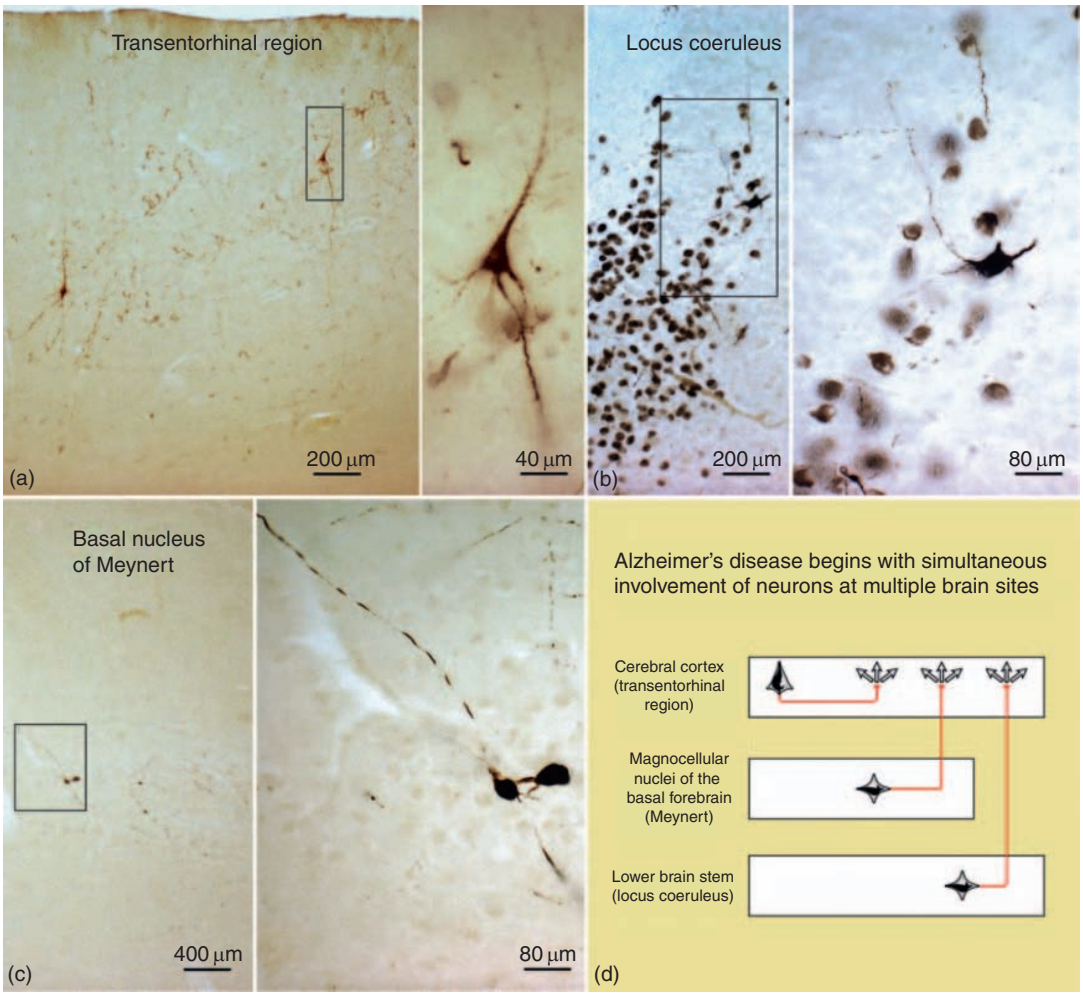

Figure 2 Pretangles displaying the earliest cytoskeletal abnormalities appear at multiple brain sites simultaneously. (a–c) 32-year-old male 'control' case, that is, brain tissue still free of NFT-bearing nerve cells. Framed areas appear at higher magnification to the right of each of the overviews. (a) Overview and detail of pretangle neurons in the transentorhinal region, the only cortical site where pretangles were seen in this case. (b) Solitary pretangle neuron in the noradrenergic locus coeruleus of the lower brainstem. (c) Pretangle-bearing neuron in the cholinergic nucleus of Meynert of the basal forebrain. These were the only two locations where pretangle pathology occurred in subcortical nuclei. (d) Although the possibly earliest predilection sites for pretangles are located at a considerable distance from each other, they share one feature in common, namely, all send projections to layer I of the cerebral cortex (arrows) (AT8 immunoreactions for abnormally phosphorylated tau protein in 100 μm polyethylene glycol-embedded tissue sections).

Prevalence of Alzheimer-Type Neurofibrillary Changes

The relationship between age and the NFT/NT-associated changes has been studied by staging large numbers of nonselected autopsy brains. **Figure 3** shows the percentage of such cases for each of the six NFT stages by age group. Data acquired in this manner indicates that NFTs and NTs are not associated with normal aging, although the lesions become increasingly prevalent with age and occur in a very large proportion of the aging population. Whereas human aging is a continuum of biological processes and adjustments in independent living skills, which transpire throughout a lifetime, and not a disease process, NFTs/NTs are not benign and not every aged individual develops them. A small number of cases display the lesions at an unexpectedly young age, that is, at a point in life when other age-related findings, such as accumulation of lipofuscin granules, neuronal atrophy, and cerebrovascular pathology, are not routinely present. Thus, advanced age is not a prerequisite for the lesions and AD is not an age-dependent but, rather, an age-related disorder because the arithmetic means of stages for NFTs/NTs increase with age (**Figure 3**).

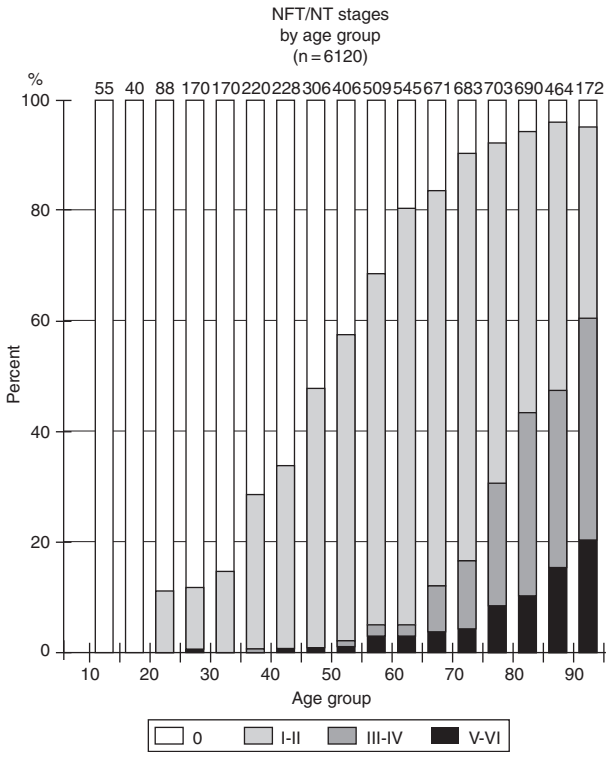

Figure 3 Schematic diagram showing the breakdown by age groups and percent for 6120 nonselected autopsy cases according to neurofibrillary stages: 0 (white), I and II (light gray), III and IV (gray), and V and VI (black). Neurofibrillary degeneration occurs with greater prevalence at later decades. Considerable variability exists with regard to the age at which the first NFTs/NTs develop: Stage I and II lesions are present in some cases even before the age of 25, which implies that advanced age is not required for their development. The white columns represent individuals whose brains lack NFTs/NTs. A tiny minority of elderly persons, even at 90 years of age, refrain altogether from developing Alzheimer's disease-associated intraneuronal lesions.

Considerable differences exist with respect to the age at which the earliest NFTs/NTs are detectable. Stage I and II lesions are found in persons under the age of 25. Around the age of 50, one-half of the cases examined exhibit the lesions, and by the age of 80, fewer than 10% are still unaffected. The age distributions from stages I–VI show that early stages occur preferentially in younger age categories, whereas more advanced stages increase in frequency with advancing age. The presence of even a few elderly subjects without NFTs and NTs is important because it demonstrates that even the very old can be resistant to the disease process.

Acknowledgments

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See also: Tauopathies.

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Neurogenic Muscle Weakness, Ataxia, and Retinitis Pigmentosa (NARP)

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Glossary

Adenosine triphosphate (ATP) – ATP is the common bioenergetic currency of the cell.
ATP synthase – Complex V of the mitochondrial pathway that generates ATP by oxidative phosphorylation.
ATP6 – ATP synthase subunit 6, which is encoded in mitochondrial DNA.
Cybrids – Cytoplasmic hybrid cells usually generated by fusing cytoplasm from patient cells harboring a mitochondrial (mtDNA) mutation with cells lacking mtDNA (rho-zero cells).
Heteroplasmy – A mixture of different forms of multicopy DNA molecules (e.g., mtDNA).
Homoplasmy – A uniform population of multicopy DNA molecules.
Leigh syndrome – A severe encephalopathy that typically manifests in infancy with psychomotor regression and lesions of brainstem, basal ganglia, or both.
Maternal inheritance – Vertical transmission of DNA from mother to progeny.
Mitochondrial DNA (mtDNA) – A small (16 569 bp) circular DNA molecule within mitochondria and encoding 37 genes.
NARP – Neuropathy, ataxia, and retinitis pigmentosa.
Respiratory chain – A set of four multisubunit enzymes (complexes I–IV) embedded in the mitochondrial inner membrane that transfer reducing equivalents (electrons) to generate a transmembrane proton gradient that is used to drive ATP synthesis through ATP synthase.

Definition and History

In 1990, Holt, Harding, and colleagues described four maternally related members of a family with neurogenic muscle weakness, sensory neuropathy, ataxia, retinitis pigmentosa, and encephalopathy due to a novel mitochondrial DNA (mtDNA) point mutation (m.8993T → G) in the ATP synthase 6 gene (ATP6). The syndrome was later called neuropathy, ataxia, and retinitis pigmentosa (NARP). Additional point mutations in the ATP6 gene have been identified in patients with the NARP phenotype. Subsequently, Tatuch and colleagues and Santorelli and colleagues reported that in some families with NARP, maternally related infants presented with Leigh syndrome, a severe devastating encephalopathy characterized by psychomotor regression with symptoms and signs of brainstem disease, basal ganglia dysfunction, or both.

Pathogenesis and Pathophysiology

NARP has been associated with four mutations at two sites in the ATP6 gene: m.8993T → G (p.156L → R), m.8993T → C (p.156L → P), m.9176T → G (p.217L → R), and m.9176T → C (p.217L → P). Curiously, at each mutation site, conserved leucines are converted to either an arginine or proline. Generally patients with the T → G (leucine to arginine) mutations are more severely affected than individuals with the T → C (leucine to proline) mutations. Heteroplasmic mutation burden correlates with severity of the phenotypes; patients with 70–90% mutation generally develop NARP while individuals with >90% mutation typically have Leigh syndrome. Individuals with <60% mutation load often do not show any neurological or retinal abnormalities.

The ATP6 mutations clearly impair oxidative phosphorylation – synthesis of ATP in the inner mitochondrial membrane; however, the molecular pathomechanism has not been fully defined. Reports indicate that the mutations may affect ATP synthase (complex V) assembly, coupling between proton transport and ATP synthesis, or both. Cell culture studies indicate that both m.8993T → G and m.8993T → C mutations cause energy deprivation and overproduction of reactive oxygen species (ROS), but the m.8993T → G mutation mainly impairs ATP synthesis while the milder m.8993T → C mutation generates higher levels of ROS.

Epidemiology/Risk Factors

NARP is a rare disorder with a prevalence rate that is probably <1:100 000. The major risk factor is presence of a NARP ATP6 mutation in the maternal lineage.

Clinical Features and Diagnostic Criteria

As the acronym implies, NARP is defined clinically by neuropathy, ataxia, and retinitis pigmentosa with onset

typically in childhood. The neuropathy manifests as proximal neurogenic weakness with stocking-glove sensory loss due to axonopathy. Encephalopathy is often prominent and can manifest as learning disability, mental retardation, dementia, and seizures. Other clinical features include short stature, sensorineural hearing loss, chronic progressive external ophthalmoplegia, cardiac conduction block, diabetes mellitus, and anxiety disorder. One patient had obstructive sleep apnea. Visual symptoms, particularly night blindness or reduced peripheral vision, may be the only manifestation and is primarily due to abnormal cone structure. On the other hand, retinitis pigmentosa may be absent in patients with other clinical features of NARP.

In families with NARP, some individuals may develop Leigh syndrome that typically begins during infancy often in association with a viral febrile illness.

Differential Diagnosis

The differential diagnosis of NARP includes other mitochondrial disorders such as Kearns–Sayre syndrome, myoclonus epilepsy with ragged-red fibers (MERRF), coenzyme Q10 deficiencies, mtDNA depletion syndrome, and multiple mtDNA deletion disorders. For NARP patients presenting with peripheral neuropathy, Charcot Marie Tooth syndrome is a differential diagnosis while for individuals with ataxia or retinitis pigmentosa, other genetic disorders may be considered.

Diagnostic Work-up/Tests

The diagnosis of NARP can be molecularly confirmed by identification of one of the known ATP6 gene mutations in blood, buccal mucosa, urine, or tissue. Additional diagnostic evaluation of patients with NARP should include: developmental assessment, complete neurological, ophthalmological, and cardiological evaluations; metabolic assessment (blood lactate and pyruvate); brain MRI; and, if seizures are suspected, electroencephalogram. Cerebrospinal fluid (CSF) lactate can be assessed by lumbar puncture or magnetic resonance spectroscopy, but is not essential. Unlike mitochondrial diseases due to mtDNA transfer RNA gene or deletion mutations or mtDNA depletion, muscle biopsies of patients with NARP do not show morphological alterations of mitochondria (e.g., ragged-red fibers or cytochrome *c* oxidase deficient fibers); therefore, muscle biopsies are not useful for the diagnosis of NARP.

Management

There are no specific treatments for ATP6 mutations. Nevertheless, supportive therapies are important, including management of seizures with anticonvulsants (such as avoiding valproic acid and barbiturates if possible), treatment of dystonia, and standard therapies for cardiomyopathy and diabetes mellitus if present. Coenzyme Q10 (50–200 mg tid) and L-carnitine (300 mg sid) have been used to improve mitochondrial function. Because ATP6 mutations, particularly m.8993T → C, may increase ROS production, antioxidants (e.g., vitamin C, α-lipoic acid, and idebenone) may be beneficial, but have not been proven to be efficacious through placebo-controlled clinical trials.

Prenatal diagnosis (PND) has been performed by measuring levels of the m.8993T → G mutation in chorionic villus or amniocyte samples. Steffan and colleagues reported that maternal mutation loads <75% in blood had no predictive value for fetal status except for women with no detectable mutation whose infants were mutation free. Based on three reports, in 10/20 PND, mutant loads were <30% and the children were healthy at ages 2–7 years while in 7/15 PND, mutation loads were ≥65% and pregnancies were terminated and tissues from six terminations showed high mutation levels in the PND samples and in all tissues of the fetuses.

Dichloroacetate (DCA) reduces lactate levels by activating the pyruvate dehydrogenase complex, and anecdotal reports indicate that in Leigh syndrome patients with the m.8993T → G mutation, during periods of acute deterioration, DCA can acutely lower lactate and may produce short-term clinical improvements.

Prognosis

The prognosis of patients with NARP is variable and depends, in part, on the particular mutation and mutation load. In general, patients with the m.8993T → G mutation are more severely affected than individuals with similar levels of the m.8993T → C mutation.

See also: Co-enzyme Q_{10}; Dystonia; Leigh Syndrome; Mitochondrial Encephalopathies; Myoclonic Epilepsy with Ragged Red Fibers (MERRF).

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Neuroimaging, Parkinson's Disease

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Parkinson's Disease

Parkinson's disease (PD) is a common neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra and dopaminergic terminals in the striatum, particularly in the posterior putamen. Usually, Lewy bodies are present in the remaining neurons, although Lewy bodies do not develop in some familial forms of PD. Striatal neurons are not affected, including postsynaptic dopamine receptors. In recent years, many structures other than the substantia nigra are known to be involved in PD, some areas are involved only late in the disease and some very early. Regions affected include the olfactory bulb, postganglionic sympathetic fibers to the heart, vagal nerve, and the dorsal motor nucleus of the vagal nucleus, raphe nucleus, locus coeruleus, pedunculopontine nucleus, ventral tegmental area, the basal nucleus of Meynert, the amygdaloid complex, and the cerebral cortex. Changes in these structures are not yet easy to demonstrate by conventional neuroimaging except for the cardiac postganglionic sympathetic terminals. For the diagnostic purpose, neuroimaging is mainly focused on the demonstration of the loss of dopaminergic neurons in the nigrostriatal system.

Structural Computerized Tomography

Structural computerized tomography (CT) is normal unless the patient has other comorbidities or complications. Mild age-related cortical atrophy and/or ventricular dilatation may be seen in old patients.

Structural Magnetic Resonance Imaging

Structural magnetic resonance imaging (MRI) using routine 1.5 T MRI is normal unless the patient has some complications. Mild age-related cortical atrophy and/or ventricular dilatation may be seen in old patients (**Figure 1**). There have been attempts to identify quantitative differences between the PD patients and healthy controls using high-resolution 1.5 T MRI such as measuring the distance between the substantia nigra pars reticulate (SNR) and the red nucleus. SNR can be identified as a T2-low signal intensity area in the ventral part of the midbrain. Although the distance is shorter in PD, likely due to the loss of neurons in the substantia nigra pars compacta, there is an overlap between the age-matched controls and PD patients. This overlap limits this technique for application in daily clinical settings. Another attempt focused on measuring the volume of the substantia nigra by inversion-recovery pulse sequences of MRI. In this case, PD patients loose a lateral-to-medial gradient of signal in the substantia nigra. This technique remains investigational. Another strategy has been the examination of possible early structural changes of the olfactory nerves in PD by diffusion weighted imaging (DWI). Diffusion weighted images can detect the water diffusivity in the brain. In the nerve fibers, water molecules tend to move along the long axis of the nerve fibers and the movement perpendicular to the axis is limited. If there are degenerative changes in the nerve fibers, loss of neurons, or gliosis, water diffusivity is thought to increase in those areas and be detectable by DWI techniques. Water diffusivity in the olfactory nerves has been

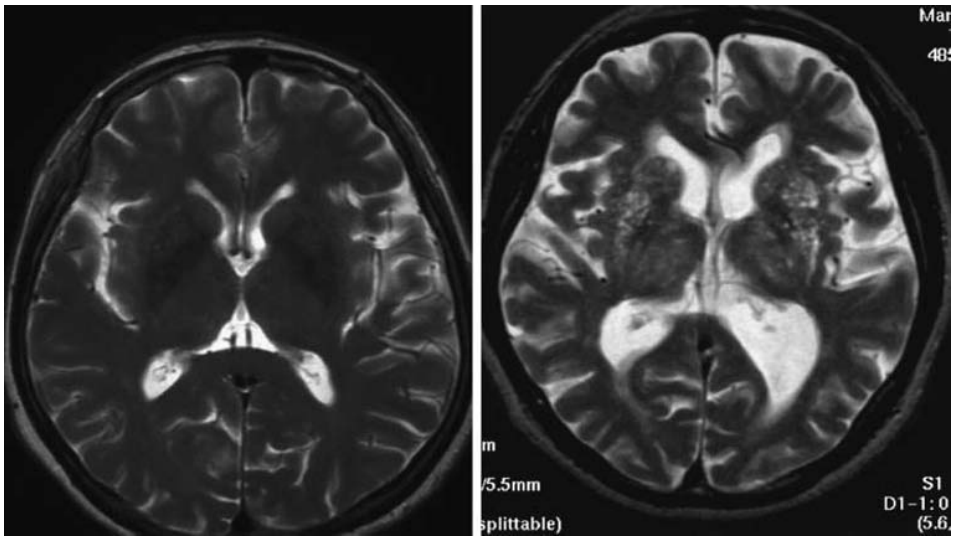

Figure 1 Left: 64-year-old man with PD. MRI is normal and cardiac MIBG uptake is markedly decreased. Right: 61-year-old woman with MSAp. The left putamen shows patchy T2-high signal lesions and the right putamen shows atrophic change, a T2-high signal lesion along the rim of the outer putamen and T2-low signal change within the putamen. Cardiac MIBG uptake is normal. In this patient, the left side of the body showed more prominent symptoms.

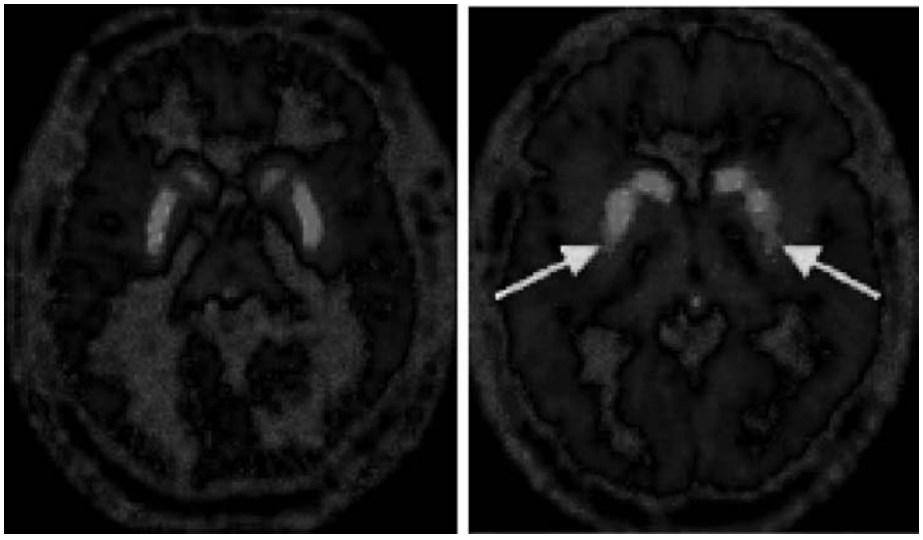

Figure 2 Right: normal, Left: a PD patient with right-sided hemiparkinsonism. 18Fluorodopa PET shows bilateral loss of uptake in the posterior part of the putamen, more on the left. Courtesy of Dr. David Brook. Reproduced from Brook (2004) Neuroimaging in Parkinson's disease. *American Society of Experimental NeuroTherapeutics* 1: 243–254, with permission from © 2004 The American Society for Experimental Neuro Therapeutics, Inc. published by Elsevier Inc.

demonstrated to be increased in patients with very mild PD, indicating the early involvement of this structure. These observations are in line with neurodegeneration observed histologically in the early stage of the disease in PD.

Positron Emission Tomography

Positron emission tomography (PET) utilizes radiolabeled ligands that emit positrons, which are detected by a gamma-camera, and the intensity of each voxel is calculated and reconstructed just as CT scan. Depending on the ligands utilized, various functions of the brain can be measured.

Dopaminergic tracers

Three kinds of tracers are being used to study the functional state of the nigrostriatal dopaminergic neurons. ^{18}F-dopa PET measures dopa decarboxylase activity in the striatum. Tropane-based tracers (^{11}C-CFT, ^{18}F-CFT, ^{11}CRTI-32) measure plasma membrane dopamine transporters (DATs) in the striatum. ^{11}C-dihydrotetrabenazine (DHTBZ) PET measures vesicle monoamine transporter density in dopaminergic terminals.

^{18}F-dopa uptake shows decreased activity in the caudal putamen in PD (**Figure 2**). Usually, 50% decrease of the uptake is present when the patient starts to show

parkinsonian symptoms. Presynaptic plasma membrane tracers bind not only to the DATs but also to serotonin and/or noradrenalin transporters. Presynaptic DAT image and vesicular monoamine transporter image tend to show lower uptake compared to ^{18}F-dopa image due to compensatory upregulation of dopa decarboxylase.

These PET scans cannot differentiate PD from multiple system atrophy (MSA) or progressive supranuclear palsy (PSP). Uptake of these dopaminergic markers is diminished in the striatum in both MSA and PSP. But PET scan is useful in the differential diagnosis of PD and essential tremor (ET). In ET, uptake of dopaminergic tracers remains normal. There is a good correlation between the severity of bradykinesia in PD and the degree of loss of uptake of dopaminergic tracers in PD, but not between the severity of tremor and the loss of dopaminergic markers. Some additional mechanisms appear to be involved in the pathogenesis of tremor.

Dopamine receptors

Postsynaptic dopamine receptors in the striatal neurons remain normal in PD. D2 dopamine receptor density is visualized by spiperone based PET and ^{11}C-racropride. D1 dopamine receptor density is visualized by ^{11}C-SCH23390. Spiperone based PET is normal in PD; ^{11}C-racropride PET may show some increases in putaminal D2 site availability; usually this is interpreted as upregulation of D2 receptor density due to denervation from dopaminergic terminals. D1 binding may show some decrease in the striatal binding. Chronic L-dopa treatment does not decrease D2 binding.

Serotonergic tracers

The raphe neurons are located in the central tegmentum of the midbrain and the upper pons. They are serotonergic neurons projecting to wide areas of the cerebral cortex and the striatum. In PD, raphe neurons are also involved but to a lesser degree compared to the substantia nigra. Loss of serotonin appears to be a cause of depression in PD, but also losses of dopamine and noradrenalin are implicated in the pathogenesis of depression in PD. Raphe serotonergic $5HT_{1A}$ autoreceptors in the presynaptic serotonergic neurons can be visualized by ^{11}C-WAY100635 PET, and one study showed loss of uptake in the raphe region. This may be due to loss of presynaptic $5HT_{1A}$ receptors on the dendritic processes of raphe serotonergic neurons. What is interesting is that there appears to be a correlation between the severity of rest tremor and loss of the $5HT_{1A}$ binding in the midbrain. Cortical uptake is not affected.

Cerebral blood flow and oxygen metabolism

Regional cerebral blood flow (rCBF) can be measured by $[^{15}O]H_2O$. In hemiparkinsonism, rCBF may show slight increase in the basal ganglia contralateral to the affected side. In bilateral patients, generalized decreases in rCBF may be seen unaccompanied by comparable changes in the regional cerebral metabolic ratio for oxygen ($rCMRO_2$). These changes are not pronounced, and its significance awaits further studies.

Glucose metabolism

Glucose metabolism, measured by ^{18}F-2-fluoro-2-deoxyglucose (^{18}FDG), is increased in the striatum, thalamus, and brain stem and decreased in the lateral premotor cortex and the supplementary motor cortex in PD. Demented PD patients show generalized impaired cortical glucose utilization, which is most prominent in the posterior cingulated cortex, lateral parietal, lateral temporal, and lateral frontal association cortex.

Single Photon Emission Computerized Tomography

Single photon emission computerized tomography (SPECT) utilizes isotopes which emit single photon, which can be detected by gamma cameras. The intensity of each voxel is calculated and reconstructed just as CT scan. SPECT is less sensitive compared to PET, but it is more widely available for clinical practice.

Dopaminergic tracers

Tropane-based SPECT tracers (^{123}I-β-CIT, ^{123}I-FP-CIT, ^{123}I-atropane, ^{99m}Tc-TRODAT-1) measure presynaptic DAT availability. Imaging using these tracers shows significant decrease in the uptake in the posterior striatum as in the case of PET (**Figure 3**). But they do not differentiate PD from MSA and PSP. This is a good marker of nigrostriatal dopaminergic involvement. There is a good correlation between the clinical severity as measured by UPDRS and loss of ^{125}I-β-CIT uptake in the striatum.

Dopamine receptors

D2 dopamine receptor density can be measured by ^{123}I-IBZM SPECT; uptake of ^{123}I-IBZN SPECT is normal in PD.

Functional MRI

Functional MRI in PD is mainly investigational. The patient is asked to perform a task and MRI is taken before and after the task. Functional MRI is based on the increase in blood flow when certain areas were used during the task. Increase in blood flow results in increased oxygen utilization and decreased deoxyhemoglobin concentration. Deoxyhemoglobin is paramagnetic and acts as an endogenous contrast agent. As the neuroimaging signal is weak, fMRI tests are usually performed on groups of patients and group averages or sums are reported, rather than data from individual patients.

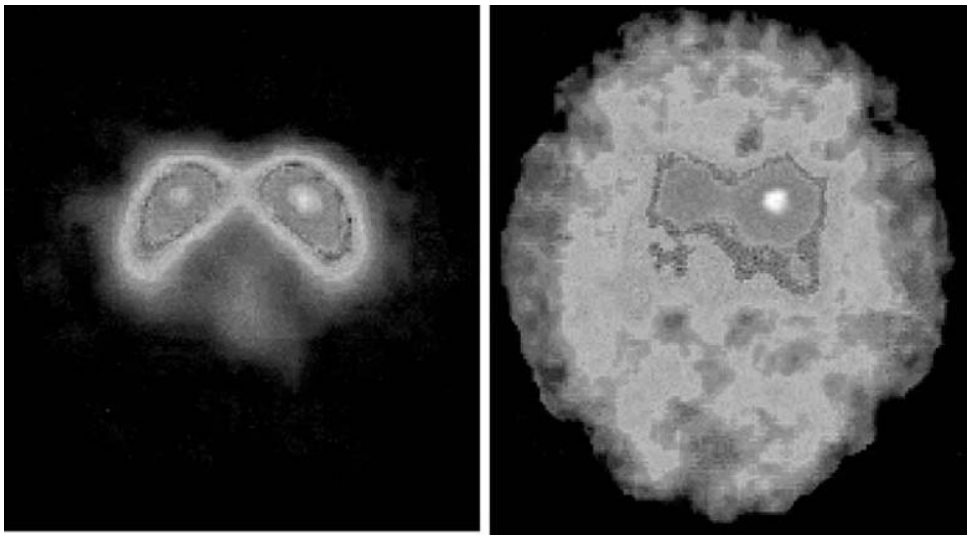

Figure 3 123I-b-CIT SPECT. Left: normal control (71-year-old woman). Right: 66-year-old man with PD. Courtesy of Drs. A. Varrone, J. P. Seibyl, et al. β-CIT uptake is diminished in an asymmetric way in the posterior putamen more on the right side.

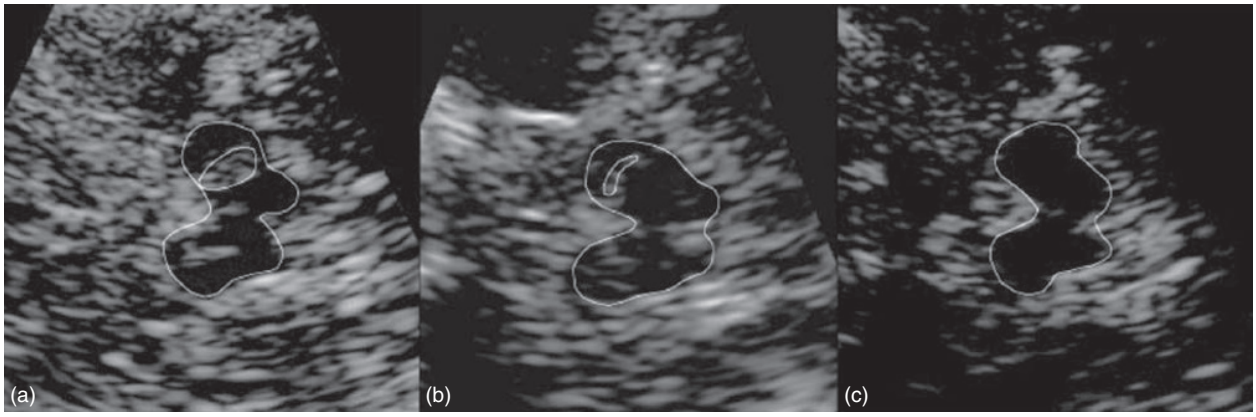

Figure 4 (a) A patient with Parkinson's disease. (b) A control subject. (c) A patient with RLS. The PD patient shows hyperechogenicity in the substantia nigra, and the patient with RLS shows hypoechogenicity. With the courtesy of Drs. W. Schmidauer, Poewe, et al. Reproduced from Schmidauer C, Sojer M, Seppi K, et al. (2005) Transcranial ultrasound shows nigral hypoechogenicity in RLS. *Annals of Neurology* 58: 630–634, with permission from Wiley Interscience © 2005.

PD patients performing a task with one hand show bilateral hypoactivation of the supplementary motor area, anterior cingulated cortex, and dorsolateral prefrontal cortex as well as the contralateral putamen. This pattern correlates well with the model of basal ganglia function in PD with regard to the motor functions.

Transcranial Ultrasound

Transcranial ultrasound is a relatively new technique to visualize the substantia nigra. The ultrasound beam is introduced from a small temporal bone window. In some patients, this temporal bone window is too small or absent and does not allow this examination. But when possible, this is a simple and useful test for daily practice. In PD, hyperechogenicity of the nigral regions is seen in majority of the tested patients. The area of SN echogenicity is larger, contralateral to the side with more severe symptoms, and therefore, transcranial ultrasound can detect asymmetry of involvement. In MSA and PSP, usually transcranial ultrasound remains normal. Hyperechogenicity is believed to be a result of iron accumulation in the substantia nigra. In patients with iron deficiencies, specifically restless leg syndrome (RLS), the substantia nigra shows hypoechogenicity (**Figure 4**).

Cardiac Metaiodobenzylguanidine SPECT

Cardiac ^{123}I-MIBG (metaiodobenzylguanidine) SPECT or scintigraphy visualizes noradrenalin transporters. Noradrenergic transporters are located on plasma membranes and synaptic vesicles of nerve terminals of the

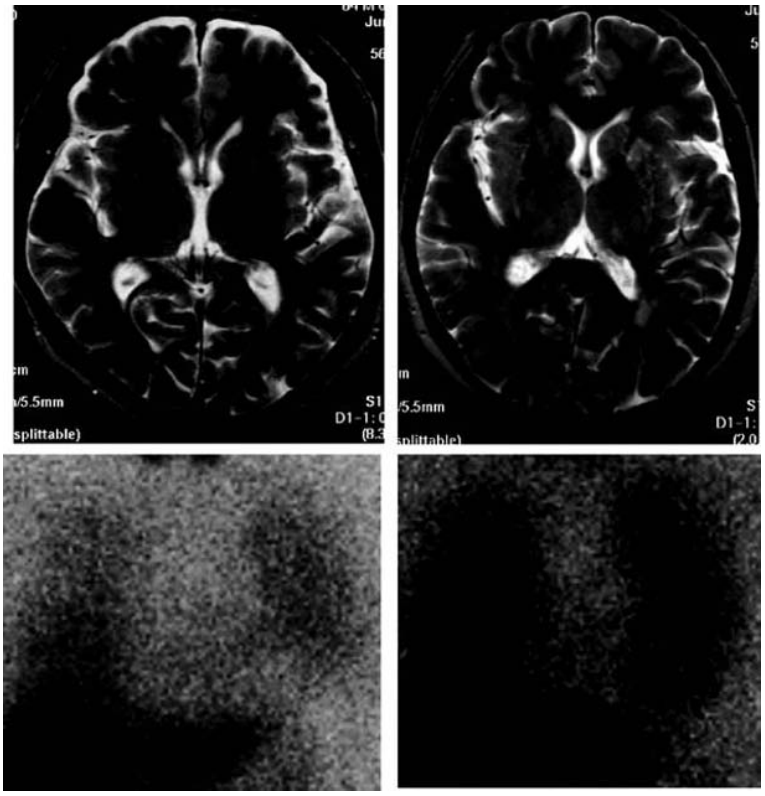

Figure 5 Left: 64-year-old man with PD. MRI is normal and cardiac MIBG uptake is markedly decreased. Right: 61-year-old woman with MSAp. The left putamen shows patchy T2-high signal lesions and the right putamen shows atrophic change, a T2-high signal lesion along the rim of the outer putamen and T2-low signal change within putamen. Cardiac MIBG uptake is normal. In this patient, the left side of the body showed more prominent symptoms.

postganglionic sympathetic fibers. In PD, postganglionic sympathetic neurons degenerate from the early stage of the disease and uptake of ^{123}I-MIBG is markedly reduced. MIBG uptake is also reduced in dementia with Lewy bodies (DLB). Thus, there is a good correlation between the presence of Lewy bodies in the brain and loss of MIBG uptake in the cardiac muscles. In MSA, the preganglionic sympathetic nerve fibers degenerate first; therefore, MIBG uptake is normal in the early stage (**Figure 5**), but in the advanced stage, postganglionic fibers are also involved and cardiac MIBG scintigram may show reduced uptake. In tauopathies such as PSP or Alzheimer's disease, and in ET, MIBG uptake remains normal. Thus, MIBG scintigraphy is a useful diagnostic tool for the differential diagnosis of parkinsonism and dementia (**Figure 6**). The reason why the postganglionic sympathetic fibers to the heart undergo degeneration from the early stage of the disease is not known. As cardiac muscles are under the high oxygen atmosphere, oxidative stress may be higher compared to the other organs, but the exact cause is not known. Aggregation of α-synuclein within the axons of the cardiac sympathetic nerve fibers was reported as the probable pathogenetic mechanism for their degeneration. Decrease in cardiac MIBG uptake is a good disease biomarker for the diagnosis of synucleinopathies, which include PD, Parkinson's disease with dementia (PDD), DLB, and primary autonomic failure associated with Lewy body formation. However, it is not a good marker for the evaluation of the disease progression, as the uptake decreases markedly from the early stage of the disease.

Differential Diagnosis of PD from MSA, PSP, and Corticobasal Degeneration (CBD)

Magnetic Resonance Imaging

Patients with MSA often show MRI evidence of atrophy of the pontocerebellar system and the putamen. In typical cases, cerebellar sulci are enlarged indicating cerebellar atrophy and atrophy of the pontine base with 'hot cross ban' sign, which is a cross form-T2-high signal intensity lesion in the pons spreading horizontally in the boundary of the pontine base and the pontine tegmentum, and vertically in the midline. Putaminal atrophy may appear as a decreased lens-form prominence along the lateral border of the putamen; the border looks more straight

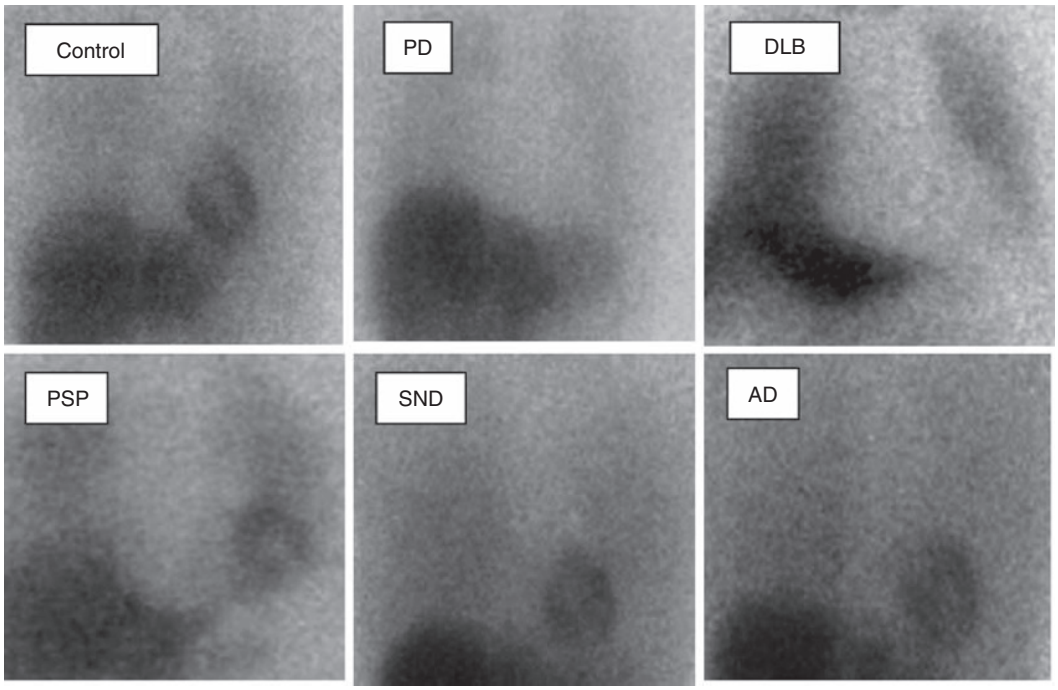

Figure 6 Cardiac MIBG uptake is markedly reduced in PD and DLB but in other conditions, it remains normal. Delayed images.

than curved. In addition, T2-low signal intensity change appears within the putamen, often with a T2-high signal linear intensity lesion along the lateral margin of the putamen. At times, T2-high signal lesions appear within the putaminal region in a patchy manner. Usually some asymmetry in these changes is seen with more prominent atrophic changes contralateral to the more affected side. The high-signal intensity change is believed to represent neuronal loss and gliosis, and the low signal intensity change represents accumulation of iron. These typical changes may not be apparent in early stage MSA patients; in such case, diffusion weighted MRI imaging is useful. If there is neuronal loss, gliosis, or degenerative changes in axons, the mobility of water molecules increases and this can be measured as the increase of 'apparent diffusion coefficient.' With this method, it is possible to differentiate MSA from PD and PSP from PD; however, differential diagnosis between MSA and PSP is impossible, as PSP and MSA show similar results.

In PSP, structural MRI may show atrophic changes in the tegmentum of the midbrain, atrophy of the base of the third ventricle in the sagittal section (humming bird sign), and the dilatation of the third ventricle. However, these changes are not clear in many cases of clinical PSP patients. In CBD, asymmetric cortical atrophy is frequently seen. Suprasylvian sensory-motor areas are involved most frequently and this atrophy, if it is on the dominant hemisphere, appears to be a cause of limb-kinetic apraxia, ideomotor apraxia, or motor neglect, which are frequently seen in CBD.

PET/SPECT

^{18}F-Fluorodopa uptake by PET cannot discriminate PD from MSA or PSP, as nigrostriatal neurons are degenerating in all of these conditions. β-CIT SPECT also cannot discriminate these conditions. Measurement of D2 dopamine receptor density in the striatum by ^{123}I-iodobenzamide and SPECT is normal in PD, but it may show low binding in MSA and PSP. However, D2 dopamine receptor density measurement by raclopride and PET cannot discriminate these three conditions.

Cardiac MIBG SPECT

Cardiac MIBG SPECT is very useful to diagnose, if the uptake is reduced. Approximately 10% of patients who fulfill clinical criteria of PD, however, show normal MIBG uptake. In MSA, PSP, and CBD, MIBG uptake usually remains normal.

See also: Parkinson's Disease: Definition, Diagnosis, and Management; PET Imaging in Movement Disorders; SPECT Imaging in Movement Disorders.

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Relevant Websites

www.movementdisorders.org – Movement Disorder Society.
www.ninds.nih.gov/disorders/msa/msaLegends for figures – MSA NIH information service.

Neuroleptic-induced Nonhuman Primate Models of EPS and TD

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Glossary

Acute dystonia – Involuntary sustained muscle contractions.
Atypical antipsychotic – Second-generation antipsychotics such as clozapine, olanzapine, and amisulpride that differ from first-generation antipsychotics in that they interact with serotonin as well as dopamine receptors or display some partial dopamine agonism.
Dyskinesia – Involuntary muscle movements such as a tic or chorea.
Neuroleptic – Term applied to first-generation or typical antipsychotics such as haloperidol, chlorpromazine, and fluphenazine, due to their observed effect of slowing movement when originally given in high doses.
Tardive dyskinesia – Dyskinesias that arise as a late side effect of long-term treatment with dopamine receptor blocking agents such as antipsychotics or upon treatment termination.

Since their introduction in the 1950s, neuroleptic drugs have become the primary agents for treating acute and chronic psychosis. However, most neuroleptics (also called typical antipsychotics) have been associated with a wide range of neurological side effects. Among the most troubling are extrapyramidal side effects (EPS) that may occur in up to 75% of patients. Although some of the newer second-generation antipsychotics (often called atypical antipsychotics) appear to have a lower risk of inducing EPS, most have been associated with at least some cases of EPS, with youths possibly having more prevalent and severe side effects than adults. Extrapyramidal side effects consist of a diverse range of symptoms, including acute dystonia, akathisia, and Parkinsonism, and may be an indicator of a predisposition to develop tardive dyskinesia (TD). TD is an involuntary dyskinetic disorder that occurs in some individuals as a late complication of prolonged neuroleptic treatment or upon treatment termination. The most common orofacial symptoms of TD include tongue protrusions and chewing motions and grimacing. TD can persist for several months to years after treatment termination and may be irreversible in some individuals.

Although substantial research has been devoted to understanding the basic mechanisms underlying the effects of neuroleptic medications and the pathophysiologic processes responsible for EPS and TD, a cohesive explanation remains to be found. Over the last four decades, several nonhuman primate models have been developed to study different hypotheses about mechanisms of EPS and for predicting the potential of new antipsychotics to induce EPS and TD.

Early Studies with Nonhuman Primates

Early studies with nonhuman primates in the late 1960s and early 1970s established that treatment with neuroleptic medications would induce movement disorders that were similar to those observed in the clinic. In 1976, the first demonstration of the development of two distinct dyskinetic syndromes in monkeys following chronic daily oral administration of haloperidol to capuchin monkeys (*Cebus apella*) was reported. One syndrome contained elements similar to acute dystonia and Parkinsonism and the other closely corresponded to TD. Although not all neuroleptic-treated monkeys developed symptoms, once acute dystonic and dyskinetic effects were established in a monkey the animal became neuroleptic sensitized and symptoms could be elicited by a single injection of the neuroleptic, even after a drug-free period of several or more years.

Nonhuman Primate Models of EPS and TD

Two nonhuman primate models of neuroleptic-induced movement disorders emerged from these early studies. These models can be categorized as homologous and correlational models. In a homologous model, a disease state is produced whose symptoms, causes, biological basis, and response to treatments are similar to those seen in humans. In a correlational model, the factors between the model and the clinical syndrome do not need to be similar, but the results of the model need to be highly predictive of the clinical situation. Induction of TD by long-term treatment with neuroleptic medications in nonhuman primates meets all the criteria of a homologous animal model. Identical symptoms occur in both humans and monkeys over a similar time-course. Initially, acute dystonias and Parkinsonism are seen. TD develops after prolonged treatment or upon discontinuation of treatment. The same antipsychotic medications induce these symptoms in humans and monkeys and, in both, acute dystonias but not TDs can be attenuated by the same medications (anticholinergics). Finally, there is individual vulnerability as not all monkeys or humans exposed to chronic neuroleptic treatment develop TD. The limitations of this monkey model of TD are the time and expense to treat a large number of monkeys for up to several years to get a large enough subgroup of animals with TD symptoms.

The nonhuman primate correlational model is derived from the correlation between the ability of drugs to induce acute EPS in neuroleptic-sensitized monkeys and the future likelihood of specific antipsychotic drugs to cause EPS and TD in the clinic. This model is used to predict the potential liability of new antipsychotics to induce acute EPS or TD in humans. An advantage of the correlational model is the lower cost and shorter time of conducting acute studies that have high predictive power for chronic treatment outcomes. A limitation is that this type of model typically does not inform about underlying mechanisms of TD.

Although neuroleptic-induced AD and TD have been demonstrated in both New World (Superfamily: *Ceboidea*) and Old World (Superfamily: *Cercopithecoidea*) monkeys, New World monkeys, and particularly capuchin monkeys (*C. apella*), appear to be much more prone to developing EPS and TD. Consequently, *C. apella* became the primate species most frequently used for studies of EPS and TD. Recent sequencing of the D_3 dopamine receptor (DRD3) gene in *C. apella* monkeys revealed that they carry the monomorphic glycine 9 DRD3 genotype. This version of the single nucleotide polymorphism has been associated with TD in humans. Although the prevalence of this genotype in other monkey species is yet to be determined, another New World monkey, the common marmoset (*Callithrix jacchus*) also may be particularly susceptible to neuroleptic-induced EPS and TD.

Homologous Model Studies

The homologous monkey model has been used to test potential treatments for TD and investigate potential new antipsychotic agents. Also, several studies investigating the effects of repeated or intermittent treatment regimens on induction of acute or TDs and Parkinsonism have supported suggestions that intermittent treatment schedules with typical antipsychotics may increase the incidence and severity of EPS and TD. A series of studies with specific dopamine receptor agents led one group to suggest that D_1 hyperfunction may be involved in the pathophysiology of oral dyskinesia and that in TD a relative D_1 hyperfunction (compared to D_2 function) may facilitate or modulate the syndrome.

Other studies with this model have led to the hypothesis that chronic neuroleptic treatment upregulates glutamatergic neurons from the subthalamic nucleus terminating in the globus pallidus and substantia nigra. Chronic upregulation has excitotoxic effects on the inhibitory GABA pathways from the globus pallidus and substantia nigra to the thalamus, giving rise to disinhibition of thalamocortical ventral anterior and ventral efferents. This results in a hyperkinetic state that underlies the choreic elements of

TD and suggests a glutamate hypothesis for neuroleptic-induced TD. Determination of mRNA for different glutamate receptor subunits in basal ganglia of neuroleptic-treated *Cebus* monkeys with TD symptoms revealed fewer NR1 expressing neurons and lower NR1 signal intensity in caudate, putamen, and globus pallidus, supporting the theory of altered glutamatergic neurotransmission in neuroleptic-induced TD.

Correlational Model or Studies with Neuroleptic-Sensitized Monkeys

Neuroleptic-sensitized animals can be used as a model for several different research strategies. One approach is to induce EPS with a typical antipsychotic and then test novel antipsychotics to evaluate their influence on these disorders as new treatments. Another strategy is to evaluate response to agents that either target specific receptors (e.g., D_1, D_2, serotonin (5-HT)) or combinations of receptors. Different methods of administration, such as oral or by injection, can also be compared. Finally, one can give acute treatments with a wide dose range of several agents to compare the range of behavioral effects (see **Table 1** for a representative list and scores of behavioral measures used). This last strategy is probably the most widely used nonhuman primate preclinical method for evaluating new antipsychotic agents. It remains as the most predictive animal model of EPS for several reasons: the acute dystonic reactions in sensitized *Cebus* monkeys are identical to acute EPS in humans; the reactions in sensitized monkeys to existing antipsychotic drugs are elicited proportional to their propensity to induce EPS in the clinic; the acute dystonias can be controlled by the same agents that control EPS in humans (anticholinergics); clozapine does not induce EPS in the clinic and does not induce acute dystonia in sensitized *Cebus* monkeys.

Table 1 Representative behavioral rating scale for testing EPS or TD liability of medications in neuroleptic-sensitized monkeys

Behavior	*Score*
Sedation	(0–3)
Arousal	(0–3)
Locomotor activity	−3 to +3 (−3 to −1 decrease, +1 to +3 increase)
Dystonia in body regions:	
Head and neck	(0–3)
Trunk	(0–3)
Upper limbs	(0–3)
Lower limbs	(0–3)
Parkinsonian features:	
Bradykinesia (slow movement)	(0–3)
Tremor	(0–3)
Rigidity	(0–3)
Salivation	(0–3)
Tardive dyskinesia features:	
Perioral grimacing or twitching	(0–3)
Tongue protrusion	(0–3)
Masticatory or chewing motion	(0–3)

Score key: 0 = no symptoms or normal behavior; 1 = mild or occasionally seen; 2 = moderate or ongoing but intermittent; 3 = continuously present.

Source: Linn GS, O'Keeffe RT, Lifshitz K, Lee K, and Camp-Lifshitz, J (2001) Increased incidence of dyskinesias and other behavioral effects of re-exposure to neuroleptic treatment in social colonies of *Cebus apella* monkeys. *Psychopharmacology* 153: 285–294.

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Casey and colleagues used this comparative strategy in neuroleptic-sensitized *Cebus* monkeys to estimate EPS and TD liability across a range of typical and atypical antipsychotics with varying ratios of D_2 and 5-HT_2 receptor antagonism. All clinically effective antipsychotic medications have some D_2 receptor affinity. Yet, all the typical neuroleptics that block D_2 receptors have the capacity to cause EPS and TD. Antipsychotics with high 5-HT_2 to D_2 antagonism ratios, such as clozapine and olanzapine, are hypothesized to have a low EPS liability at effective antipsychotic doses. (Alternatively, EPS liability may be related to D_2 dissociation constants or high D_2 receptor occupancy.) Neuroleptic-sensitized monkeys were exposed to a range of doses of each agent (remoxipride, sulpiride, haloperidol, fluphenazine, clopenthixol, melperone, sertindole, risperidone, clozapine, quetiapine, ritanserin) and observed for signs of acute dystonia or Parkinsonism. For each compound, the researchers then predicted a dystonia-inducing threshold dose range for humans by multiplying the threshold dose for monkeys by a conversion factor. The conversion factor was derived by dividing the haloperidol-induced threshold dose for monkeys into the accepted EPS-producing dose range for haloperidol in humans. Results (shown in **Table 2**; compounds are arranged in order of high D_2/low 5-HT_2 to low D_2/high 5-HT_2 occupancy) indicated that, with the exception of clozapine, all the compounds tested had the potential to produce EPS in *Cebus* monkeys and, by extension, in humans. The separation between effective dose–response ranges for antipsychotic and EPS effects, which predicted low EPS liabilities for effective doses of sertindole, quetiapine, lower doses of risperidone and olanzapine, has been supported by clinical studies. Their finding of low EPS liability for antipsychotics with high 5-HT_2/D_2 receptor affinity ratios, such as clozapine, quetiapine, and olanzapine is compatible with the hypothesis that 5-HT_2 / D_2 antagonism ratios may underlie the favorable EPS profiles of atypical antipsychotics.

Neuroleptic-sensitized *C. apella* monkeys have also been used to study the antipsychotic properties and EPS liability of a muscarinic M1/M4 receptor agonist. Antipsychotic effect was evaluated by attenuation of D-amphetamine-induced motoric unrest and stereotypies. Results indicate

Table 2 Neuroleptic-inducing dystonia dose thresholds in monkeys and patients

Drug[a]	*Dystonia-inducing threshold in monkeys (mg kg^{-1})*	*Conversion factor × 100*	*Clinical dose (mg day^{-1})*	*Estimated dystonia-inducing threshold in humans (mg day^{-1})*
Remoxipride	5.0	2–8	150–600	1000–4000
Sulpiride	10	2–8	800–2000	2000–8000
Haloperidol	0.025	2–8	5–20	5–20
Fluphenazine	0.025	2–8	5–20	5–20
Clopenthixol	0.1	2–8	30–60	20–80
Melperone	1.0	2–8	300–600	200–800
Sertindole	0.5	2–8	20–24	100–400
Risperidone	0.025	2–8	4–16	5–20
Clozapine	>25	2–8	250–900	>5000
quetiapine	5.0 (estimated)	2–8	300–400	1000–4000
Ritanserin	10	2–8	?	2000–8000

[a]Ordered from high D_2/low 5-HT_2 to low D_2/high 5-HT_2 occupancy.
Reproduced from Casey DE (1996b) Extra pyramidal syndromes and new antipsychotic drugs: Findings in patients and non-human primate models. *British Journal of Psychiatry* 168 (supplement 29): 32–39; permission requested.

that the agents that target these receptors are potential antipsychotics with low EPS liability.

Combining Models to Test Antipsychotic Efficacy and EPS Liability: Prepulse Inhibition in Neuroleptic-Sensitized Monkeys

A limitation of most studies with neuroleptic-sensitized monkeys is that they cannot directly test for potential antipsychotic effect in the same animals in which EPS liability is evaluated. Several studies have used D-amphetamine-induced motoric unrest and stereotypies to model psychosis and then tested putative antipsychotics for efficacy in relieving symptoms and for inducing adverse effects in neuroleptic-sensitized monkeys. However, a criticism of this model is that dopaminergic agents, such as amphetamine, induce behaviors similar only to positive symptoms of schizophrenia, and so this model may not be able to distinguish atypical-like compounds that also improve negative or cognitive symptoms.

An alternative model for testing potential antipsychotics for treatment efficacy and EPS liability uses phencyclidine (PCP)-induced deficits in prepulse inhibition (PPI) in neuroleptic-sensitized *Cebus* monkeys. PPI of the acoustic startle reflex is a measure of sensorimotor gating that occurs across species and is deficient in severe neuropsychiatric disorders such as schizophrenia. Deficits in PPI correlate closely with cognitive dysfunction in schizophrenia patients. PCP, a potent drug of abuse that induces positive, negative, and cognitive schizophrenia-like symptoms by blocking neurotransmission at *N*-methyl-D-aspartate-type glutamate receptors, disrupts PPI in monkeys. In one study, the atypical antipsychotic clozapine reversed PCP-induced PPI deficits in monkeys whereas the typical antipsychotic haloperidol did not significantly attenuate PCP-induced PPI deficits even at doses that significantly attenuated effects of a dopaminergic agent (apomorphine). This suggests that PCP-induced PPI deficits in neuroleptic-sensitized monkeys can be a valuable preclinical model for evaluating the EPS liability at effective treatment doses in putative atypical antipsychotics.

In summary, neuroleptic-induced nonhuman primate models of EPS and TD have been effective tools for investigating the underlying mechanisms of EPS or TD and for predicting EPS liability in new antipsychotic agents. Newer antipsychotic medications need to be developed that treat positive, negative, and cognitive symptoms of schizophrenia and are devoid of neurological side effects. Combined models will allow the study of antipsychotic treatment efficacy and EPS liability in the same subjects. Until alternative models of equivalent effectiveness can be developed, nonhuman primate models of EPs and TD will continue to serve an important preclinical research function.

See also: Dopamine Receptors; Drug-induced Movement Disorders; Dyskinesias: Animal Models; Dyskinesias; Neuroleptics and Movement Disorders; Oral Dyskinesia.

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Neuroleptics and Movement Disorders

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Glossary

Agonist – A molecule that binds to a receptor and stimulates the signaling processes associated with the receptor.
Agranulocytosis – A potentially serious condition characterized by an absence of white blood cells exposing an individual to infection risk.
Antagonist – A molecule that binds to a receptor and neutralizes the periodic signaling processes associated with the receptor without affecting the constitutive activity of the receptor.
Atypical – A reference to the characteristic of a neuroleptic to attenuate psychosis without producing motor side effects.
Delusions – False, fixed irrational beliefs out of keeping with the person's educational, cultural, and social background.
Extrapyramidal symptoms – A group of side effects to neuroleptics consisting of, but not limited to, dystonia, parkinsonism, akathisia, and tardive dyskinesia.
First generation antipsychotics (FGAs) – The initial group of antipsychotic drugs based on the original pharmacological mechanism; also referred to as typical or conventional antipsychotics.
Hallucinations – Perceptions in any sensory modality occurring in the absence of an external stimulus.
Inverse agonist – A molecule that binds to a receptor and inhibits the signaling processes associated with the receptor if signaling is constitutively active.
Mesolimbic pathway – The dopamine pathway from the ventral tegmental area of the midbrain to the nucleus accumbens or ventral striatum involved in antipsychotic treatment response among other functions.
Metabolic syndrome – A collection of symptoms including obesity, hypertension, glucose intolerance, and dyslipidemia, which increase the risk of coronary artery disease and stroke, caused by the weight gain associated with second generation antipsychotics.
Neuroleptics – The class of psychotropic medications efficacious as antipsychotics.
Nigrostriatal pathway – The dopamine pathway from substantia nigra to the dorsal striatum affected in Parkinson's disease.
Partial agonist – A molecule that binds to a receptor and stimulates the signaling processes associated with the receptor to a lesser degree than a full agonist.
Phenothiazines – One of the major antipsychotic families that includes the agent chlorpromazine.
Second generation antipsychotics (SGAs) – A more recent group of antipsychotic drugs based on a transition to a different pharmacological mechanism; also referred to as atypical or novel antipsychotics, they are purported to carry less risk of neurological adverse effects.

Definition and History

Neuroleptics comprise a large, diverse group of medications known for their ability to attenuate hallucinations and delusions, the core symptoms of psychosis. The term

Table 1 Neuroleptics listed by class and generation

First generation
Phenothiazines
Acetophenazine
Butaperazine
Carphenazine
Chlorproethazine
Chlorpromazine[a]
Cyamemazine
Dixyrazine
Fluphenazine[b]
Mesoridazine[c]
Methotrimeprazine
Perazine
Pericyazine
Perphenazine
Piperacetazine
Pipotiazine[d]
Prochlorperazine
Promazine
Propericiazine
Sulforidazine
Thiopropazate
Thioproperazine
Trifluoperazine[e]
Triflupromazine
Nonphenothiazines
Benperidol
Bromperidol
Chlorprothixene
Clocapramine
Clopenthixol
Clothiapine
Droperidol[f]
Fluanisone
Flupenthixol[b,g]
Fluspirilene
Haloperidol[b,h]
Loxapine[i]
Melperone
Molindone[j]
Moperone
Mosapramine
Nemonapride
Oxypertine
Penfluridol
Pimozide[k]
Pipamperone
Sulpiride
Sultopride
Thiothixene
Tiapride
Timiperone
Trifluperidol
Zuclopenthixol[l]
Second generation
Amisulpride
Asenapine
Bifeprunox
Clozapine[m]
Iloperidone
Mazapertine
Olanzapine[n]
Paliperidone
Perospirone
Quetiapine[o]
Risperidone[b, p]
Sertindole
Ziprasidone[q]
Zotepine
Aripiprazole[r]

[a]Example of aliphatic phenothiazine.
[b]Oral and depot (long-acting intramuscular) formulations.
[c]Example of piperidine phenothiazine.
[d]Depot formulation only.
[e]Example of piperazine phenothiazine.
[f]Parenteral form only.
[g]Example of thioxanthene.
[h]Example of butyrophenone.
[i]Example of dibenzoxazepine.
[j]Example of dihydroindolone.
[k]Example of diphenylbutylpiperidine.
[l]Oral and short-acting and long-acting depot formulations.
[m]Example of dibenzodiazepine.
[n]Example of thienobenzodiazepine.
[o]Example of dibenzothiazepine.
[p]Example of benzisoxazole.
[q]Example of benzothiazolylpiperazine.
[r]Example of dihydrocarbostyril, aripiprazole is considered to be the next generation of antipsychotics due to its novel partial dopamine agonist pharmacology.

neuroleptic is Greek meaning 'to take hold of the nerves.' This refers to the absence of movement induced in experimental animals by early antipsychotics that was akin to the loss of dopamine neurons in Parkinson's disease. Historically, the therapeutic efficacy of these agents was believed to correlate with their capacity to produce psychomotor slowing and a calm emotional indifference. This led to their anachronistic classification as major tranquilizers. Most neuroleptics are antipsychotic agents although metoclopramide is one example of a drug in the neuroleptic class used primarily as an antiemetic. There are currently close to seventy antipsychotics from over a dozen chemical families prescribed around the world. These are listed in **Table 1**. The most clinically useful categorization divides them into two groups: (1) the conventional, typical, or first generation antipsychotics (FGAs) that are more likely to cause motor side effects, and (2) the novel, atypical, or second generation antipsychotics (SGAs) that are less prone to do so.

Neuroleptics trace their origin to the manufacturing of dyes in England in the nineteenth century. In 1856, Perkin devised mauve, which led to Caro's development of methylene blue, a phenothiazine derivative. Ehrlich, a German bacteriologist credited with discovering the biotherapeutic effects of these dyes, recognized in 1891 that methylene blue could treat symptoms of malaria.

However, quinine proved more effective for this purpose. In World War II, with access to quinine limited, unsuccessful attempts were made by Gilman and others to manipulate the phenothiazine ring to produce alternative antimalarial compounds.

Serendipitously, French scientists chose to evaluate the phenothiazines for their antihistaminergic effects. Laborit, an anesthesiologist, found that promethazine's long duration of action could potentiate the effects of other anesthetics, allowing for lower dosages. In 1950, chlorpromazine demonstrated the same quality as well as calming and antiemetic properties in animals. The following year, Laborit and Huguenard noted that chlorpromazine quieted patients preoperatively without inducing coma, and they supplied it to two groups of Parisian psychiatrists led by Hamon and Delay. The first patient, a 57 year old laborer admitted to the Val de Grace Hospital for erratic, grandiose, and assaultive behavior, responded dramatically. Chlorpromazine was released in 1952 with open-label studies and a 1960 controlled trial in the United States confirming its efficacy. It replaced reserpine, a plant derivative that had been used as an antihypertensive in the late 1940s and subsequently as an antipsychotic due to its tranquilizing properties.

The magnitude of the discovery of chlorpromazine's antipsychotic therapeutic benefit cannot be understated. Worldwide inpatient populations decreased significantly. Theories of mental illness were powerfully influenced and treatments transformed from restrictive to compassionate. The locus of care changed from asylum to community. The risks of more invasive biological therapies were avoided, and the physical and mental wellbeing of countless ill patients was improved.

In the 1960s, when reserpine was found to deplete biogenic amines such as dopamine, norepinephrine, and serotonin, the dopamine hypothesis of schizophrenia and the monoamine hypothesis of depression emerged. Although overly simplistic, these theories remain the cornerstones of our pathophysiologic understanding of these psychiatric disorders. Carlsson and Linquist supported the dopamine hypothesis further by attributing to dopamine antagonism – the ability of nonreserpine neuroleptics to reduce amphetamine-induced psychomotor agitation in animals and to cause extrapyramidal symptoms in humans.

The psychopharmacological revolution continued with the proliferation of phenothiazine-related compounds, although chlorpromazine remained the most prescribed antipsychotic through the 1960s and 1970s. They eventually became known as low-potency neuroleptics because they required high doses for antipsychotic efficacy. Soon high-potency agents, which at small doses reduced stimulant-related hyperkinetic behavior in rodents, were synthesized. However, these new compounds were found to dramatically increase the incidence of extrapyramidal symptoms to as many as one in three patients in 1958, the year haloperidol was introduced. The following year, Sigwald reported the first case of antipsychotic-induced tardive dyskinesia.

The motor side effects of high-potency antipsychotics drove scientists, in particular German and Swiss psychiatrists, to search for atypical compounds. Clozapine, the antipsychotic least susceptible to motor complications, was synthesized in 1959 but could not be used until the late 1970s or marketed until the late 1980s due to its infrequent but life-threatening risk of agranulocytosis. In 1990, clozapine was finally released to the United States market and, shortly thereafter, its limited liability for extrapyramidal symptoms and tardive dyskinesia and its efficacy in treatment-refractory patients were uncovered. Riding on the coat tails of clozapine's success, risperidone was approved and marketed using its claim of atypical features in 1994, then olanzapine in 1996, quetiapine and sertindole in 1997, and ziprasidone, aripiprazole, and others more recently. The significant morbidity due to the metabolic syndrome of obesity, hypertension, dyslipidemia, and glucose intolerance from these agents, and their overstated therapeutic benefits continue to motivate the search for more suitable compounds.

Pharmacology

Pharmacokinetics

To maximize absorption, orally administered neuroleptics are given with food. Age, gender, drug interactions affecting protein binding or cytochrome P450 activity, hepatic or renal impairment, and caffeine and nicotine consumption affect plasma concentrations.

The half-life of the various neuroleptics ranges although most are given once daily. Peak levels are established within 4 h if given orally. In acute settings, intramuscular delivery is preferable. Bioavailability can also be augmented with short-acting (2–3 days) and long-acting (2–4 weeks) depot intramuscular formulations. Parenteral administration of certain agents is appropriate for acute monitored medical settings.

Pharmacodynamics

Chlorpromazine was marketed outside the United States as Largactil, a name reflecting its large number of actions in the central nervous system. In general, neuroleptics claim a vast array of neurotransmitter receptor affinities. Those that are quantifiable are listed in **Table 2**. Each medication is characterized by unique pharmacodynamics and receptor affinities, particularly in the dopamine, serotonin, and acetylcholine systems.

Table 2 Receptor systems affected by neuroleptics and their postulated effects

Dopamine D_1 blockade: antipsychotic
Dopamine D_2 blockade: antipsychotic; parkinsonism and motor side effects; hyperprolactinemia
Dopamine D_3 blockade: antipsychotic
Dopamine D_4 blockade: antipsychotic
Dopamine partial agonism: antipsychotic; attenuation of motor side effects and hyperprolactinemia
Dopamine reuptake inhibition: antidepressant; antiparkinsonian; psychomotor acceleration
Histamine$_1$ blockade: antiemetic; sedation; hypotension; weight gain; potentiation of other CNS drugs
Muscarinic M_1 blockade: attentuation of parkinsonism, dystonia, and akathisia; dry mucous membranes; blurred vision; constipation; urinary retention and incontinence; sinus tachycardia; ECG changes; memory disturbances; sexual dysfunction; potentiation of other anticholinergics
Norepinephrine reuptake inhibition: antidepressant
α_1 Norepinephrine blockade – postural hypotension, dizziness, reflex tachycardia, sedation, hypersalivation, urinary incontinence; potentiates other alpha blockers
α_2 Norepinephrine blockade – sexual dysfunction; may antagonize antihypertensives and increase cholinergic activity
Serotonin (5-HT$_1$) blockade (A, D): antidepressant; anxiolytic; inhibition of impulsivity
Serotonin (5-HT$_2$) blockade (A, C): antidepressant; anxiolytic; attenuation of motor side effects; hypotension sedation; weight gain; sexual dysfunction
Serotonin (5-HT$_{3,6,7}$) blockade: undefined
Serotonin reuptake inhibition: antidepressant

As early experimenters surmised, a reduction in postsynaptic dopamine activity by D_2 receptor binding predicts the efficacy of antipsychotics. All compounds share this mechanism. PET studies in schizophrenia confirm an increased release of dopamine and increased baseline D_2 receptor occupancy in the striatum of psychotic individuals. When an antipsychotic reaches 48% D_2 receptor occupancy, dopamine activity begins to normalize. D_2 blockade in the mesolimbic pathway, specifically the ventral striatum, correlates with antipsychotic efficacy, whereas blockade in the dorsal striatum, leading to low endogenous dopamine activity and consequently increased acetylcholine, is associated with extrapyramidal symptoms. D_2 blockade in the tuberoinfundibular pathway causes hyperprolactinemia as dopamine inhibits prolactin release. An antipsychotic effect is also postulated to occur by modulation of D_1, D_3, and D_4 receptor activity. Serotonergic blockade produces anxiolytic and mood-enhancing effects and antihistaminergic activity sedation. Other receptor affinities result in untoward effects. The search for pharmacodynamic factors that explain atypicality, the mitigated risk of motor complications with certain antipsychotics, has resulted in a number of possibilities described below.

Variability in D_2 blockade

The magnitude of D_2 blockade does not differentiate the agents that are more or less likely to cause motor side effects. Studies of D_2 striatal receptor occupancy leave little margin for error suggesting that a therapeutic antipsychotic effect occurs between 60 and 70% occupancy and extrapyramidal symptoms between 74 and 82%. At higher doses, the SGAs begin to resemble FGAs. It was therefore considered that at certain doses, the SGAs might fall within the therapeutic window of ~70% occupancy, but studies tend to show similar peak occupancy levels as conventional agents and, in fact, occupancy measurements of newer atypical agents are reported to reach as high as 90%. An alternative explanation is that minimal motor side effects may be attributable to neuroanatomical selectivity of D_2 receptor blockade. SGAs have lower striatal:cortical D_2-binding ratios compared to FGAs and greater preference for A_{10} mesolimbic dopamine neurons over A_9 nigrostriatal neurons. This is complicated by a drug's capacity to penetrate the blood–brain barrier that also determines its variable effects in various dopamine pathways.

A range in D_2 receptor affinity can also distinguish FGAs from SGAs. Physiological dopamine transmission occurs in phasic bursts in response to task requirements or stress-induced demands. Medications that block these receptors more permanently have a greater impact on these functions. Some SGAs have been found to have lower affinities for the D_2 receptor with quetiapine and clozapine having particularly fast dissociation rates. Following recognition of the receptor and alteration of the associated signaling system, these compounds quickly detach. In vitro studies of the dissociation coefficient, K_d, predict motor side effects clinically. The rapid psychiatric relapses seen when patients discontinue these compounds may also relate to an accelerated physiological displacement of these drugs by endogenous dopamine. While rapid dissociation is a characteristic of some SGAs, others have slower dissociation coefficients. It is possible that D_2 receptor affinity is affected by binding at other receptors.

Serotonin–dopamine blockade

Serotonin modulates presynaptic dopamine release from axon terminals to varying degrees depending on the pathway involved. In the nigrostriatal and tuberoinfundibular pathways, dopamine may be released by 5-HT$_{2A}$

antagonism, a common SGA characteristic, thus limiting motor side effects and hyperprolactinemia. Alternatively, when 5-HT_{2A} antagonism occurs in the mesocortical and mesolimbic pathways, the efficacy of the therapeutic dopamine blockade may be complemented. However, serotonin antagonism is not the critical defining feature of atypicality. Some conventional neuroleptics that commonly produce motor side effects are also serotonin antagonists. Some SGAs that produce few motor side effects have minimal serotonin blockade. The likelihood of avoiding neurological complications does not correlate with the 5-HT_{2A}/D_2 binding affinity ratios for some SGAs. At higher doses, even SGAs with serotonin blockade become increasingly liable to produce extrapyramidal symptoms. Finally, PET studies confirm that even in the presence of serotonergic blockade, there is high striatal D_2 blockade.

Dopamine partial agonism

In 1993, haloperidol was shown to stimulate the release of prolactin in vivo in the absence of dopamine. Previously thought to act as an antagonist at the dopamine receptor by neutralizing periodic receptor activity, this demonstrated that its mode of action was actually that of an inverse agonist, inhibiting all signaling activity. A number of in vitro tests confirmed this as the mechanism of many neuroleptics of both generations. Partial agonists at the D_2 and D_3 receptors inhibit excessive dopamine activity by ensuring high occupancy but low efficacy. This low-level stimulation of postsynaptic receptors also prevents the dopamine tone of the synapse from declining excessively. The end result is moderate antipsychotic efficacy with minimal motor side effects and hyperprolactinemia. However, this mechanism of action is claimed only by the most recent antipsychotics, and therefore cannot fully explain the atypical effects of SGAs.

Other explanations of atypicality

It is unlikely that one hypothesis explains atypical antipsychotic activity. High intrinsic muscarinic and histaminergic blockade are also considered protective against motor side effects. Other theories put forth include: a discrepancy between the effects of FGAs and SGAs on different signaling pathways such as G proteins; modulation of ligand-gated ion channels by atypical antipsychotics; and neuronal and glial cell proliferation as an intrinsic mechanism of some antipsychotics but not others.

Indications

Psychiatric

The primary indications for the use of antipsychotic agents are psychiatric. FGAs and SGAs are the standards of care in schizophrenia, mood disorders especially bipolar affective disorder and unipolar depression with psychotic features. They are also effective in attenuating the psychosis accompanying schizoaffective disorder, delusional disorder, dementia, substance abuse, neurological conditions such as epilepsy, and organic brain syndromes such as acute intermittent porphyria. Certain agents are approved for refractory generalized anxiety disorder. Low-dose SGAs improve the behavioral disturbances associated with autism and pervasive developmental disorders. Off label uses include: aggression, hostility, and impulsivity in neuropsychiatric illness such as traumatic brain injury; refractory OCD, depression, and posttraumatic stress disorder (PTSD); trichotillomania; assaultive and self-mutilatory behavior; personality disorders; insomnia; substance use disorders; anorexia nervosa; and disruptive behavior disorders and comorbid attention deficit/hyperactivity disorder in children.

Neurological

Migraine headaches

Included in the many off-label strategies for the abortive treatment of acute migraine are antipsychotics from either the first or second generation.

Movement disorders

Chronic tic disorders respond favorably to neuroleptic treatment. Pimozide and haloperidol are approved medications in Tourette's syndrome, but many other FGAs and SGAs are commonly used. Antipsychotics, particularly clozapine, are also prescribed off label to suppress ballismus, essential tremor, akinetic disorders, chorea, blepharospasm, Meige syndrome, and tardive dyskinesia.

Psychosis, tremor, and dyskinesias in Parkinson's disease

Few pharmacological options exist for patients with Parkinson's disease functionally compromised by hallucinations or delusions. First generation antipsychotics, risperidone, olanzapine, and aripiprazole have all been reported to worsen parkinsonism. The effects of ziprasidone remain unclear. Quetiapine is favored for its ease of use despite complaints of sedation and postural hypotension. In open label and prospective studies in the Parkinson's population, it is modestly effective as an antipsychotic at an average dose of 50 mg day^{-1}. Controlled studies, however, do not demonstrate this effect. In fact, clozapine is the only agent successful in treating psychosis in Parkinson's disease in double-blind controlled trials. Despite this evidence as well as reports of improvement in tremor and dyskinesias, clozapine, even at a low dose of 25–37.5 mg day^{-1}, introduces the risk of agranulocytosis although no deaths have been reported in this population. As a result, weekly monitoring of complete blood count with differential for 6–12

months is required then monthly monitoring if no abnormalities are detected. Patients also struggle with the side effects of sedation and exacerbations in drooling and postural dizziness.

Psychosis and chorea in Huntington's disease

Conventional agents have for some time been part of the pharmacological armamentarium for suppressing choreiform movements in early Huntington's disease. Once gait disturbance and postural instability are marked, the parkinsonism and other motor side effects which often accompany long-standing antipsychotic use can put patients at increased risk of falls. SGAs may be useful at this stage. For patients who also suffer from psychosis, usually presenting as delusions, clinical experience supports the use of FGAs early in the course of disease and SGAs, specifically quetiapine and clozapine, at later stages.

Dementia

Antipsychotic agents are given off-label for the behavioral and psychological symptoms of dementia. Treatments are exclusively short-term due to a black box warning by the FDA following the discovery of higher mortality and stroke risk associated with chronic use of antipsychotics in the elderly. Visual hallucinations in dementia with Lewy bodies are treated with quetiapine or clozapine when cholinesterase inhibitors are ineffective or contraindicated.

Other Uses

Antipsychotics are also prescribed to reduce nausea and vomiting, to relieve intractable hiccups or pruritus especially when associated with neurodermatitis, and to serve as adjunctive anaesthesia or tetanus therapy.

Contraindications

From the available data, no conclusions can be drawn about the risk/benefit profile of the majority of antipsychotics in breast-feeding or pregnancy, with the exception of clozapine, which can be potentially life threatening in the infant, and olanzapine, which poses an increased risk of motor side effects in breast-fed babies. While they are not clearly teratogenic as a class, antipsychotics should be avoided in pregnancy, particularly in the first trimester. Moderate to high doses in the last trimester produce extrapyramidal symptoms and temperature regulation difficulties in the newborn.

Caution should be exercised in patients with extensive heart, lung, liver, and kidney disease, glaucoma, prostatic enlargement, or a QTc interval > 450 ms.

Side Effects

While each antipsychotic has a unique side effect profile, overall tolerability does not seem to differ between FGAs and SGAs. More patients discontinue treatment with the FGAs due to extrapyramidal symptoms and the requirement for anticholinergic agents. Greater weight gain is observed with the SGAs. **Table 3** lists reported adverse effects of antipsychotics. Further discussion of some psychiatric, neurological, and endocrine complications follows.

Psychiatric

Sedation, particularly in children and adolescents, is the most common psychiatric side effect of neuroleptics. Although it often attenuates over time, sedation impairs cognition and decreases function even when the agent is prescribed at bedtime. De novo depression and panic attacks, the provocation of mania, and the exacerbation of aggression, agitation, and insomnia are all linked to antipsychotic use. Cognitive impairment occurs with agents with anticholinergic properties, although as a class antipsychotics are less likely than the illnesses they treat to cause cognitive dysfunction. Discontinuation symptoms such as restlessness, insomnia, nausea, vomiting, tachycardia, diaphoresis, akathisia, extrapyramidal symptoms, and florid psychosis have long been described with sudden cessation of treatment. These phenomena are mediated by rebound from blockade of multiple receptors and can be difficult to distinguish from relapse. Longer tapers or the addition of anticonvulsants and benzodiazepines while tapering are prophylactic.

Neurological

Although attempts to avoid extrapyramidal symptoms are extensive, these side effects are habitually missed on clinical examination. While FGAs pose a higher risk, SGAs are still associated. Baseline assessment for movement disorders prior to antipsychotic initiation with repeat examination twice yearly is minimum standard of care.

Acute dystonia

Attributed to strong D_2 blockade, acute and painful prolonged spasms are commonly localized to the neck although involvement of the tongue, trunk, and limbs is also reported. Oculogyric crises, opisthotonus, and laryngospasm are fortunately rare. Usually occurring in the first week of treatment, with drug initiation or escalation, dystonia is treated with parenteral benztropine, diphenhydramine, or lorazepam, but may recur necessitating an antipsychotic dose reduction or daily oral anticholinergics. Risk factors include male gender, African–American

Table 3 Adverse effects of antipsychotics

Nervous system
Agitation
Discontinuation symptoms
Extrapyramidal symptoms (parkinsonism, dystonia, akathisia, tremor[a], myoclonus[a], Pisa syndrome[a], perioral tremor/rabbit syndrome[a])
Insomnia
Sedation
Seizures
Tardive symptoms (dyskinesia, dystonia, parkinsonism[a], akathisia[a], ballismus[a], tics[a], vomiting[a], temperature dysregulation[a])
Anxiety[a]
Cognitive impairment[a]
Depression[a]
Headache[a]
Neuroleptic malignant syndrome[a]
Pain, myalgias, or paraesthesiae[a]
Stroke[a]
Head and Neck
Blurry vision
Cataracts
Epistaxis[a]
Lenticular pigmentation[a]
Pigmentary retinopathy[a]
Rhinitis[a]
Cardiovascular
ECG changes: prolonged PR, QRS, or QTc
Hypotension[b]
Tachycardia
Cardiomyopathy[c]
Cardiac conduction abnormalities including *torsades de pointes*[d]
Edema[a]
Respiratory
Hypoventilation[c]
Pulmonary thromboembolism[c]
Gastrointestinal
Constipation
Dry mouth
Sialorrhea
Transient liver enzyme elevation
Cholestatic jaundice[a]
Diarrhea[a]
Dyspepsia[a]
Dysphagia[a]
Glossitis[a]
Pancreatitis[c]
Reflux esophagitis[a]
Insterstitial nephritis[a]
Genitourinary
Sexual dysfunction
Urinary incontinence
Urinary retention
Priapism[a]
Dermatological
Photosensitivity
Altered skin pigmentation[a]
Flushing of the skin[a]
Rash[a]
Endocrine
Hyperprolactinemia
Galactorrhea and breast engorgement
Hypogonadism
Menstrual irregularities
Osteopenia/osteoporosis[e]
Sexual dysfunction
Temperature dysregulation[a]
Weight gain
Diabetes
Gall bladder disease
Hyperlipidemia
Hypertension
Osteoarthritis
Hypothyroidism[a]
SIADH[c]
Hematological
Agranulocytosis[a]
Eosinophilia[a]
Exacerbation of thromobocytopenia[a]
Transient neutropenia[a]
Uric acidemia[a]

[a]Incidence $< 2\%$.
[b]Worse with rapid dose increases and higher doses.
[c]Case reports only.
[d]Malignant arrhythmias rare; avoid doses of pimozide > 20 mg, thioridazine > 800 mg, and higher doses of ziprasidone.
[e]Monitoring of bone loss recommended in female patients with hyperprolactinemia.

ethnicity, young age, treatment naïveté, thyroid and parathyroid irregularities, and recent cocaine use.

Parkinsonism

Correlating with nigrostriatal dopamine reduction, antipsychotic-induced parkinsonism emerges in a typical although more symmetrical fashion after several weeks of treatment. Risk factors include older age, female gender, comorbid neurological disorders, and high doses of FGAs. The differential diagnosis includes negative symptoms of schizophrenia, depression, and idiopathic Parkinson's disease. Parkinsonism is expected to resolve after drug tapering and discontinuation, but may take up to 6 months. In those cases that persist longer with parkinsonian signs, the diagnosis of Parkinson's disease, unveiled by neuroleptic exposure, is likely.

Akathisia

In up to 20% of patients started on neuroleptics, a dose-related subjective sense of unease, restlessness, and dysphoria develops in the first few weeks. The clinician observes repetitive movements of the lower limbs, pacing, and rocking. Psychomotor agitation, anxiety, drug seeking, and withdrawal may confound the recognition of akathisia. Associated with the elderly, women, mood and anxiety disorders, concurrent treatment with selective serotonin reuptake inhibitors (SSRIs), excess caffeine intake, and low iron, akathisia may attenuate with

β-blockers or benzodiazepines but tends to persist for at least the first several months of treatment and is a common contributor to noncompliance, insomnia, violence, and suicide. Akathisia can also be a part of a tardive syndrome, starting after months of therapy (see later text).

Tardive dyskinesia

Although an upregulation or supersensitivity of postsynaptic D_2 receptors has been proposed, the exact mechanism of tardive dyskinesia is poorly understood. After several months or years of treatment in younger adults, or weeks in the elderly, often when an antipsychotic is tapered or discontinued, patients begin to display orofacial choreoathetosis, chewing or jaw clenching, protruding the tongue, grimacing, frowning, pursing, smacking, or puckering the lips, and blinking. Involvement of the limbs, trunk, neck, and diaphragm, with grunting, are seen. Movements are difficult to suppress and potentially embarrassing, although there is often a lack of awareness. Worsened by stress and the use of anticholinergics, tardive dyskinesia is absent in sleep. The differential diagnosis includes dyskinesias that can occur spontaneously in neuroleptic-naïve patients, Huntington's, and Tourette's. The movements persist in 75% of patients after 5 years and worsen with ongoing treatment, limiting adherence to medications, quality of life, and health status. Risk factors include previous extrapyramidal symptoms, diabetes, older age, mood disorders, cognitive impairment, and female gender in some reports. Concomitant lithium therapy may be protective. There is little rigorous data on exact incidence and prevalence. Conservative estimates suggest a rate of 5–8% per year for FGAs and 1–3% in SGAs in adults, and 5–30% per year in those over 45 years old depending on the agent used and population sampled. Children experience tardive dyskinesia at a rate of 0.4%, but they are often exposed to lower doses for shorter durations. Treatment efficacy is lacking and options include switching to clozapine, reintroducing the causative agent, and slowly tapering it, or starting tetrabenazine. Vitamin E or B_6, clonazepam, clonidine, and anticonvulsants are minimally effective. Deep brain stimulation remains experimental.

Other tardive phenomena

Delayed onset dystonias associated with prolonged use of FGAs and SGAs require distinction from Wilson's disease and idiopathic dystonia. Treatment with anticholinergics, clozapine, tetrabenazine, or BoTox is modestly effective. Tardive dyskinesia may coexist. Tardive parkinsonism, akathisia, ballismus, Tourette's, vomiting, and hypothalamic syndrome (sense of cold accompanied by polydipsia) are rare.

Other movement disorders

Rabbit syndrome or a rhythmic, fine, perioral tremor occurs in association with neuroleptics. Female gender, age, and previous brain injury predispose. This facial tremor is thought to be a manifestation of drug-induced parkinsonism. Movements tend to respond to a reduction in therapy, cessation of antipsychotics, or introduction of anticholinergics. Less commonly, Pisa syndrome or persistent lateral flexion of the trunk to one side may begin after months of treatment. The predisposed demographic and treatment are similar to rabbit syndrome. Exacerbation of tic disorders, de novo cataplexy, and myoclonus are also reported.

Other neurological complications

Generalized tonic–clonic seizures occur with an incidence rate as high as 10% in children and 4% in adults, especially with polypharmacy. Headaches are infrequent with most agents. Stroke and TIA are three times more common in demented elderly patients on antipsychotics compared to placebo.

Neuroleptic malignant syndrome

An emergent condition characterized by varying combinations of hyperthermia, diaphoresis, muscle rigidity, elevated serum creatinine kinase, altered level of consciousness, labile blood pressure, tachycardia, and hypersalivation, NMS is associated with a 25% mortality rate. A precipitous decrease in dopamine levels in the striatum and hypothalamus is responsible. Not only occurring with FGAs and SGAs when rapidly increased or initiated, but also with metoclopramide and withdrawal of dopamine replacement therapy, it must be differentiated from heat stroke, catatonia, serotonin syndrome, delirium tremens, toxidromes, and thyrotoxicosis. Risk factors include male gender, young age, associated brain injury or illness, mood disorder, and dehydration. Treatment consists of rehydration, preventing myoglobinuria and renal failure, and cooling. Dantrolene up to 10 mg kg^{-1} or until rectal temperature normalizes, bromocriptine, reinstatement of levodopa, and steroid pulse therapy are all useful.

Endocrine

Metabolic syndrome

Weight gain due to some FGAs and most SGAs is a serious cause of morbidity and a leading contributor to medication nonadherence. On average, one-half of patients taking neuroleptics gain 20% of their body weight increasing their probability of developing the metabolic syndrome, which involves hypertension, dyslipidemia, glucose intolerance, and subsequent coronary artery and cerebrovascular disease. Risk factors include females, children, adolescents, and patients experiencing their initial episode of schizophrenia, although this may be due to SGAs being first-line agents in these populations. Compounds with greater histaminergic, serotonergic, and alpha blockade are often implicated. Strict monitoring of

weight, diet, exercise, blood pressure, lipids, and glucose levels is encouraged. Strategies for pharmacological intervention are not yet well elucidated.

Interactions

Pharmacodynamic

The increasingly common practice of combining antipsychotics magnifies the risks of excessive D_2 antagonism with associated neurological complications and NMS, and serotonin and anticholinergic toxicity. Antipsychotics produce additive: hypotension with antihypertensives and monoamine oxidase inhibitors; motor side effects with SSRIs, cholinesterase inhibitors, lithium, and metoclopramide; hyperprolactinemia with some oral contraceptive pills; and sedation with benzodiazepines.

Pharmacokinetic

The most likely etiology for any drug interaction with antipsychotics derives from the inhibition or induction of hepatic cytochrome P450 1A2, 2D6, and 3A4 subtypes. Tegretol is a potent inducer of 1A2 and 3A4 lowering FGAs and SGAs to undetectable levels. Smoking induces 1A2, so altered smoking status, including abstinence in hospital, affects antipsychotic levels. Various genetic polymorphisms of the 2D6 enzyme, although present in a minority of individuals, lead to increases or decreases in activity, necessitating dose changes. Many antipsychotics are 2D6 inhibitors, so cautious use of other 2D6 substrates is necessary. Side effects to medications may be additive like the combined lowering of seizure threshold by lithium and clozapine. Interactions such as cardiotoxic levels of pimozide due to impaired clearance by clarithromycin, and decreases in the INR due to induction in warfarin metabolism by quetiapine, are of adequate frequency and severity to demand careful consideration prior to introducing neuroleptics.

Dosing

Principles

Antipsychotic prescribing involves: an estimate of the drug's starting dosage and potency based on its D_2 affinity with 2–10 mg day^{-1} of haloperidol equivalence; individualized dosing based on symptom severity, comorbidity, age, potential drug interactions including nicotine and caffeine intake, side effect profile, dosing schedule, and personal and family history of prior response to a particular compound; choice of appropriate route of administration based on the acuity of the setting, the duration of treatment, and the expectation of compliance; lowering doses for chronic maintenance therapy; gradual titration over at least 2–4 weeks with increases of every five half-lives; and adjusting the dose based on response and not drug level.

Switching

After several weeks, if lack of response is attributable to medication choice, switching antipsychotics is advised. Symptoms, side effects, and quality of life measures improve with a change from FGAs to SGAs. Olanzapine and clozapine are considerations for improved efficacy. Switches from one SGA to another or to the FGAs can optimize triglyceride levels and weight. Switching strategies should consider the relevant pharmacology of the involved agents and the risks of rebound and additive effects.

See also: Acetylcholine; Akathisia; Anticholinergics and Movement Disorders; Antidepressants and Movement Disorders; Benzodiazepines and Movement Disorders; Beta-blockers and Movement Disorders; Botulinum Toxin; Central Nervous System Stimulants and Movement Disorders; Cholinesterase Inhibitors in Parkinson's Disease; Chorea; Choreiform Disorders; Deep Brain stimulation; Dementia with Lewy Bodies; Dopamine; Dopamine Receptors; Dopaminergic Agonists in Parkinson's Disease; Drug-induced Movement Disorders; Dyskinesias; Dystonia, Drug-induced (Acute); Gait Disturbances in Parkinsonism; Hallucinations and Movement Disorders; Hemiballismus; Huntington's Disease; Levodopa; Locus Coeruleus and Norepinephrine; Myoclonus; Neuroleptic-induced Nonhuman Primate Models of EPS and TD; Nicotine; Obsessive-Compulsive Disorder; Parkinson's Disease: Definition, Diagnosis, and Management; Pisa Syndrome; Psychosis in Parkinsonism; Rabbit Syndrome; Serotonin and Tryptophan; Serotonin Syndrome; Tardive Dystonia; Tardive Syndromes; Tourette Syndrome; Tremor, Essential (Syndromes); Tremor: Drug-induced; Wilson's Disease.

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Neuronal Ceroid Lipofuscinosis

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Glossary

Autosomal recessive – Genetic mutations can be passed on from one generation to the next by different patterns of Mendelian inheritance. In autosomal recessive disorders (like Batten disease), an individual needs to have two mutated copies of the disease-causing gene to be affected. Their parents are both carriers who have one mutated copy of this gene, but are themselves asymptomatic. Each time they reproduce, they have a 25% chance of having an affected child, 50% chance of producing another carrier, and 25% chance of having a completely unaffected child.

Cross-correction – Many of the therapeutic strategies used to combat LSDs depend upon this simple principle, so that an enzyme produced by a cellular subpopulation can be used to treat neighboring deficient cells. Much of the lysosomal enzymes normally made by a cell are secreted into the extracellular space, but will be recaptured and delivered back to the lysosome via binding to mannose-6-phosphate receptors that are present at the plasma membrane of all cells. In LSDs, the missing enzyme is typically delivered by direct enzyme replacement, gene transfer, or the transplant of stemcells. This delivered enzyme is then taken up by deficient cells to 'cross-correct' their functional defect.

Genetically engineered mutant mice – If the disease-causing gene has been identified, it is now relatively routine, to generate a mouse model of this disorder via genetic manipulation. Homologous recombination is used to replace the gene of interest with a construct in which this gene has been altered in some way. This may be to completely disrupt a gene so that no protein is made – a 'knockout' mouse. Alternatively, in a 'knockin' mouse, a particular disease-causing mutation can be introduced into the gene to recreate the human disease. More complicated targeting constructs, allow genes to be switched on or off, either globally or more usually in a particular cell type or tissue.

Lysosomal storage disorder – Lysosomes are acidic organelles that contain over 50 hydrolytic enzymes that degrade a wide variety of substrates. In addition to this classical role as the cell's 'waste-disposal unit,' lysosomes form an important part of the machinery for antigen presentation and are in a key position to influence both endocytosis and exocytosis, and intracellular trafficking. Lysosomal storage disorders (LSDs) are monogenic inherited disorders, each caused by a mutation in a single gene. This may encode one of the lysosomal enzymes, or one of the many lysosomal membrane proteins that regulate the environment within the lysosome. Many LSDs have prominent neurologic and neurodegenerative components, and these are uniformly fatal.

Definition and History

The neuronal ceroid lipofuscinoses (NCLs or Batten disease) is the collective name for a group of at least 10 fatal inherited lysosomal storage disorders, which affect mostly children and young adults. These are profoundly disabling, and progressive neurodegenerative disorders that have a devastating impact upon affected individuals and their families. Common features include visual failure, seizures of increasing severity, and relentless declines in motor and cognitive abilities, invariably ending in premature death as there are no effective therapies available. Although varying widely in their age of onset and rate of progression, all forms of NCL display pronounced accumulation of autofluorescent material within the lysosome due to its dysfunction.

Despite being first described by the Norwegian physician Otto Christian Stengel in 1826, the NCLs are more widely known as Batten disease, after the British pediatrician Fredrick Batten, who reported juvenile onset cases in 1903. Each form of NCL is caused by a defect in a single gene, and inherited almost exclusively in an autosomal recessive fashion. Dependent on which of these genes are mutated, the age of onset varies from congenital to adult onset forms. Although neuronal ceroid lipofuscinosis is usually abbreviated as NCL, rather confusingly these disease-causing genes are instead called 'ceroid lipofuscinosis neuronal' (CLN) and designated by gene symbols *CLN1–10* (see **Table 1**). Initially four forms of NCL were described, including infantile (INCL, caused by mutations in *CLN1*), late infantile (LINCL, caused by mutations in *CLN2*), juvenile (JNCL, caused by mutations in *CLN3*), and adult onset forms. However, it is now apparent that many other forms exist, with an ever-increasing number of variant forms (caused by mutations in *CLN5–9*) and a congenital form (caused by mutations in *CLN10*) recently identified. Regardless of the gene defect present, all forms of NCL are commonly referred to as Batten disease, using the prefix 'infantile,' 'late infantile,' and so on to distinguish between them, for example, infantile Batten disease or INCL, late infantile Batten disease or LINCL, and so on. Alternatively, these disorders are sometimes described by the name of the deficient gene, for example, *CLN1*, or palmitoyl protein thioesterase-1 deficiency in infantile NCL (see **Table 1** for details).

Pathogenesis/Pathophysiology

Although eight different disease-causing genes have now been identified, the mechanisms by which their mutation results in the profound effects of these disorders upon the brain remain poorly understood. This situation is further complicated by not knowing the normal function of many of these gene products, or how this is altered by mutation. The *CLN* genes fall into two broad categories encoding either soluble lysosomal enzymes (*CLN1*, *CLN2*, *CLN10*) or glycoproteins (*CLN5*), or a series of transmembrane proteins that are expressed in the lysosome (*CLN3*, *CLN7*) or elsewhere in the endosomal–lysosomal system (*CLN6*, *CLN8*). As discussed later, the nature of the gene product has a significant impact upon the possible therapeutic options available (see section Prognosis), but at present, all forms are incurable. There is a broad correlation between the type of gene products and disease severity, with earlier onset and faster progressing forms of NCL caused by mutations in the genes that encode lysosomal enzymes (*CLN10*, *CLN1*, and *CLN2*). In these forms, there is some evidence for genotype–phenotype correlations, with mutations that leave a higher residual enzyme activity resulting in a markedly later and slower disease progression. However, in the remaining forms of NCL, the situation is not as clear as with many different mutations and heterogeneous presentations evident.

Although little detailed information is available about disease mechanisms, the advent of genetically accurate animal models of NCL has greatly advanced the understanding of the events that happen in each form of the disorder. The vast majority of these models are genetically engineered ('knockout' or 'knockin') or naturally occurring

Table 1 List of genes mutated in each form of NCL, with a description of the type of gene product, its nature, and main intracellular location

Form of NCL	*Gene symbol*	*Gene product*	*Nature and main intracellular location of gene product*
Infantile (INCL)	*CLN1/PPT1*	Palmitoyl protein thioesterase-1	Lysosomal enzyme
Late infantile (LINCL)	*CLN2/TPP-1*	Tripeptidyl peptidase-1	Lysosome enzyme
Juvenile (JNCL)	*CLN3*	CLN3	Endosomal/lysosomal transmembrane protein
Adult	*CLN4*	Gene not identified	Unknown
Variant LINCL	*CLN5*	CLN5	Lysosomal glycoprotein
	CLN6	CLN6	Endoplasmic Reticulum transmembrane protein
	CLN7/MFSD8	CLN7/MFSD8	Lysosomal transmembrane protein
	CLN8	CLN8	Endoplasmic reticulum transmembrane protein
	CLN9	Gene not identified	Unknown
Congenital	*CLN10/CTSD*	Cathepsin D	Lysosome enzyme

mutant mice, but several large animal models (most notably sheep and dogs) also exist, and have particular advantages for modeling human disease. Models in more simple species, including yeast, *Drosophila* (fruit-fly), and zebrafish are also being used to address disease mechanisms and to discover the functional pathways in which the CLN genes normally operate.

Analysis of these models has provided a detailed series of landmarks of CNS disease progression. These data have informed the timing and targeting of therapeutic approaches in preclinical studies, and identified events that are specific to each form of NCL that may be amenable to therapeutic intervention. Examples include blockade of excitotoxicity and immunomodulation strategies to target the autoimmune response in JNCL. Broad themes in pathogenesis have also emerged from these studies. Unexpectedly, neuron loss is not global, but displays remarkable selectivity, especially in the early stages of the disease with the thalamus and populations of inhibitory interneurons particularly affected. However, there is no direct relationship between this selective neuron loss and the widespread build-up of storage material, which appears to be a by-product of the disease process. Instead, localized neuron–glial interactions appear more important in pathogenesis with the distribution of early glial activation accurately predicting the sites of subsequent neuron loss, which occurs many months later. This glial activation is already evident prenatally, and it will be important to determine whether these astrocyte and microglial responses are neuroprotective or contribute directly to neuron loss. The selectivity of effects upon the NCL brain extends to a cellular level, and the synapse is emerging as an important early pathological target. Although reaching a common pathological endpoint, it is clear that the precise sequence of events, their timing, and the place they occur differs markedly between forms of NCL. Indeed, this distinct pathological profile of each disorder challenges the notion that these disorders should be grouped together.

Epidemiology/Risk Factors

The NCLs have been described collectively as the most common inherited neurodegenerative disorder of childhood. Estimates of prevalence have been reported as high as 1 in 12 500 live births, but are more likely to be in the region of 1 in 20 000 or 30 000. The incidence of some forms is much higher in certain populations, most notably in Finland for INCL/*CLN1* and *CLN5*. However, as diagnosis and genetic testing has become more efficient, it is now apparent that each of these disorders has a far wider geographical distribution. With the exception of some rarer types of adult onset NCL, all forms display a classic autosomal recessive pattern of inheritance. Once identified within a family, the issue of carrier testing of siblings and prenatal diagnosis becomes important, and appropriate genetic counseling support is advised.

Clinical Features and Diagnostic Criteria

Although sharing a broadly similar clinical presentation, the age at which the symptoms are first detected and the rapidity of disease progression differ greatly between forms. This age of onset, combined with the symptoms that occur first, may provide the first important clue to which disease form is present. However, this situation is complicated by the wide clinical spectrum of disease for each form, and the influence of different mutations in a particular gene, with widely heterogeneous presentation, even among affected siblings. The early development of all NCL children is thought to be largely normal with no overt signs of the disease.

INCL children typically begin to lose fine motor skills late in their first year, and subsequently display clumsiness, irritability, loss of speech and vision, and sleep disturbances. Visual failure progresses rapidly to blindness, and a variety of seizure types (myoclonic, clonic, tonic, or hypomotor features) become more evident together with a loss of all cognitive and voluntary motor skills by 3 years. Affected children often persist in this highly dependent state for a number of years, before dying between 8 and 13 years of age.

The first symptoms in LINCL children usually appear between 2 and 4 years of age as declining motor ability with clumsiness and ataxia, together with speech deterioration. Motor function and speech decline rapidly in parallel from 3 years onwards, with children completely dependent by 5 years. Seizures usually appear by 3 years as partial, generalized tonic–clonic, secondarily generalized, or sometimes absence seizures. These should be distinguished from the myoclonus that presents a major problem for these children, frequently disturbing their sleep. A gradual decline in vision occurs from 4 years, with blindness usually evident from 7 years, although this may be delayed. The loss of swallowing ability and associated problems often requires fitting a gastrostomy tube, and these children will typically die in the mid-teenage years.

The first presentation of JNCL is usually visual failure between 4 and 7 years of age, often leading to blindness 2–4 years later, and accompanied by learning difficulties in the early school years. Generalized tonic–clonic seizures typically develop ~10 years and worsen progressively, often with complex partial seizures present. Predominantly extrapyramidal motor signs, including rigidity, hypokinesia, stooped posture, shuffling gait, and impaired balance also present from 10 years onwards, accompanied by increasing speech difficulties and leading to a complete loss

of independent mobility. A great range of disturbing psychiatric symptoms is evident in these individuals with anxiety, aggressive and depressive behaviors, sleep disturbances, and a variety of hallucinations. An early onset of puberty in girls, and progressive cardiac involvement are also reported with premature death typically occurring in the mid-to-late twenties.

The features of variant forms of late infantile NCL (*CLN5*, *CLN6*, *CLN7*, and *CLN8*) are variously described as resembling later onset forms of *CLN2* deficiency, or earlier onset forms of *CLN3*. With a wide range of mutations and presentations possible, it may be difficult to distinguish between these disorders. With improved tools for obtaining an accurate molecular diagnosis, it is now apparent that these variant forms are not as geographically restricted as once thought, and should not be excluded from differential diagnosis.

Diagnostic Work-up/Tests

With the advent of widely available enzymatic and genetic testing protocols, it should now be relatively straightforward to produce a definitive diagnosis of the major forms of the Batten disease, without relying as heavily on previously used electron microscopic analysis of skin or rectal biopsies. These depend upon the expert detection and ability to distinguish between the form-specific appearances of accumulated storage material, although light microscopy screening for the presence of vacuolated lymphocytes specific to JNCL in blood smears is still informative. Enzymatic testing for deficiencies in *CLN1* and *CLN2* is now comparatively standard, and can be performed on blood or saliva samples. This testing should be considered in all potential NCL cases as a higher level of residual activity may result in a later onset and slower progression. Identifying the presence of two mutated copies of a *CLN* gene provides a definitive diagnosis, and can also be performed using blood samples, although cheek swabs are now increasingly used. Sequencing through an entire gene may prove prohibitively costly and/or time-consuming, but routine tests for the most common mutations (e.g., the 1.02 kb or 'big' deletion in *CLN3*) are now available. However, if these prove negative, a more detailed mutational analysis may be required, and is important for subsequent carrier or prenatal testing. Some families with a known history of NCL have also opted for preimplantation diagnosis following *in vitro* fertilization procedures. See websites provided under Relevant Websites for details of diagnostic protocols and testing laboratories.

Management

With no effective therapy existing for any form of NCL, treatments are supportive and aimed at minimizing the distressing and disabling symptoms of these disorders. The rapidity of disease progression in INCL and LINCL leaves less scope for these approaches than in the more slowly progressing JNCL, in which many psychiatric and extrapyramidal motor symptoms need to be addressed. The management of seizure activity is difficult and usually requires a complex series of medications that need to be regularly monitored and modified as the disease progresses. In contrast, approaches that minimize pharmacological intervention and focus on supporting the quality of life are more often used in parts of Europe. With progressively declining visual and cognitive performance, supportive educational approaches are increasingly employed, especially in JNCL. With disease progression, problems of mobility increase, and occupational and physical therapy become particularly important. The difficulty in arranging suitable support for children who are rapidly declining cannot be underestimated, and careful advance planning and dialog between different agencies is beneficial. Copious mucous secretions and reduced ability to swallow often prove particularly distressing, with regular suction frequently required. The question of whether to have a gastrostomy is an emotive one for many families, but offers significant nutritional and practical benefits. For all similar logistical issues, Batten disease charities offer a wealth of invaluable expert advice and support, especially for newly diagnosed families.

Prognosis

The therapeutic outlook for individuals diagnosed with any form of NCL is currently uniformly bleak. However, concerted preclinical research in animal models is ongoing to test and refine a variety of therapeutic strategies, although it is realistically going to be some time before any of these reach the clinic.

Theoretically, more options are available for forms of NCL due to a defect in a soluble lysosomal enzyme (*CLN1*/INCL, *CLN2*/LINCL), since delivered enzyme can be bound to surface receptors to cross-correct deficient cells. This could be achieved by enzyme replacement (delivery of recombinant enzyme) or gene transfer approaches (providing a functional copy of the missing gene via viral or nonviral vectors). These approaches have shown promise in mouse models, especially of LINCL, if given early in disease progression, but many technical issues remain before these strategies can be transferred to a clinical setting. A phase I trial of AAV2 mediated gene transfer for LINCL has been undertaken at Cornell University, but it is likely that newer generations of vectors that are much more successful in mice will be required to improve the clinical efficacy. An alternate approach to deliver the missing enzyme is to use intracerebral grafts of neural stemcells. Following preclinical tests in INCL mice, a Phase I trial

of this strategy has been performed in INCL and LINCL at Oregon Health Sciences University (sponsored by Stemcells Inc.), but it is too early to know its outcome. Despite this activity, it must be stressed that these highly experimental approaches are still in their early stages, and it may take many years before they reach the clinic.

The therapeutic options for NCL types caused by mutations in transmembrane proteins (*CLN3*/JNCL and variant forms *CLN6*, *CLN7*, *CLN8*) are much more limited. This is because these proteins cannot be released from cells to cross-correct deficient neurons within the brain. Moreover, strategies that overexpress these proteins widely are likely to prove harmful to neuron survival. Until the precise function of these transmembrane proteins is revealed and more specific mechanistic based therapies become available, the current strategy is to investigate the consequences of mutations in these genes, and see if blocking these effects provides any therapeutic benefit to mouse models. In JNCL mice, this approach has been used by blocking AMPA-mediated excitotoxicity and by using immunosuppression to target the autoimmune response specific to this form of NCL. Although providing partial benefit in mice, these novel treatment forms are yet to reach clinical trials. In readiness, a Batten Disease Diagnostic and Clinical Research Center has been established at the University of Rochester and the Unified Batten Disease Rating Scale devised for assessing disease progression.

A variety of other approaches have been suggested as treatments for different forms of NCL. These include dietary supplements, fish oils, antioxidants, and the analgesic flupirtine, with many of these given regularly to children. However, there is no evidence that any of these approaches provide any benefit.

See also: Niemann–Pick Type C; Rett Syndrome.

Further Reading

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Mole SE, Jalanko A, and Dawson G (2006) Special Issue: Molecular basis of NCL. *Biochimica et Biophysica Acta* 1762: 849–954.

Mole SE, Williams RE, and Goebel HH (2009) *The Neuronal Ceroid Lipofuscinoses (Batten Disease)*, 2nd edn. Oxford University Press.

Relevant Websites

www.bdsra.org – Batten Disease Support and Research Association (BDSRA). US nonprofit organization, providing a resource for families affected by Batten disease.

www.bdfa-uk.org.uk/ – Batten Disease Family Association (BDFA). UK based Batten disease charity.

http://www.ncl-stiftung.de/englisch/home/index.php – NCL Stiftung. German nonprofit organization.

http://www.ucl.ac.uk/ncl/index.shtml – NCL Resource: A gateway for Batten disease. Regularly updated UK based site with information for families, clinicians and researchers. Contains many links to international parents organizations. http://www.ucl.ac.uk/ncl/familysupport.shtml – research laboratories. http://www.ucl.ac.uk/ncl/researchlabs.shtml – diagnostic laboratories. http://www.ucl.ac.uk/ncl/diaglabs.shtml – diagnostic algorithms. http://www.ucl.ac.uk/ncl/algorithms.shtml

http://dbb.urmc.rochester.edu/labs/pearce/bddcrc/index.htm – University of Rochester Medical Center Batten Disease Diagnostic and Clinical Research Center. NIH funded Diagnostic and Clinical Research Center concentrating mainly upon juvenile NCL.

http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim – OMIN-Online Mendelian Inheritance in Man.

Neuroprotection in Movement Disorders

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Glossary

Clinical Trials – Research studies that administer an intervention to human participants. May or may not be randomized or use a placebo or a control group.

Disease-modifying therapies – Treatments that change the time course of the disease or delay the development of later complications or disability. This does not necessarily equal neuroprotection.

Neuroprotection – The ability to delay or prevent neuronal death, which will lead to slowing of disease progression.

Parkinson Plus Disorders – Degenerative disorders that manifest with symptoms similar to Parkinson disease. Including multisystem atrophy, progressive supranuclear palsy, and corticobasal degeneration, these disorders are typically less responsive to current therapies and carry a worse prognosis.

Definition and History

Neuroprotection is typically defined as the ability to delay or prevent neuronal death and dysfunction, which should translate into delayed disease onset or slowed disease progression in human disease. In movement disorders, the search for neuroprotective therapies concentrates within neurodegenerative movement disorders, primarily Parkinson disease (PD) but also Huntington disease (HD) and parkinsonian syndromes such as multisystem atrophy (MSA), progressive supranuclear palsy (PSP), and corticobasal degeneration. Despite the clinical differences, neuroprotective strategies to date have been remarkably similar, focusing on improving antioxidant activity and stabilizing mitochondrial function.

Unfortunately, the search for a neuroprotective therapy has proved difficult. This difficulty stems from several issues: understanding of disease pathophysiology, proper selection of potential therapeutics, appropriate selection of outcome measures, and the type of clinical trial design. Additionally, the definition of neuroprotection requires that researchers demonstrate improved neuronal survival or function. This task is feasible in preclinical models but difficult to prove in humans. Recognition of these problems has led to the development of innovate trial designs and a reconsideration of which outcomes should be used in efficacy trials.

Neuroprotection and Parkinson Disease

Since 1989, 15 published trials have examined putative neuroprotective effects in PD and at least four trials are ongoing (**Table 1**). These trials have generally enrolled participants with early PD on minimal or no treatment. Potential agents have included dopaminergic compounds (selegiline, pergolide, levodopa, rasagiline); antioxidants and mitochondrial enhancers (tocopherol, coenzyme q10, creatine); antiapoptotic compounds and trophic factors (lazabemide, riluzole, TCH-346, GPI-1485, CEP-1347); and antiinflammatory compounds (minocycline). Despite positive results of several trials, no trial has been accepted as providing sufficient evidence of neuroprotection to warrant regulatory approval for this indication. There are several potential reasons for this that span both preclinical work and clinical trials: inadequate disease models, errors in selection of agents or dosages, inability to document activity against the proposed biological target in humans, confounding of symptomatic with disease-modifying effects, or using the wrong outcome or study design. Although all of these reasons are important, this chapter concentrates on issues in clinical development.

Outcome Selection

Appropriate outcome selection is a recurring question in clinical trials of PD. In the absence of an accepted biomarker for disease progression in PD, trials must rely on clinical rating scales or assessments of disability. Although these outcomes are designed to measure clinically important aspects of PD, they are susceptible to several influences. The Unified Parkinson's Disease Rating Scale, for example, is the most widely used scale in PD. It is clinically relevant, reliable, and reproducible. It is weighted heavily, however, toward the motor aspect of PD. This leads to two issues in measuring disease-modifying effects: first, the motor symptoms of PD are highly responsive to dopaminergic therapy, making it difficult to use the scale

Table 1 Published clinical trials of neuroprotection in Parkinson disease

Clinical trial	*Agents used*	*Total sample size*	*Primary outcome examined*
Tetrud & Langston (1989)	Selegiline	54	Time to disability requiring levodopa therapy
DATATOP (1993)	Selegiline, tocopherol (vitamin E)	800	Time to disability requiring levodopa therapy
SINDEPAR (1995)	Selegiline	101	Change in UPDRS
ROADS (1996)	Lazabemide	321	Time to disability requiring levodopa therapy
Swedish Selegiline (1998)	Selegiline	157	Time to disability requiring levodopa therapy
Norwegian-Danish (1999)	Selegiline	163	Change in UPDRS
QE2 (2002)	Coenzyme Q10	80	Change in UPDRS
Jankovic & Hunter (2002)	Riluzole	20	Change in UPDRS
TEMPO (2004)	Rasagiline	404	Change in UPDRS
ELLDOPA (2004)	Levodopa	361	Change in UPDRS
U.K. Low-dose Pergolide (2005)	Pergolide	106	Time to disability requiring levodopa therapy
NET-PD futility (2006)	Minocycline, creatine	200	Change in UPDRS
TCH-346 (2006)	TCH346	301	Time to disability requiring dopaminergic therapy
NET-PD futility (2007)	GPI-1485, coenzyme Q10	213	Change in UPDRS
PRECEPT	CEP-1347	806	Time to disability requiring dopaminergic therapy

in individuals already on treatment. Second, the UPRDS is less sensitive at measuring nonmotor aspects of PD, which take on increasing importance as the disease progresses and are typically unresponsive to current therapies. Assessment of disability sufficient to require dopaminergic therapy is another commonly used outcome in clinical trials. Again, while relevant and meaningful to providers and patients, this outcome can be affected by depression, type of employment, family environment and resources, and several other factors not captured by either the assessment or the UPDRS.

All rating scales can only measure clinically observable effects. They are unable to determine what caused those changes – for example, UPDRS motor scores may improve, but whether this is due to a symptomatic effect, a neuroprotective effect, or a nonmotor effect is unknown. For example, UPDRS motor scores and assessment of disability are affected by nonmotor effects such as depression, making causal interpretation impossible. In addition, rating scales are impacted by inevitable variation in the administration, scoring, and interpretation of these scales. This problem can be minimized but not eliminated by standardized training and certification.

Given the complex pathophysiology and clinical presentation in PD, some researchers have suggested using a global statistical test instead of separate scales. In this analysis, multiple correlated outcome measures are combined into a single measure of effectiveness. When all outcome measures respond to treatment in the same direction, the power of this test is enhanced over traditional methods. This makes it especially useful for an intervention that would be expected to affect global function, but less ideal for an intervention designed to impact a single aspect of PD.

Functional outcomes include assessments of quality of life or assessments of functional transitions such as loss of independent walking or loss of independent living. These measures suffer the same flaw, in that they cannot address the underlying biological processes of PD, but offer intuitively meaningful outcomes that are relevant to clinicians and patients alike. Combined with potential biomarkers of disease activity, these outcomes may become increasingly useful in measuring a disease-modifying effect.

Biomarkers as Outcomes

The difficulty in interpreting current rating scale outcomes, when combined with the slow progression of PD, have spurred the search for biomarkers that could reliably measure disease progression and ideally also represent a biological target for early stage trial designs. Several potential markers have been identified, but unfortunately, none are yet ready to serve as an interim endpoint in clinical trials. α-Synuclein remains an appealing candidate because it is the main component of Lewy bodies, the pathologic inclusion in PD, and because mutations in α-synuclein genes lead to familial forms of PD. Although it has been used to distinguish individuals with PD from unaffected controls, its correlation with disease activity or progression is not known, nor is it known whether changes in α-synuclein levels predictably correlate with changes in clinical disease manifestation. Other candidate biomarkers include smell testing, changes in gene expression, metabolomics, and proteomics. These biomarkers are also being considered as potential tools to identify early PD and to distinguish PD from other conditions such as vascular parkinsonism, MSA, or PSP.

Neuroimaging has been extensively studied for use as a potential biomarker in PD. Radiotracer imaging of the nigrostriatal dopaminergic system has been evaluated in three large pharmacologic clinical trials: ELLDOPA, CALM-PD, and REAL-PET. In all instances, the group that did better on the primary clinical outcome performed worse on the neuroimaging outcomes. This contradiction between clinical and imaging outcomes needs to be solved before dopamine-based radiotracer imaging can be used as a marker for underlying disease progression, and also emphasizes the challenges in demonstrating an actual neuroprotective effect in humans. In addition, measurements of the dopamine system may not account for important nondopaminergic aspects of the disease. Other tracers or different forms of neuroimaging will likely be needed to better capture additional aspects of the underlying pathologic processes in PD.

Clinical Trial Design

Currently, clinical trials in PD suffer from the successful development of dopaminergic therapy for PD. Because of the powerful symptomatic effects of these medications, it is difficult to measure disease progression clinically. For this reason, clinical trial populations for potential disease-modifying treatments are generally early, treatment-naïve PD. New trial designs are emerging to attempt to detect disease-modifying effects, even in the presence of symptomatic treatment. The delayed-start design has been proposed as a method for detecting such effects. In this design, all patients eventually receive active therapy. However, one group is randomized to placebo first, and their exposure to active therapy is delayed, typically by 6–12 months. If the therapy under investigation is purely symptomatic, then the delayed group should catch up to the early-treatment group. If the intervention modifies the disease, however, then the delayed group should continue to lag behind the early group. This design is promising and has been used in two recent clinical trials of rasagiline, the TEMPO and ADAGIO trials.

The delayed start design is not without potential flaws. One concern is the potential for differential dropout

between the early and delayed treatment arms, especially during the initial placebo phase. This endangers the benefits of randomization by making the groups inequivalent. Also, the method for analyzing missing data in a delayed start design may affect the results. For example, dropout may occur for different reasons in the two different groups. When the last observation is carried forward for these dropouts, the data may be biased to either reduce or enhance the treatment effect, depending on the reasons for dropout. This concern may be addressed by performing a sensitivity analysis, in which multiple methods for dealing with missing data are compared. This can provide an assessment of the robustness of the observed treatment effect.

The futility trial is an early-stage clinical trial design that attempts to identify ineffective therapies within a relatively short timeframe while minimizing cost and patient exposure to less promising therapies. A futility trial saves cost and time by using a single active treatment arm and comparing their response to historical controls. These trials may be unblinded or may use a small placebo group to preserve blinding and minimize placebo effect. Futility trials save cost because using historical controls minimizes sample size while preserving power. Also, because they use one-sided statistical tests to prove a treatment is ineffective, they increase power for a defined sample size. Because they are not designed to prove efficacy, futility trials can be completed more quickly, allowing promising therapies to move forward rapidly.

The limitations of the futility design are inherent in its purpose. First, it is not a comparative efficacy trial and should not be judged as such. They are an early-stage screening design that works best when the hypothesized treatment effect is modest, because large treatment effects can be measured efficiently within a traditional efficacy design and do not require a futility design. This design requires that the historical control response be constant and well-defined. Changes in this rate will increase the chance for error, and may lead to either rejecting an effective treatment or falsely proceeding with an ineffective treatment. If the outcome measures are susceptible to changes in ancillary care or changes in practice style, this variability will damage a futility trial and obscure its interpretation.

Emerging Interventions in PD

As trial design and outcome selection continue to evolve, potential interventions continue to emerge for Parkinson disease. The ADAGIO study, recently completed, should provide additional evidence about whether rasagiline represents a disease-modifying intervention for PD. Creatine and coenzyme Q10 are both in definitive comparative efficacy trials, while inosine is being examined in an early-stage trial and should be enrolling participants in 2009.

Neuroprotection and Huntington Disease

Two of the most promising experimental interventions in HD are high dose coenzyme Q10 (CoQ_{10}) and high dose creatine monohydrate. An initial NIH-funded study of 600 mg per day of CoQ_{10} in manifest HD showed a nonsignificant trend toward improvement on the Total Functional Capacity scale. A subsequent study in transgenic R6/2 HD mice showed a dose-dependent increase in therapeutic benefit at higher doses of CoQ_{10}. High-dose CoQ_{10} significantly improved both the behavioral and neuropathological phenotype of R6/2 mice, delaying the development of weight loss, motor deficits, grip strength, gross brain atrophy, striatal neuron atrophy, and huntingtin aggregates in R6/2 mice. Based on this combination of animal and clinical data, a second clinical trial was developed. This NIH-funded study is studying up to 2400 mg per day of CoQ_{10} and is currently enrolling subjects with manifest HD.

Based on the interest in mitochondrial function and data in transgenic models of HD, there have been several small clinical trials of creatine in HD at a variety of dosages. A recent clinical trial has studied up to 40 g per day of creatine monohydrate in manifest HD (S. Hersch, personal communication). While the sample size was small (<20), this open label study showed that creatine was safe and well tolerated for over one year and led to dose-dependent increases in plasma and brain creatine levels and dose-dependent suppression of serum 8-hydroxydeoxyguanosine (8-OHdG), a marker of oxidative DNA injury. These findings led to an NIH-supported comparative efficacy study of creatine monohydrate in HD. This flexible dose study will allow subjects to take up to 40 g per day of creatine and is expected to begin recruitment in early 2009.

These studies illustrate two important points for future clinical trials. First, dose-ranging studies are critical in both preclinical and early clinical work. Underdosing, especially for dietary supplements, may partially explain why prior clinical trials in neurodegenerative diseases have failed. Dose ranging can evaluate short-term safety, examine the relationship between dosage and exposure, and possibly assess biological activity on potential markers such as 8-OHdG. These studies provide additional information that then allows for more rational dose selection in comparative efficacy trials. Second, functional outcomes and parallel group designs provide clearly interpretable information about disease. Unlike PD, there is little interest in the distinction between short-term symptomatic effects and long-term effects on disease progression in HD. Rather, agents have been selected because of their potential to ameliorate the underlying pathophysiology of HD and the definitive trials are designed to demonstrate benefit on functional outcomes. This straightforward

approach may also be useful in PD given the many unmet therapeutic needs and the lack of biomarkers to measure disease progression.

Neuroprotection in MSA and PSP

Neuroprotective trials in MSA and PSP are hampered by their relative rarity and the difficulty in separating them from PD. The potential for misdiagnosis is maximal early in the course of disease, when disease-modifying therapies would be most useful. Still, multicenter study groups have formed to organize clinical research for both conditions, leading to a growing pool of potential trial participants. In MSA, no efficacy trials are currently registered, but lithium, valproate, and CoQ_{10} are all under investigation for PSP.

Summary

Neuroprotection is a difficult but important goal in the treatment of neurodegenerative movement disorders. Despite early setbacks, continuing advancement in preclinical works, improvements in study design and outcome measurement, and the development of possible biomarkers all offer continued hope for the development of disease-modifying therapies for these fatal diseases.

See also: Co-enzyme Q_{10}; Dopamine; Huntington's Disease; Mitochondrial Dysfunction; Multiple System Atrophy; Neuroimaging, Parkinson's Disease; Parkinson's Disease: Definition, Diagnosis, and Management; Progressive Supranuclear Palsy; Rating Scales in Movement Disorders; Unified Parkinson's Disease Rating Scale (UPDRS) and The Movement-Disorder Society Sponsored-unified Parkinson's Disease Rating Scale (MDS-UPDRS).

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Nicotine

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Glossary

Dopamine – Dopamine is mainly a neurotransmitter occurring in a wide variety of animals, including both vertebrates and invertebrates. In the brain, it works as a neurotransmitter, activating the five types of dopamine receptors – D1, D2, D3, D4, and D5, and their variants. Dopamine is produced in several areas of the brain, including the substantia nigra and the ventral tegmental area.

Neuroprotection – Mechanisms within the nervous system that protect neurons from apoptosis or degeneration.

Neurotoxins – A neurotoxin is a toxin that acts specifically on neurons, usually by interacting with membrane proteins such as ion channels.

Nigrostriatal pathway – The pathway that connects the substantia nigra to the striatum. It is one of the four major dopamine pathways in the brain and is particularly involved in movement, forming part of a system called the basal ganglia motor loop.
Receptor – A protein molecule, embedded in either the plasma membrane or cytoplasm of a cell, to which a mobile signaling molecule may attach. A molecule which binds to a receptor is called a 'ligand,' and may be a neurotransmitter, a hormone, a pharmaceutical drug, or a toxin, and when such binding occurs, the receptor undergoes a conformational change which ordinarily initiates a cellular response.

Nicotine

Nicotine is an alkaloid found in the nightshade family of plants (Solanaceae) predominantly in tobacco, and in lower quantities in tomato, potato, eggplant, and green pepper. Nicotine can also be found, along with cocaine, in the leaves of the coca plant. Nicotine constitutes ~0.6–3.0% of dry weight of tobacco, with biosynthesis taking place in the roots and accumulation in the leaves. It functions as an antiherbivore chemical, being a potent neurotoxin with particular specificity to insects. As nicotine enters the body, it is distributed quickly and can cross the blood–brain barrier. Nicotine is metabolized in the liver by cytochrome P450 enzymes (mostly CYP2A6, and also by CYP2B6). A major metabolite is cotinine.

The neurochemical systems involving the neurotransmitter acetylcholine are divided into muscarinic and nicotinic, the latter receptors responding to nicotine and its derivatives. Nicotine interacts with multiple nicotinic receptor (nAChR) subtypes in the peripheral and central nervous system, as well as in skeletal muscle. In small concentrations, it activates these receptors. Toxic symptoms from nicotine can occur in children with doses as low as 1 mg and in adults with doses as low as 2–5 mg. The lethal dose of nicotine in adults is from 0.5 to 1.0 mg kg^{-1} or a total dose of 30–60 mg. Symptoms of nicotine poisoning include: central nervous system signs ranging from dizziness, to tremor to lethargy and coma; sympathetic or parasympathetic autonomic signs such as hypertension or hypotension, cardiac arrhythmias, salivation, and diaphoresis; and neuromuscular effects including neuromuscular excitability followed by weakness and even rhabdomyolysis.

The nAChRs are members of the large family of ligand-gated ion channels and are constituted by the assembly of five subunits arranged pseudosymmetrically around the central axis that forms a cation-selective ion pore. They are widely distributed in both the nervous system and nonneuronal tissues and can be activated by endogenous agonists such as acetylcholine or exogenous ligands such as nicotine. Neuronal nAChRs may play a role in neurodegenerative disorders. Smoking may have a protective effect against Parkinson's disease (PD) and multiple system atrophy. Both retrospective and prospective epidemiologic studies have consistently demonstrated an inverse association between cigarette smoking and PD, leading to theories that smoking in general and low-dose, chronic nicotine exposure in particular might be neuroprotective. Within twin pairs, the risk of PD is inversely correlated with the dose of cigarette smoking. This effect is most pronounced in monozygotic twins. Cigarette smoke contains many different chemicals, but nicotine seems to be the strongest candidate as the agent responsible for neuroprotection against PD for several reasons. First, nicotine is known to protect against the degenerative effects of toxic insults in different experimental systems. Second, nicotine pretreatment consistently reduces the detrimental effects of excitotoxin exposure in cultured cells, including neurotoxin-induced degeneration of nigral dopamine-containing neurons. In rats and mice, nicotine can protect against parkinsonism-inducing neurotoxins, like 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and methamphetamine, probably by increasing the level of neurotrophic factors. Nicotine has also shown to stimulate the release of dopamine in the striatum of animals and to preserve nigral neurons and striatal dopamine levels in laboratory animals with lesioned nigrostriatal pathways. As a result, nicotine seems to stimulate brain dopaminergic systems, provides some potentially symptomatic benefits in PD, and may have neuroprotective actions. However, the dose of nicotine that is employed appears to be critical since low doses and not high seem to be protective. As a result, despite the evidence that nicotine is neuroprotective, it is clear that nicotine can be toxic under some circumstances. The balance between nicotine neuroprotection and toxicity depends on dose, developmental stage, and regimen of administration.

There is a well-established loss of nAChRs in postmortem brains from patients with Alzheimer's disease, PD, and a range of other disorders. Nicotine and subtype selective nAChR ligands provide neuroprotection in in vitro cell culture systems and in in vivo studies in animal models of such disorders. Most studies agree that nicotine is protective against glutamate and β-amyloid toxicity in various culture systems. This effect appears to be mediated by α7 subtype nAChRs since the protection is blocked by α-bungarotoxin and is mimicked by α7 selective agonists. In vivo studies indicate that α7 receptors play a critical role in protection from cholinergic lesions and enhancing cognitive function. The exact subtype involved in the neuroprotective effects seen in animal models of PD is not clear, but in general, broad spectrum nAChR agonists appear to provide protection, while α4β2

receptors appear to mediate symptomatic improvements. Recently, α6 subunits have been associated with both potential symptomatic and neuroprotective effects of nicotinic agonists in MPTP-pretreated primates. These observations suggest that development of nAChR agonists or antagonists targeted to α6β2-containing nAChRs may represent a particularly relevant target for PD therapeutics. On the other hand, brain expression of cytochromes P450 2B6, 2D6, and 2E1 is higher in smokers, and is induced by nicotine in animals. These enzymes can metabolize many of the neurotoxins associated with PD. Since smoking is considered as protective against PD, it has been hypothesized that nicotine-induced elevations of brain CYPs in smokers may contribute to neuroprotection against PD.

Smoking has also been associated with a lower risk of incident essential tremor. Likewise, nicotine alone (delivered by gum, or transdermal patch, or in combination with neuroleptics) may improve tics and improve attention-related behaviors. Finally, nicotine may have neuroprotective effects in an experimental model of Huntington's disease and has been reported to reduce hemiballism–hemichorea and akathisia.

Against this backdrop, it is essential to emphasize that nicotine exposure in the form of cigarette smoking is not recommended by physicians. The danger of smoking-related medical disorders, including nausea, vomiting, tachycardia, and with long term use, lung cancer, outweigh arguments of benefit. To this end, significant pharmacological research efforts are currently directed towards developing drugs that can activate central nicotinic receptors outside of cigarettes and specifically to develop agents that are not associated with systemic side effects.

See also: Neuroprotection in Movement Disorders; Parkinson's Disease: Definition, Diagnosis, and Management.

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Niemann–Pick Type C

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Glossary

Filipin – A polyene antibiotic that binds to unesterified cholesterol, used to identify abnormal cholesterol accumulation patterns in NPC.

Glycosphingolipids – A subtype of glycolipids involved in cell membrane structure, modulation of membrane protein function, and cell recognition, which accumulate in central nervous system tissues in NPC. Gangliosides are a subtype of glycosphingolipids.

Niemann–Pick disease (NP) – A heterogeneous group of neurovisceral lipid storage disorders with different underlying biochemical defects and clinical presentations.
Niemann–Pick Type C (NPC) – A subtype of Niemann–Pick disease related to accumulation of lipids in the cells of multiple tissues.
Polymorphous cytoplasmic bodies – Characteristic cellular inclusions detected in NPC-affected cells by electron microscopy.

Definition and History

Niemann–Pick disease (NP) is a heterogeneous group of neurovisceral lipid storage disorders with a wide spectrum of clinical presentations. The first case was described by Albert Niemann in 1914, with further pathological characterization of the disease by Ludwick Pick in the 1920s. In 1958, Crocker and Farber reviewed 18 patients with a wide range of clinical features, unified by findings of increased tissue sphingomyelin and 'Niemann–Pick cells' (foamy macrophages). Four subtypes were delineated by Crocker in 1961 (A, B, C, and D); Type C was defined as a chronic neuropathic form, which in the 1980s was found to be associated with defects in cholesterol storage.

Pathogenesis/Pathophysiology

While NP Types A and B are associated with primary mutations in the structural gene for acid sphingomyelinase (ASM), resulting in accumulation of sphingomyelin in cells, NP Type C (NPC) is characterized by impaired cholesterol transport from lysosomes, with only milder, secondary deficiency decrease in ASM activity. The hallmark biochemical finding in NPC is intracellular accumulations of several types of lipids in the endosomes and lysosomes of multiple tissues, with unesterified cholesterol predominating in nonneuronal organs and glycosphingolipids being more prevalent in the central nervous system.

NPC is inherited in an autosomal recessive manner, affecting males and females equally. Approximately 90% of patients have mutations in the *NPC1* gene (mapped to 18q11), while 4% have mutations in the *NPC2/HE1* gene (mapped to 14q24.3). The exact functions of the abnormal protein products remain unclear, but are postulated to be involved in the intracellular trafficking or transport of cholesterol and glycolipids.

Epidemiology

NPC is a pan-ethnic disease, with prevalence estimated at ~1:150 000 in Western Europe, but higher frequency has been noted in some isolated populations. Prevalence is likely underestimated because of underrecognition of atypical phenotypes.

Clinical Features and Diagnostic Criteria

Clinical manifestations vary widely depending on the age of presentation, which ranges from the perinatal period to the sixth decade of life, with a large variety of psychiatric, neurological, pulmonary, hepatic, or splenic signs. Neurologic progression is independent from other systemic involvement. Cases have been categorized based on age of onset and predominant symptoms:

Perinatal: Symptoms may be variable and nonspecific, with liver disease (cholestasis, hepatosplenomegaly, ascites) as the most frequent sign. A minority of cases develop rapid liver failure without neurologic symptoms or pulmonary failure secondary to infiltration of lungs with foam cells.

Infantile: Isolated hepatosplenomegaly, though not always present, may be the only sign until 12–18 months, when hypotonia, developmental delay or regression, pyramidal signs, and ataxia may develop.

Childhood/adolescent: The most common manifestation, accounting for 60–70% of cases. Ataxic gait is common with presentation at age of 3–5, while cognitive decline and decreased fine motor control are more commonly seen with onset between 6 and 12 years. Frequent signs include ataxia, dystonia, dysarthria, choreoathetoid movements, intellectual impairment, and vertical supranuclear gaze palsy (VSGP). One-third may develop seizures, and gelastic cataplexy occurs in 10–20%. Dystonia typically develops distally, spreading proximally to become generalized. Later complications include spasticity, pyramidal signs, psychosis, and severe dysphagia. Visceromegaly is less common than in earlier presentations.

Adult: Late presentations are rare, with prominent psychiatric or cognitive disturbance possibly overshadowing other signs of the disease, mimicking schizophrenia, depression, or bipolar disease. Clinical signs are similar to earlier phenotypes, including ataxia (76%), VSGP (75%), dysarthria (63%), or cognitive decline (61%); movement disorders occur in 58%, including dystonia (40%), chorea (19%), or parkinsonism (10%). Progression is slower, with less frequent occurrence of seizures, cataplexy, or visceromegaly. Rare cases have presented with isolated splenomegaly or spontaneous splenic rupture.

Differential Diagnosis

The differential diagnosis is broad and varies by age of onset and phenotype. In younger patients, other storage diseases (Gaucher's disease, other forms of NP) or inborn errors of metabolism, Wilson's disease, mitochondrial

disorders, dopa-responsive or primary dystonia, encephalitis, or other dementing illnesses should be considered. Adult presentations may mimic primary psychiatric disease, multiple sclerosis, or neurodegenerative disorders such as Alzheimer's disease, frontotemporal dementia, or progressive supranuclear palsy.

Diagnostic Work up/Tests

Diagnosis of NPC may be confirmed by biochemical or genetic testing, which has superseded the need for tissue biopsies:

Biochemical testing: Diagnosis of NPC can be confirmed by the demonstration of abnormal intracellular cholesterol homeostasis. In majority of cases, affected cells show the classic results of markedly reduced or absent cholesterol esterification after loading cultured fibroblasts (obtained by skin biopsy) with exogenous low density lipoprotein (LDL)-type cholesterol. In addition, staining of fibroblasts with filipin shows a punctate, perinuclear pattern of fluorescence, highlighting the accumulation of unesterified cholesterol (**Figure 1**). In 15% of affected individuals, more commonly in adult cases, there may be a 'variant' biochemical phenotype, with less distinctive staining patterns or intermediate cholesterol esterification abnormalities. Normal ASM activity in leukocytes excludes other forms of NP.

Genetic testing: Molecular genetic testing is mainly used to confirm the diagnosis of NPC in cases with equivocal findings on biochemical testing. Given the size of the *NPC1* gene, the large number of known mutations, and high frequency of polymorphisms, interpretation of DNA changes may be difficult.

Histology: Microscopic examination of spleen, liver, or bone marrow may demonstrate the presence of lipid-laden macrophages (foam cells), with sea-blue histiocytes in the bone marrow of advanced cases. Brain tissue examination demonstrates minimal cholesterol deposition and marked accumulation of multiple glycolipids in gray matter, with numerous, widespread degenerative changes in cortical and subcortical neurons, manifest earliest in the cerebellum and brainstem. Purkinje cells are most vulnerable to NPC pathology, accounting for the high incidence of ataxia seen clinically. Chronic cases may display neurofibrillary tangle pathology remarkably similar in quality and distribution to Alzheimer's disease, in addition to accumulation of amyloid precursor protein. Polymorphous cytoplasmic bodies may be seen with electron microscopy of brain, conjunctival, rectal, or skin tissues, and are more pathognomonic for NPC than light microscopic findings.

Neuroimaging: Imaging findings are nonspecific, and may be normal in early stages, with only late development of prominent cerebellar, callosal, and cerebral atrophy or periatrial white matter abnormalities.

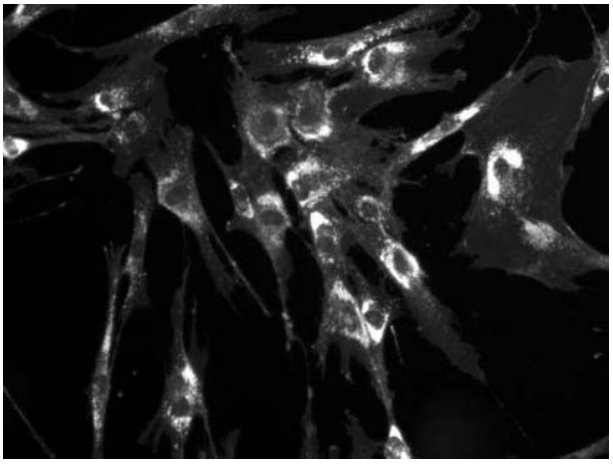

Figure 1 Filipin-stained cultured skin fibroblasts in the classic form of NPC show increased perinuclear fluorescence, reflecting abnormal accumulation patterns of unesterified cholesterol.

Management

There is no specific treatment for NPC, although several treatment approaches are being investigated. As demonstrated in a randomized controlled trial, Miglustat is the only agent to show improvement or stabilization of markers of neurologic progression in some patients. Miglustat is an inhibitor of ganglioside synthesis currently used to treat Gaucher's disease, and crosses the blood–brain barrier to reduce the biosynthesis of glycosphingolipids, resulting not only in the reduction of pathological substrates in the brain but possibly the normalization of lipid trafficking abnormalities. Neither strategies to reduce somatic or hepatic lipid overload, including low-cholesterol diets and various combinations of cholesterol lowering agents, nor hepatic or bone marrow transplantation have altered the course of neurodegeneration.

Symptomatic treatment is indicated for the management of dystonia, spasticity, seizures, or sleep disorders. Cataplexy has responded to clomipramine or modafanil. Secondary complications may be prevented by monitoring swallowing, gastrointestinal, and respiratory function for avoidance of aspiration, malnutrition, or severe constipation. Physical, occupational, and speech therapy may assist in functional adaptation and prevent complications of immobility. Genetic counseling is indicated for family planning and guidance of testing for other family members.

Prognosis

The rate of disease progression is variable, depending on age of presentation. Neonatal disease may cause death within months, while patients presenting in childhood

usually die before the age of 5. Childhood/adolescent forms typically die in teenage years from aspiration pneumonia, but have been reported to survive to the fourth decade. Adult onset forms may have prolonged courses, potentially over 2–3 decades.

See also: Ataxia; Chorea; Dementia, Movement Disorders; Dysarthria; Dystonia; Eye Movement Abnormalities in Movement Disorders; Sleep Attacks; Supranuclear Eye Movement Control; Tauopathies.

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http://www.niemannpick.org.uk/ – Niemann–Pick Disease Group.

Nitric Oxide

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Glossary

Apoptosis – A process of programmed cell death where cells die in a controlled and regulated manner.
Cyclic GMP (cGMP) – A second messenger similar to cyclic AMP. Nitric oxide activates guanylate cyclase to produce cGMP from GTP.
NMDA receptor – An ionotropic receptor for glutamate, critical for learning and synaptic plasticity by means of allowing the influx of calcium ions.
Nitric oxide – A gaseous molecule that participates in several physiological and pathological processes in neurons and other mammalian cells.
***S*-nitrosylation** – A process of modification of cysteine residues in proteins by nitric oxide.

Definition

Nitric oxide (NO) is a gaseous molecule with autocrine and paracrine effects on many cell types. NO is synthesized from the amino acid L-arginine by NO synthase (NOS) and is involved in a myriad of cellular functions, including muscle relaxation, neuronal signaling, and immune function. NO synthesis is dependent on the availability of cofactors such as tetrahydrobiopterin (BH4), heme, flavin adenine dinucleotide (FAD), and reduced nicotinamide–adenine dinucleotide phosphate (NADPH). The rate limiting enzyme, NOS, exists in three different isoforms: neuronal NOS (nNOS), endothelial NOS (eNOS), and inducible NOS (iNOS). nNOS and eNOS are Ca^{2+}/calmodulin-dependent, constitutively active enzymes, whereas the activity of iNOS is independent of Ca^{2+}. The human nNOS gene is located on chromosome 12, iNOS on chromosome 17, and eNOS on chromosome 7. nNOS has been localized to discrete populations of central neurons and in peripheral autonomic nerves; eNOS is abundant in endothelial cells, including cerebral blood vessels, while iNOS can be induced in macrophages, astrocytes, and microglia following injury or inflammation. In the brain, nNOS labeling coexists with NADPH-diaphorase staining, and purified nNOS shows NADPH-diaphorase activity.

NO may diffuse readily across plasma membranes up to 200 μM in vivo in normal brain tissue. Under physiological conditions, NO may affect neuronal function by at least two independent mechanisms: (1) NO activates soluble guanylyl cyclase and increases intracellular levels of cyclic guanine monophosphate (cGMP) that in turn modulates neurotransmitter release, receptor efficacy, signaling, and synaptic plasticity and (2) NO *S*-nitrosylates a variety of

proteins, including NMDA receptor subunits, catalytic subunits of caspases, α-tubulin, and sodium pump ATPase, thereby affecting intracellular signaling. In addition, by modulating the release of neurotransmitters, NO affects neurotransmission indirectly. NO increases the release of dopamine and serotonin in the rat medial preoptic area, and noradrenaline and glutamate in the hippocampus, while suppressing GABA release in the hippocampus. At physiological concentrations, NO is neuroprotective, although higher levels may be neurotoxic.

nNOS-containing neurons are abundant in motor areas of the brain, including the frontal cortex, basal ganglia, pontine tegmentum, midbrain dopaminergic centers, and the cerebellum. NO participates in physiological activities in these centers, including altering neurotransmitter release, modulating the efficacy of receptor function and signaling, and synaptic plasticity. NO also regulates long-term depression in striatal neurons, an effect critical for learning and motor control of basal ganglia.

nNOS-containing neurons are distributed throughout the cerebral cortex and in the subcortical white matter. In rat sensorimotor cortex, they are aspiny interneurons, which coexpress GABA and are distributed primarily in layers II and III. NADPH-diaphorase or nNOS activity is seen in ~2% of striatal neurons and is localized to a subpopulation of GABAergic interneurons containing somatostatin and neuropeptide Y in all mammals. NADPH-diaphorase-containing striatal neurons in rats receive glutamatergic projections from the cerebral cortex, GABAergic fibers from the globus pallidus external segment, dopaminergic projections from the substantia nigra pars compacta, and innervate striatal projection neurons. Burst firing of nigral dopaminergic neurons activates striatal nNOS neurons via D_5 dopamine receptors, leading to the synthesis of NO that increases the levels of cGMP in striatal projection neurons, facilitating long-term depression at corticostriatal synapses. nNOS is physically attached to the postsynaptic density protein 95 (PSD95) which is part of the NMDA receptor complex. Consequently, NMDA activity in the striatum causes nNOS-mediated NO synthesis and a subsequent increase in cGMP levels. In cholinergic neurons, this leads to NMDA-induced acetylcholine release in the striatum.

Pharmacological blockade of nNOS suppresses spontaneous locomotion and exploratory activity in rats. Coadministration of nNOS inhibitors reduces the hyperlocomotion produced by the NMDA antagonists or dopamine agonists. However, no abnormalities have been observed in the voluntary motor activity or basal ganglia function in mice following targeted deletion of nNOS. Interestingly, these mice showed deficits in balance and coordination only in the dark, while their visual acuity appeared normal. In addition, the male $nNOS^{-/-}$ mice are hyperaggressive and show increased sexual behavior. It is worth noting that in these mice, NADPH-diaphorase activity is only partially reduced in the cerebral cortex and the striatum, while the cerebellum and amygdala showed a complete loss of activity.

Increased concentrations of NO affect mitochondrial function, facilitate apoptotic signaling, and promote oxidation, nitration, and excessive *S*-nitrosylation of proteins, leading to interference with their function and clearance, and thereby causing neurotoxicity. nNOS is physically coupled to NMDA receptors and excessive NMDA activity leads to increased production of NO, augmenting the excitotoxicity. Increased concentrations of NO inhibit cytochrome C oxidase (COX), leading to disruption of mitochondrial membrane integrity and depletion of cellular energy, allowing the diffusion of superoxide ions from mitochondria. Apart from this, superoxide ions are also produced as a by-product of dopamine metabolism. Superoxide ions avidly bind to NO to form peroxynitrite, which is degraded into hydroxyl and reactive oxygen radicals. These free radicals, along with peroxynitrite, cause serious damage to proteins, lipids, and DNA, forcing cells to undergo apoptosis. NO and these radicals themselves and the process of DNA damage activate poly-ADP-ribose-polymerase (PARP) to cause further depletion of energy, thereby driving cells toward apoptosis. PARP also facilitates translocation of apoptosis-inducing factor (AIF) from the mitochondria to the nucleus to cause further DNA damage (**Figure 1**).

Excessive levels of NO also lead to nitration of molecules causing impairment of cellular functions. High levels of nitrotyrosine have been seen in the brains of patients with Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Alzheimer's disease. Apart from nitration, NO-mediated *S*-nitrosylation of reactive cysteine residues of proteins interferes with their function and clearance. NO-mediated *S*-nitrosylation of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) facilitates the formation and nuclear translocation of mutant Huntingtin-GAPDH-Siah 1 complex in the neurodegenerative process of striatal neurons in Huntington's disease. Similarly, NO *S*-nitrosylates parkin. Parkin is a ubiquitin ligase involved in protein degradation via the ubiquitin–proteosome system, and mutations of parkin are the most common cause of familial, early-onset parkinsonism.

In conclusion, NO is produced in the brain by neurons, astrocytes, microglia, and endothelial cells, and participates in a number of physiological functions such as learning and plasticity, as well as several degenerative processes. NO mediates its effects by increasing the concentration of cGMP, and causing oxidation, nitration, and *S*-nitrosylation of cellular proteins. At high concentrations, NO affects mitochondrial permeability, impairs cellular energy production, alters protein structure, trafficking, function and degradation, causes DNA damage, and induces the apoptotic-signaling

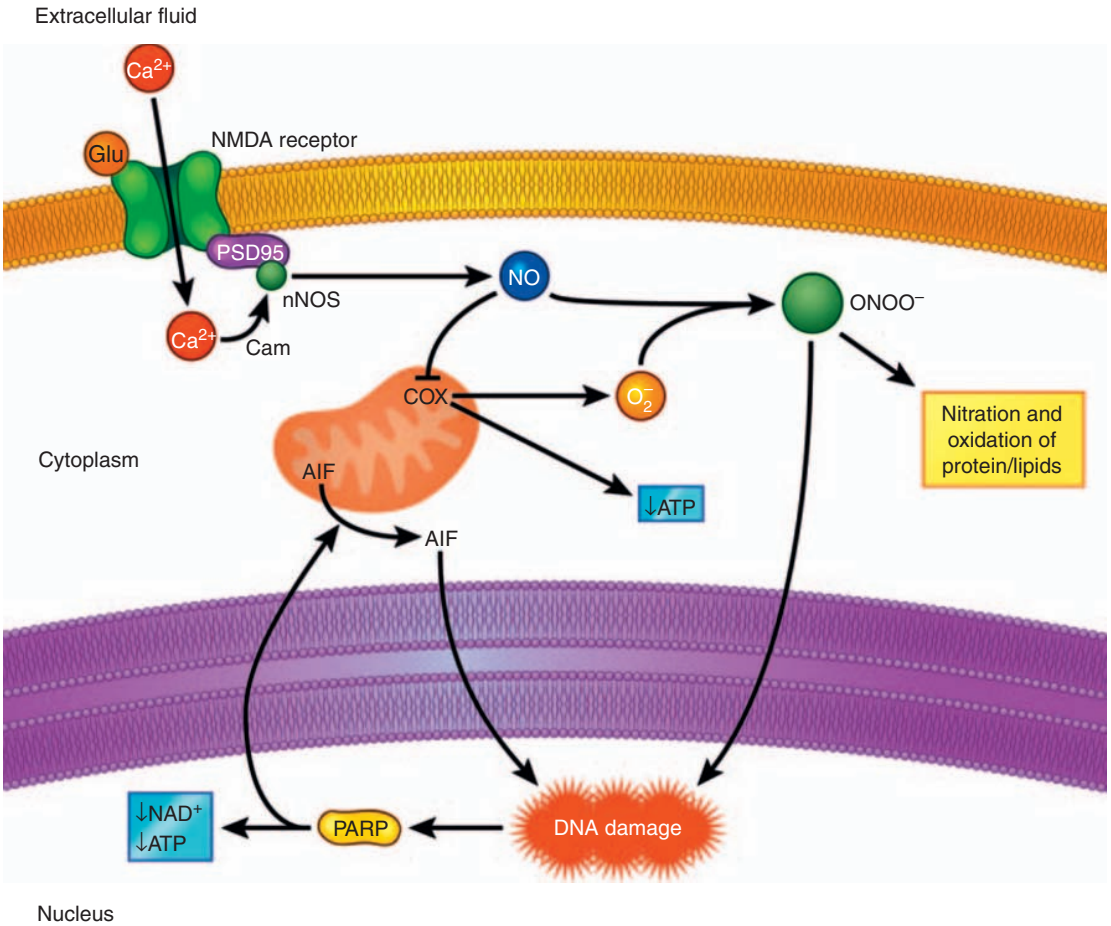

Figure 1 Glutamate binding to NMDA receptors results in Ca^{2+} influx leading to a local increase in Ca^{2+} concentration and the consequent formation of the calcium–calmodulin complex that activates nNOS at the postsynaptic density. Activated nNOS produces NO that rapidly defuses and blocks COX, leading to a reduction in ATP and compromised mitochondrial permeability, allowing diffusion of superoxide ions (O_2^-) from mitochondria. Superoxide ions bind to NO and form peroxynitrite ($ONOO^-$). Peroxynitrite diffuses freely and cause nitration and oxidation of proteins and lipids, and DNA damage. DNA damage activates PARP. Activated PARP depletes energy production by depleting the levels of NAD^+, as well as facilitating the translocation of AIF from the mitochondria to the nucleus to cause further DNA damage leading to apoptosis.

cascade. NO signaling is emerging as a potential therapeutic target in neurological disorders such as Parkinson's and Huntington's disease.

See also: Basal Ganglia; Parkinson's Disease: Definition, Diagnosis, and Management.

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Normal Pressure Hydrocephalus

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Glossary

Class 1 evidence – Data derived from prospective, randomized, controlled clinical trials;
Class 2 evidence – Prospective data collection with retrospective analysis of clearly reliable data;
Class 3 evidence – Studies based on retrospective analysis, such as chart reviews, clinical series, data bases or registries, case reports, and expert opinion.
Evidence-based medicine – The conscientious, explicit, and judicious use of current best published scientific evidence in making decisions regarding patient care strategies. The quality of the scientific evidence is grouped into three classes, as follows:
Guideline – A particular strategy or range of management strategies that reflect a *moderate* degree of clinical certainty.
Guidelines for clinical practice – Evidence-based medical treatments are based on a systematic analysis of all available scientific literature on a topic, and are divided into three categories, defined as follows:
Hydrocephalus – Pathologic condition characterized by abnormally elevated cerebrospinal fluid pressure.
Idiopathic normal pressure hydrocephalus (iNPH) – Clinical syndrome characterized by gait ataxia, dementia, and urinary incontinence with evidence of ventriculomegaly on an imaging study and favorable response to reduction in cerebrospinal fluid pressure.
Lumbar drainage trial – Inpatient diagnostic test for iNPH in which a sterile, flexible catheter is placed in the lumbar spine for several days and serial assessment of gait, cognition, and continence are assessed; generally used to predict probability of favorable response to cerebrospinal fluid shunting procedure.
Options – Remaining strategies for patient management for which there is *unclear* clinical certainty.
Standard – Accepted principles of management that reflect a *high* degree of clinical certainty.
Ventriculomegaly – Imaging evidence of abnormally large ventricular size; usually refers to CT or MR images.

Definition and History

Hydrocephalus has been recognized as a cause of brain dysfunction and movement disorders for several centuries. (**Figure 1**) The first use of the term 'normal pressure hydrocephalus (NPH)' appeared in 1964 in a thesis by the Columbian neurosurgeon Salomon Hakim '*Some Observations on CSF Pressure: Hydrocephalic Syndrome in Adults With 'Normal' CSF Pressure.*' The concept was more fully developed in an article that appeared the next year in the *New England Journal of Medicine*. This article described a newly recognized syndrome in aging adult patients who were discovered to have ventriculomegaly *without* increased intracranial pressure after presenting to medical attention with gait difficulty, cognitive disturbance, and urinary incontinence. Subsequent work described improvement in the symptoms of patients with the 'classical triad' of gait ataxia, dementia, and incontinence with lowering of cerebrospinal fluid (CSF) pressure.

At the current time, the most common definition of idiopathic normal pressure hydrocephalus (iNPH) is a progressive disorder, without identifiable cause, that results in reported and observed gait ataxia, cognitive loss, and/or urinary incontinence, accompanied by imaging evidence of ventriculomegaly.

Pathogenesis/Pathophysiology

The initial description of NPH as 'symptomatic occult hydrocephalus with "normal" CSF pressure' included one patient with idiopathic and two patients with posttraumatic hydrocephalus. This, as well as the recognition that patients with subarachnoid hemorrhage, stroke, and meningitis could also develop ventriculomegaly without elevated pressure on the lumbar puncture (LP) led to controversies regarding the nomenclature, diagnosis, and treatment of the condition.

The gait disturbance in iNPH appears to be a disturbance of the phased activation of muscle groups, as would be observed in dysfunction of subcortical motor control, rather than a primary pyramidal tract imbalance. Dysfunction of the subcortical dopaminergic pathways may also contribute to the gait disturbance.

In regard to dementia, the locus of dysfunction in iNPH is not known, but the frontostriatal system and periventricular projection fibers have been implicated. In addition to cognitive disturbances, psychiatric features with behavioral disturbances ranging from aggressiveness

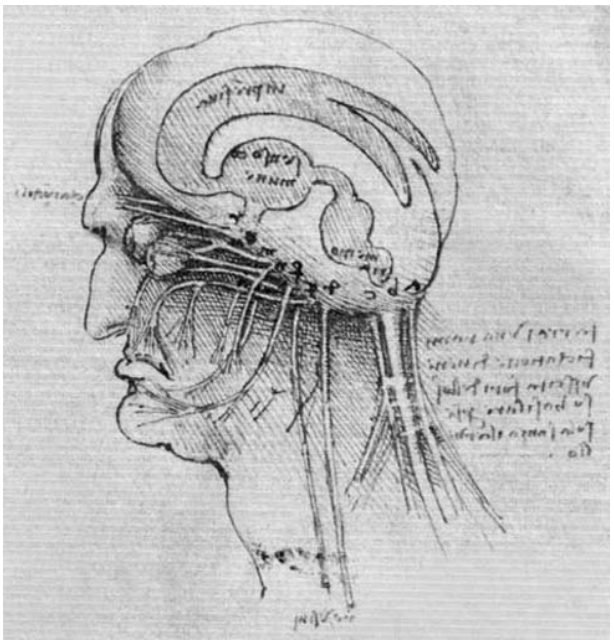

Figure 1 Leonardo da Vinci (1452–1519): Anatomic study of the ventricular system.

and impaired impulse control to depression and hallucinations have been reported, but their association with iNPH is poorly understood.

There are no generally accepted neuropathological criteria for postmortem diagnosis of iNPH. While potentially causative abnormalities, such as arachnoid fibrosis, have been reported in postmortem brain autopsies of some patients who carried the diagnosis of INPH, this has not been studied in a systemic manner, and therefore, cannot verify a clinical diagnosis of iNPH.

Epidemiology/Risk Factors

There is an ongoing need for standardized diagnostic criteria that will permit study of the incidence and prevalence of iNPH. These results may differ among the community-independent, community-assisted, and institutionalized populations. Details of age, gender, comorbidities, and risk factors need to be collected and analyzed to determine the extent of the problem, and to plan diagnostic and treatment services for a growing elderly population in North America.

Clinical Features and Diagnostic Criteria

Clinicians of multiple medical specialties may be the initial evaluator of a patient with suspected iNPH, including internal and family medicine, neurology, neurosurgery, gerontology, urology, and psychiatry. It is, therefore, important that the presenting symptoms and signs, and initial noninvasive diagnostic evaluation be widely understood. As cognitive disturbance is a hallmark of the condition, a knowledgeable informant who can describe the change in the patient's condition over a period of several years is very helpful.

Clinical Diagnosis

All three components of the classic triad of gait, cognitive, and sphincteric disturbance need not be present to establish the diagnosis of iNPH. Medical students have coined the mnemonic 'wobbly, weird, and wet' to help themselves, as well as patients and families, keep in mind the three clinical components of this condition. The initial clinical manifestation and order of appearance of symptoms is variable. The most common and earliest abnormality is usually gait ataxia. Signs and symptoms in iNPH are bilateral, unless accompanied by an identifiable comorbidity, such as stroke or lumbar degenerative spine disease, that accounts for a lateralizing feature. Dementia does not occur in all patients, and its speed of progression and severity are variable. Urinary urgency and incontinence in iNPH are difficult to distinguish from other causes of such urologic dysfunction, and may be secondary to the gait disturbance, which may prevent the patient from attending to an urge to void in a timely manner.

Gait

The gait disturbance in iNPH is often likened to walking on a boat: wide-based, side-to-side, bent forward, and with feet 'glued' to the deck. It is described as 'magnetic' and with a characteristic manner of turning that requires several steps, and is referred to as 'en bloc' or clocklike, rather than the easy pivot of a healthy turn. Videotape or computer analysis reveals reduced speed, decreased step height, and stiffness resulting from reduced counter rotation of the shoulders and pelvis during walking.

Dementia

Impaired speed and accuracy of gross and fine motor functions, decreased attention and apathy, impaired executive function, and personality/behavior changes are all observed. Often, these features of the clinical presentation are best described by family and friends. Neuropsychologic testing and mini-mental status testing (MMSE), as well as functional scales of wellness, are useful in establishing the degree of disability and assessing response to treatment.

The cognitive disturbance in iNPH includes slowed reaction time and recall, inattention, apathy, and decreased executive functions. Decreased volume and output of speech are common, but true aphasia is rare.

Imaging

Ventriculomegaly is most often a qualitative and subjective finding in clinical radiologic practice. Quantification of ventricular enlargement on CT or MR images is defined as an Evan's index of 0.3 or greater, reflecting an increased ratio of diameter of the biventricular size compared to the cranial size.

MRI provides additional anatomic detail, and may demonstrate periventricular halo on standard T-1 weighted images. Fluid-attenuated inversion recovery (FLAIR) sequences may best depict the degree of leukoaraiosis associated with iNPH. Both static and dynamic MR imaging may demonstrate the flow void associated with aqueductal stenosis. None of these studies are pathognomonic for iNPH.

The role of functional imaging techniques is under evaluation. This includes investigations such as single-photon emission computed tomography (SPECT) and positron emission tomography (PET). The routine use of these studies and/or the use of older investigations, such as nuclear cisternography, is not recommended.

Differential Diagnosis

Variations in the clinical presentation complicate the accurate diagnosis of iNPH and the frequency of comorbidities further complicates both the diagnosis and treatment of the condition. The vast majority of patients with iNPH will have comorbidities, which include cerebrovascular disease and neurodegenerative disorders, which both mimic features of iNPH and may coexist with iNPH in a single patient. In addition, several other causes of ventricular enlargement may also be observed in this population, including compensated childhood hydrocephalus, and the syndrome of long-standing overt ventriculomegaly in adults, both of which normally may be distinguished by enlarged head circumference and/or erosion of the sella turcica. In cerebral atrophy, passive enlargement of the ventricular walls by loss of brain volume produces 'hydrocephalus ex vacuo.' Secondary hydrocephalus is readily distinguished by its precipitating event, such as trauma, spontaneous subarachnoid hemorrhage, and/or meningitis. Aqueductal stenosis produces characteristic imaging abnormalities, with enlarged lateral and third ventricles and normal fourth ventricular size.

Hypertension, lumbar stenosis, peripheral neuropathy, and vestibular dysfunction may accompany or complicate the diagnosis of iNPH. In men, prostatism should be investigated as a common cause of urinary urgency and/or incontinence.

In general, patients in whom ventriculomegaly is associated with cerebrovascular disease, neurodegenerative disorders, and cerebral atrophy will not respond favorably to a lumbar drainage trial or CSF shunting procedures (**Table 1**).

Table 1 Conditions to consider in the differential diagnosis of iNPH

Neurodegenerative disorders
Alzheimer's disease
Parkinson's disease
Vascular dementia
Cerebrovascular disease
Stroke
Multi-infarct state
Binswanger's disease
Vertebrobasilar insufficiency
Other hydrocephalus disorders
Aqueductal stenosis
Arrested hydrocephalus
Long-standing overt ventriculomegaly syndrome
Noncommunicating hydrocephalus
Neurodegenerative disorders
Lewy body disease
Frontotemporal dementia
Amyotrophic lateral sclerosis
Multisystem atrophy
Spongiform encephalopathy
Infectious diseases
Lyme
Human immunodeficiency virus
Syphilis
Urological disorders
Urinary tract infection
Bladder or prostate cancer
Benign prostatic enlargement
Miscellaneous
B_{12} deficiency
Collagen vascular disorders
Depression
Traumatic brain injury
Spinal stenosis
Wernicke's encephalopathy
Carcinomatous meningitis
Spinal cord tumor

Diagnostic Work-Up/Tests

A number of invasive and noninvasive tests have been used to establish the diagnosis of iNPH. In clinical practice, the diagnosis is most often suggested by clinical correlation of symptoms, physical exam, and imaging. The most reliable technique at present for selecting patients who would benefit from surgery appears to be a two-step process. In step 1, patients are selected for an inpatient trial of lumbar drainage based on an appropriate clinical history of one, two, or three components of the classical triad, correlative physical exam, and imaging study demonstrating ventriculomegaly. In step 2, patients undergo a 3-day inpatient lumbar drainage trial, with serial measurement of response of gait, cognition, and

continence to the lowered CSF pressure. Prolonged lumbar drainage of 300 ml or greater is associated with a sensitivity of 50–100%, and a positive predictive value of 80–100% in estimating favorable response to surgical treatment. Therefore, surgery is most readily offered to those patients who undergo prolonged lumbar drainage in whom improvement is documented on standardized gait scales and/or videotaped gait analysis.

In patients with iNPH, CSF opening pressure averages slightly higher than in normal subjects, but the range of pressures in iNPH overlaps the range of pressures observed in normal subjects.

A high volume LP, usually defined as removal of 40–50 ml of CSF, has been used in the outpatient setting as a diagnostic test, with symptoms assessed during the first 24 h after the procedure. Its low sensitivity, estimated at 26–61%, eliminates its utility as an exclusionary test. A positive response to a high volume LP is, nevertheless, a more reliable indicator of positive response to shunting than the clinical exam alone.

Measurement of CSF outflow resistance via an infusion test with lumbar catheter in place has a higher sensitivity at 57–100%. The positive predictive values for both the high volume LP and infusion test have been estimated to be 75–92%.

Some authors have suggested that the most reliable test for the diagnosis of iNPH is response to surgical placement of a ventriculoperitoneal shunt. Prolonged positive response to shunting has been estimated to occur less than 30% of the time when shunt placement is used as both diagnosis and treatment for iNPH. It seems preferable, therefore, to use other diagnostic criteria, including the invasive inpatient testing of a lumbar drainage trial, in order to allow more accurate patient selection prior to surgery.

Surgical Management

Surgical diversion of CSF is recommended in patients with iNPH in whom the benefits of surgical treatment outweigh the potential risks. There is little data on the degree or duration of improvement that may be expected with surgical treatment; degree of improvement with 3 days of lumbar drainage appears to be the best available estimate. Comorbidities such as functional status, cerebrovascular and cardiac status, and immune competency should be considered. The natural history of untreated iNPH has not been studied well.

The most common shunt configurations performed are ventriculoperitoneal and ventriculoatrial shunts. The ventriculoperitoneal shunt has the advantage of not requiring access to the vascular system, thus obviating the risk of the rare complication of shunt nephrosis caused by long-standing subclinical shunt infections. The ventriculoatrial shunt has the advantage of not being subject to dysfunction due to intraabdominal adhesions or pressures. Lumboperitoneal shunts are seldom used due to the difficulty in assessing their function, and lack of suitable configurations for valve placement. Endoscopic third ventriculostomy has been reported with some success, but needs confirmation, due to theoretical concerns that the intracranial pressures in iNPH may not be sufficient to maintain patency of the ventriculostomy.

Valve selection is a controversial and highly debated topic among neurosurgeons. Multiple valve types are available, including mechanisms based on differential pressure, gravity compensation, and flow limitation. The value of externally programmable valves has not definitively been established.

Complications include immediate and delayed adverse procedure-related effects. The risk of intracerebral hematoma along the ventricular catheter track may be as high as 3%. Delayed morbity includes infection (3–6%), seizures (3–11%), subdural hematomas or effusions (2–17%), and other complications of overdrainage and underdraingage of CSF. The risk that patients may require operative shunt revision in the first 5 years after surgery may be as high as 21%.

Prognosis

Patients whose symptoms of gait disturbance, dementia, and/or urinary incontinence have been of 2 years or less in duration tend to be more responsive to surgical treatment than patients with more advanced or longstanding manifestations of the clinical triad of iNPH. Thus, early diagnosis and intervention is recommended for optimal outcomes.

Summary

NPH is increasingly recognized as a treatable cause of gait disturbance, cognitive decline, and urinary incontinence in the aging population. The impact of treatment on both improved quality of life and decreased need for institutional care is potentially substantial, and will only increase as the population ages. This article provides a state of the art review of the presentation, diagnosis, surgical treatment, and clinical management of iNPH. In particular, new clinical guidelines and recently developed programmable valve technology that make the diagnosis more sure and the treatment safer are detailed.

See also: Binswanger's Subcortical Arteriosclerotic Encephalopathy; Freezing of Gait; Gait Disturbances in Parkinsonism; Gait Ignition Failure; Parkinsonism: Vascular; Primary Progressive Freezing Gait.

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NR4A Subfamily

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NR4A Subfamily

The NR4A subfamily includes three members, notably NUR77 (NGFI-B/TR3/NAK-1/N10/ST59/T1S1/NR4A1), NURR1 (NR4A2/NOT/TINUR/RNR-1/HZF-3), and NOR-1 (MI-NOR/TEC/CHN/NOR-2/NR4A3). Since the ligands for these transcription factors have not yet been found, they are member of 'orphan' nuclear receptor superfamily of transcription factors. NR4A subfamily consists of a central DNA-binding domain (DBD), a C-terminal ligand-binding domain (LBD), and a N-terminal transactivation domain. These family members have been shown to play an important neuroendocrine regulatory role at all levels of the hypothalamic/pituitary/adrenal axis, and they participate in cell proliferation, growth, differentiation, and apoptosis. In addition, these transcription factors are immediate-early genes (IEG) whose expression and activity are regulated in cell-specific manner by a variety of extracellular mitogenic, apoptotic, and differentiation stimuli with a rapid and transient manner. Protein kinase A, protein kinase C, calcium–calcineurin, nuclear factor kappa B (NF-κb), and mitogen-activated pathway kinases (MAPK) are upstream signal of NR4A members. These signals can activate the expression of cyclic adenosine monophosphate responsive element-binding protein, activator protein 1, and myocyte enhancer

factor 2 (MEF-2), which leads to an upregulation of expression of NR4A through interaction with NR4A promoters.

The members of the NR4A subfamily are well conserved in the DBD (~91–95% homology) and the C-terminal LBD (~60% homology), but are divergent in the N-terminal domain (~30% homology).

Nurr1

NURR1 was mapped to human chromosome 2q22–q23 in 1994. The DNA sequence of *Nurr1*, especially in the CyS2–CyS2, overlaps with that of *NURR77 and NOR-1. Nurr1* is expressed predominantly in the central nervous system (CNS), especially in substantia nigra (SN), ventral tegmental area (VTA), limbic area, olfactory bulb, hippocampus, temporal cortex, subiculum, cerebellum, posterior hypothalamus, and habenuclear nuclei. *Nurr1* plays a critical role in the development of dopamine (DA) neurons. Nur77 and NOR-1 are highly expressed in vascular smooth muscle cells (SMCs) and atherosclerotic lesion macrophages or foam cells. Nur77 and NOR-1 are involved in vascular response to injury through inhibiting the process of inflammation includes the formation of macrophage form cell in vascular-endothelia.

Structure of *Nurr1* Gene

Nurr1 gene embraces eight exons and seven introns; the total length of the gene is 9.822 kb (**Figure 1(a)**). The open reading frame of *Nurr1* gene contains 1794 bases that encode for 598 amino acids. The initiation site of translation is in the third exon, and the termination of translation is at the upstream region of the eighth exon. There is a 3′-untranslated region (UTR) that contains ATTTA repetitive sequence at the downstream region of the eighth exon, and the total length is ~0.3 kb. UTR is important for the stabilization of mRNA transcription. This feature of *Nurr1* gene as an immediate early gene facilitates rapid transcription in response to stimulation by any of the several factors involved in the regulation of the gene expression. Promoter and transcription regulatory element (cAMP-response element, CRE, CArG-like element, SP-1 element) of *Nurr1* is located at the upstream region of transcription initiation site. CRE plays an important role in the signal transduction mediated by cAMP. The sequence of CArG-like element, CC (A/T) 7GG, takes part in the transcription regulation, which is known to participate in delayed early response. The sequence of human *NURR1* gene is highly conserved compared with the *Nurr1* gene of mice. Many transcription regulators can regulate the expression of *Nurr1* gene through interaction with CRE. Parathyroid hormone (PTH) can

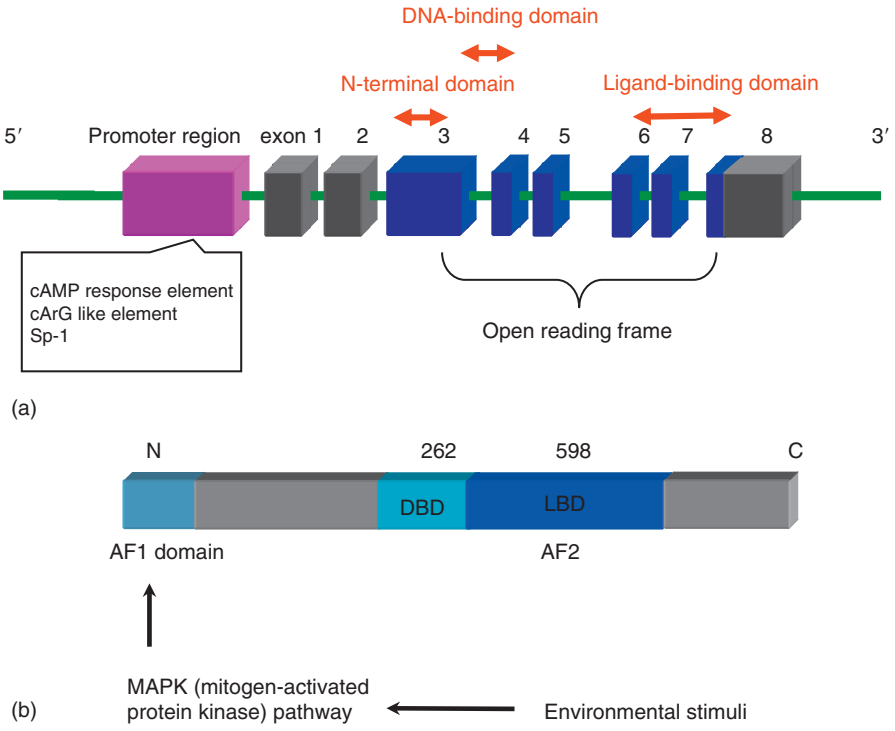

Figure 1 The structure of *Nurr1* gene and protein. (a) *Nurr1* gene includes eight exons. The open reading frame initiates in the third exon and terminates at the upstream region of the eighth exon that encode for 598 amino acids. Promotor region contains three elements: CRE, cArG, and SP-1. Four mutation sites located in exon 1 and 3 have been identified with PD. (b) Nurr1 contains DBD (DNA-binding domain) and ligand-binding domain (LBD) AF1 domain is in N terminal region that can be activated by MAPK pathway due to the environmental stimuli.

induce expression of *Nurr1* in bone cells. This process is mediated primarily through the cAMP/PKA pathway.

Structure of Nurr1 Protein

Nurr1 includes three major parts: LBD, DBD in the central region of Nurr1, and variable region (**Figure 1(b)**). Nurr1 LBD, similar to the LBD of holo retinoic acid receptor γ (RARγ), adopts a canonical protein fold resembling that of agonist-bound and transcriptional active LBDs in nuclear receptor. The structure of Nurr1 has two distinctive features. The first feature is that Nurr1 LBD has no cavity that is normally occupied by ligands because of the tight packing chains from several bulky hydrophobic residues. The second feature is that Nurr1 LBD lacks the binding site for coactivators. DBD of Nurr1 is well-conserved (over 90% homology) and consists of two zinc-fingers which can bind to nerve growth factor inducible-β-binding response element; NGFI-B response element (NBRE: AAAGGTCA) of DNA as monomers or to the palindromic Nur-responsive element (NurRE: TGATATTTX6AAAGTCCA) as homodimers, which participates in the process of transcription that includes the activation of expression of tyrosine hydroxylase (TH) and dopamine transporter (DAT). In addition, Nurr1 can also form heterodimers with retinoid X receptor (RXR) and binding to RXR response element. Nurr1 contains an amino-terminal activation function 1 (AF1) domain and a carboxy-terminal activation function 2 (AF2) domain, both of which are important for transcriptional activity. N-terminal region (AF1) of Nurr1 is highly conserved, which can be activated by mitogen-activated protein kinase (MAPK) pathway as a consequence of several environmental stimuli.

Isoforms of Nurr1

Because of multiplicity of cleavage and splicing, there are at least six isoforms of Nurr1 (Nurr1a, Nurr1b, Nurr1c, TINUR, Nurr2, Nurr2c) that have been reported. Nurr1a lacks the carboxy-terminus (most of LBD and entire AF2 domain) produced by an alternative splicing in exon 7, which exhibits less transcription activity than Nurr1. The LBD of Nurr1b lacks 18 amino acids, but the carboxy-terminus is intact. The function of Nurr1b is not known yet. An alternative splicing in exon 3, truncating the AF1 domain, produce transcriptional inducible nuclear receptor (TINUR), which is known to be dominant negative. Nurr2 is produced by alternative splicing of exon 3 and exon 7, truncating of Nurr1a and TINUR. Both Nurr2 and Nurr2c have no intrinsic activity, but bind to Nurr-response DNA sequence such as NBRE. A novel splicing variant of Nurr1, named Nurr1c, has been identified in non-neuronal tissues including lymphocytes, liver, muscle, and kidney, which has 25 amino acids deletion in the C-terminal region of exon 5. This splicing variant shows a significant reduction of luciferase activity in vitro as compared to Nurr1.

Nurr1 Distribution in CNS

Nurr1 is distributed widely in cell nucleus in CNS, especially in DA neurons. The proportion of neurons that expressed Nurr1 is 96% in SN, 95% in VTA, 91% in liner nucleus raphe, 85% in olfactory bulb, and 61% in cortex. Neurons of paraventricular area and nucleus of hypothalamus only modestly express Nurr1 and TH, whereas the noradrenaline neurons in the brainstem do not express Nurr1. Thus, the expression of Nurr1 is confined to periglomerular cells of the olfactory bulb, and DA neurons to mesencephalon. The level of Nurr1 expression is different in the different stages of development. While it is highest in the embryonic stage than other stages, its expression remains high in DA neurons throughout life.

Function of Nurr1 in Central Nerves System

Nurr1 is first expressed at E10.5 in the mouse, just before Pitx-3 and TH (E11.5). Nurr1 is essential for differentiation of the mesencephalic DA precursor cells as well as maintains the function of the DA neurons. Numerous lines of evidence demonstrates that dysfunction of Nurr1 is related with degeneration of DA neurons. Nurr1 can regulate several gene expressions, including TH, L-aromatic amino acid decarboxylase (AADC), DAT, and vesicular monoamine transporter (VMAT-2). These genes are essential for synthesis, transport, and secretion of DA. Furthermore, Nurr1 can directly transactivate the osteocalcin gene and regulate adrenal aldosterone production. There is an emerging body of evidence suggesting a 'cross-talk' between Nurr1 and several other transcriptional factors and neurotrophic growth factors in different development and maturation stages of mensencephalic DA neurons. Lmx1b is a member of the LIM hemodomain family that is essential for the development of DA neurons. Pitx-3 is the bicoid-related homeodomain-containing transcription factor that is only expressed in mesencephalic DA neurons. Lmx1b–Pitx-3 pathway is critical for specific location of DA neurons in SN. Although the expression of these two factors is independent of Nurr1, Nurr1 may have a role in the maintenance of Lmx1b and Pitx-3 in the late stages of DA neuron development. Nurr1 may be associated with several neurotrophic factors such as glial-derived neurotrophic factor (GDNF) and fibroblast growth factor (FGF), which is important in the process of neuronal growth and differentiation. Nurr1 is essential for the expression of GDNF receptor Ret in mesencephalic DA neurons. Furthermore, in Nurr1-overexpression neuronal stem cells,

FGF-20 significantly promotes neuronal stem cells into TH-positive neurons, indicating a 'cross-interaction' between Nurr1 and neurotrophic factors. Nurr1 also interacts with Wnts, a family of glycoproteins that regulates cell proliferation and differentiation. Another factor with which Nurr1 interacts is p57kip2, a kinase inhibitor of the CIP/KIP family, whose expression in postmitotic differentiating midbrain DA neurons partly depends on Nurr1. Nurr1 can also interact with the *GRIK5* gene, which codes for kainate receptor (KA2), a subunit of the glutamate receptor. Nurr1 is able to protect dopaminergic neurons by suppressing inflammatory gene expression in astrocytes and microglia. Nurr1 exerts anti-inflammatory effects by recruiting CoREST co-repressor complex to clear NF-κB-p65. Other downstream genes and interacting protiens of Nurr1 include SUMO (small ubiquitin-like modifier)-E3 ubiquitin-protein isopeptide ligase (PIASγ), Neurophilin 1, vasoactive intestinal peptide (VIP), P53, and Nurr1 interacting protein (NuIP).

Nurr1 and Parkinson's Disease (PD) and Related Disorders

Following evidence suggests that NURR1 may be associated with PD and several other neurodegenerative disorders: (1) PD patients have declined NURR1-ir in DA neurons which contains α-synuclein inclusions in SN. (2) Quantitatively measuring the level of NURR1 mRNA in human peripheral blood lymphocytes has revealed a significant decrease in individuals with PD and parkinsonian syndromes. These results suggest that *NURR1* might be useful biomarker for early diagnosis of PD and related disease. (3) Abnormalities in *NURR1* gene might be a risk factor for both familial PD and sporadic PD. Genetic analyses in 201 individuals with PD identified two variants in NURR1 (−291T del and −245 T → G), which mapping to in 5′ untranslated region of the first exon and affect one allele in apparently autosomal dominant form of familial PD but not in sporadic cases. Recently, two novel variants at exon 3 of *NURR1* gene were identified in two nonfamilial PD patients. First, a heterozygous C→G transversion at exon 3 (−253) changes the amino acid serine to cysteine, and the second is a −223C → T sequence. Both of these mutations affect phosphorylation procedure in transcription of the gene encoding TH. Furthermore, one of the single nucleotide polymorphisms (SNP) is in the BseRI restriction site resulting in a homozygous7048G7049 in intron 6 (NI6P), which shows a significantly higher frequency in familial and sporadic PD and diffuse Lewy body disease. (4) NURR1 is also reported in association with other diseases such as schizophrenia and depression. Two different missense mutations in the third exon of NURR1 have been found in two schizophrenic patients, and another missense mutation in the same exon has been found in manic-depressive patients. (5) Long-time uptake of cocaine may lead to markedly decreased level of NURR1 expression within the DA neurons. NURR1 is known to regulate transcription of the gene encoding the cocaine-sensitive DAT, which is markedly reduced in the DA neurons of NURR1-deficient cocaine abusers, suggesting that NURR1 plays a critical role in controlling human DAT gene expression and adaptation to repeated exposure to cocaine.

Nur77 and *NOR-1*

Nur77 and NOR-1 are also early response genes. The activators of these transcriptional factors include 6-mercaptopurine (6-MP, a metabolite of the immunosuppressive drug azathioprine), prostaglandin A2 (PGA2), and certain 1, 1-Bis (3V-indolyl)-1-(psubstituted phenyl)-methanes as well as benzimidazole derivatives, which can bind to LBDs of these transcriptional proteins. Rapid and transient response to these activators as well as several unknown environmental stimuli is hallmark of Nur77 and NOR-1. The process of regulation of Nur77 and NOR-1 is through protein kinase A, protein kinase C, calcium–calcineurin, NF-κb, and mitogen-activated kinases (MAPK) pathways. Furthermore, Nur77 can also form heterodimers with RXR to bind DR5 motifs that mediate retinoid responses process, which could down-regulate and affect the activity of mitochondrial proteins such as Bcl-2 family and Cyt C, like Nurr1 protein, which indirectly participate in the process of mitochondrial-mediated cellular survival and apoptosis. In addition, Nur77 and NOR-1 can be phosphorylated by protein kinase B/Akt on the site of serine-350, which could suppress its activity of DNA-binding domain. These findings indicate a cross relationship between Nur77 and NOR-1 with function of cellular apoptosis, growth, differentiation, and survival.

NR4A Family and Atherosclerosis and Vein-Graft Disease

NR4A family members, Nur77 and NOR-1, are expressed in SMCs and macrophages, which can be regulated by several environmental stimuli and signals relevant to atherogenesis. Nur77 and NOR-1 can bind to NF-κb, which leads to the suppression of inflammatory gene expression. Atherosclerosis may result from the proliferation of SMC and macrophage as well as other factors responsible to the athero-injury such as stretch response leading to the reduction of $p27^{Kip1}$, calponin, and SMα-actin. This process can be inhibited by over-expression of Nur77 and NOR-1. Nur77 and NOR-1 can also suppress the expression of other inflammatory cytokines, including interleukin-1β (IL-1β), IL-6, chemokines IL-8, monocyte chemoattractant-1, macrophage

inflammatory protein-1a, and macrophage inflammatory protein-1b. Therefore, Nur77 and NOR-1 may promote a quiescent SMC phenotype and inhibit the formation of macrophage foam cell, and prevent cardiovascular sclerosis.

See also: Dopamine Transporter: Aging and Parkinson's Disease; Dopamine; Parkinson's Disease: Definition, Diagnosis, and Management; Substantia Nigra.

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O

Object Retrieval-detour Task

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Glossary

Grasp reflex – Flexion clenching of the fingers or toes on stimulation of the palm or sole.
Neurotrophic factors – A generic term for any of a family of substances with roles in maintenance and survival of neurons.
Prepotent response – A response that is or has been previously associated with reinforcement.
Striatum – Include putamen and caudate nucleus.

Definition and History

The maturation of frontal and prefrontal cortex proceeds by construction and acquisition of novel behavioral functions and by inhibition of some reflexive or automatic reactions. Conversely, dysfunction of frontal and/or prefrontal cortex is related to impairment of the acquired neuronal function associated with a loss of inhibition of these neonatal reflexes. For example, the role of frontal cortex in aiding attention appears to depend on the inhibitory functions of frontal cortex. Thus, damaged frontal cortex fails to inhibit the tendency to be drawn towards any compelling or interesting stimulus, and to sharpen the signal-to-noise ratio. The absence of such inhibition results in difficulties for the subject to concentrate on a specific task. Similarly, inhibition of the grasp reflex depending on the maturation of the supplementary motor area or inhibition of the prepotent response tendencies depending on the maturation of the dorsolateral region of prefrontal cortex is also impaired when frontal cortex is injured. These latter reflexes have been carefully studied in both human and monkey infants by Diamond et al. They used a specifically designed task to assess the dorsolateral prefrontal function called the object retrieval detour task (ORDT). The ORDT was designed to evaluate the ability to inhibit the natural tendency to reach straight for what the subject wants when an object is seen through one of the closed sides of a transparent box. For example, an infant must inhibit the impuls to reach directly for the object, and instead detour around to the open side of the box. Between 6 and 12 months, human infants show a clear developmental progression in their ability to retrieve an object from inside a clear, open box whereas infant monkeys show similar developmental progression between 1.5 and 4 months after birth. Adult monkeys with a lesion of the dorsolateral prefrontal cortex show the same error on this task as do infants, whereas lesions located in the parietal cortex or hippocampus of adult monkeys do not induce any impairment in the ORDT.

Is the ORDT Task Capable of Detecting a Frontal-Type Cognitive Deficit Generated by Subcortical Neuronal Dysfunction?

Subcortical frontal cognitive deficits are observed in Parkinson's disease (PD), Wilson's disease, Progressive supranuclear palsy, and Huntington disease (HD). They can be clinically differentiated from deficits in other neurodegenerative diseases that primarily affect the cerebral cortex such as Alzheimer's disease, Creutzfeldt–Jakob, or Pick's disease. Qualitative cognitive performance analyses in diseases associated with subcortical dementia point not so much to altered cognitive programming, but rather to disruptions in initiation, planning, and use of these cognitive programs. Thus, cortical and subcortical dementias differ from each other by the disruption of these functions used to regulate cognitive behavior and by a relative preservation of instrumental 'activities' including memory and language.

It comes as no surprise that in late stage PD and HD patients, a frontal-type cognitive deficit is prevalent, as the head of the caudate nucleus receives fibers arising

from the dorsolateral prefrontal cortex and from the orbito-frontal cortex. Indeed, cardinal features of late stage PD and HD dementia include difficulties in retrieving memories, slowed information processing, cognitive inflexibility, perseverative behavior as well as a severe impairment in the ability to elaborate set-shifting strategies. The hypothesis that a primary striatal lesion could be associated with such a frontal-type syndrome has been reinforced by observations in patients presenting with uni- or bilateral infarcts in the caudate nucleus, who exhibit cognitive alterations very similar to those observed in HD.

All these observations therefore suggest that the dementia observed in PD and HD is of a frontal type, associated with subcortical damage and very similar to that observed in patients with lesions of the dorsolateral prefrontal cortex. Thus ORDT appears to be an appropriate cognitive task to detect such a frontal deficit in animal models of HD and PD.

Replication of a Subcortical Frontal-Type Cognitive Deficit in Nonhuman Primate

One possible way to develop such a primate model based on progressive bilateral caudate nucleus degeneration is to systemically administrate daily doses of a mitochondrial toxin, 3-nitropropionic acid (3NP), an irreversible inhibitor of succinate dehydrogenase.

The ORDT task was initially used in 3NP-treated primates to detect the earliest manifestation of frontal cognitive impairment during the initiation of 3NP intoxication. In primates, the ORDT is capable of assessing the ability to retrieve an object (in the present case, a piece of fruit) from inside a transparent box only open on one side (**Figure 1**(**a**)). The level of difficulty can be modified by the experimenter by varying the location of the box, the location of the reward in the box, and finally the orientation of the open side of the box in relation to the subject (**Figure 1**). Each ORDT test session consisted of 15 trials corresponding to different configurations related to either the position of the reward in the box or the position of the box on the tray facing the animals (**Figure 1**). The reward was visible to the animal only after raising an opaque screen placed between it and the box. Subjects were then allowed a 60-s time period to retrieve the reward, after which the screen was put back in place and the box set up for the next trial. The animals' responses were video recorded and measures of performance included: number of 'success' responses (retrieval of the reward on the first attempt of the trial), number of 'correct' responses (retrieval of the reward within the 60-s time period, whatever the strategy used by the animal to retrieve the piece of fruit). This 'correct' response represents the ability for the animal to perform the task. Finally, 'barrier hits' responses (hitting the closed transparent side of the box instead of making a detour) and 'motor problems' responses (reaching the open side of the box but failing to retrieve the reward) were quantified.

Following 4 weeks of systemic injection of a mitochondrial toxin 3NP, 4 consecutive ORDT test sessions were performed on a weekly basis in three baboons intoxicated with 3NP and their performances compared to those of 10 control animals. Compared to intact animals, 3NP-treated animals were significantly less successful in obtaining the

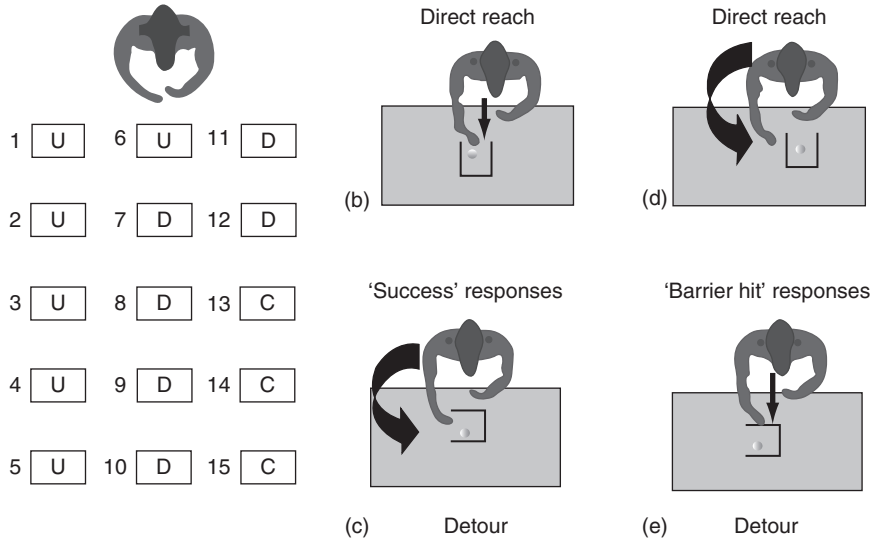

Figure 1 The ORDT: experimental set-up and principles. In the ORDT the ability of monkeys to retrieve an object from inside a transparent box only open on one side can be assessed. (a) A total of 15 different configurations are randomly presented to the animals. Measures of performance include: (b and c) number of 'success' responses (retrieval of the reward on the first reach of the trial), (d and e) 'barrier hits' responses (hitting the closed transparent side of the box instead of making a detour). Examples of easy trials (direct reach possible, b and d) and difficult trials (i.e., when a detour around the transparent side of the box is required, c and e) are illustrated.

reward on the first reach and were making more barrier hits as soon as 6 weeks after the initiation of 3NP treatment, indicating that they were impaired in their ability to respond using the appropriate strategy. Importantly, 3NP-intoxicated animals were not impaired in motor problems or correct responses indicating that they were as able as the controls to get the rewards. Postmortem neuropathological examination of 3NP-treated animals presenting cognitive deficit showed histological abnormalities restricted to the striatum. The lesion always began in the most lateral part of the putamen, encompassing later the dorsolateral aspect of the body of the caudate nucleus. No other histological lesion was observed in the brain, particularly in the frontal, parietal cortex, and the hippocampus.

Using the same ORDT task, similar frontal cognitive deficits have been documented in other nonhuman primate species with caudate lesions (such as *Macaques fascicularis* or *Cebus appella*) following repetitive daily doses of 3NP. In another study, impairment on the ORDT task was also observed in primate animals with severe striatal dopamine depletion following MPTP administration, suggesting that neuronal dysfunction without striatal cell loss could also induce a frontal-type cognitive deficit.

Further experiments in macaques with either striatal allografts in the caudate nucleus to reconstruct the interrupted frontostriatal circuitry, or neurotrophic factors such as CNTF to protect striatal neurons from degeneration showed a progressive restoration of frontal cognitive deficits using the ORDT task. These latter experimental findings reinforce the crucial role of subcortical structures in frontal-type cognitive deficits observed in neurological diseases with predominance of subcortical pathologies.

See also: 3-Nitropropionic Acid; Cognitive Assessments and Parkinson's Disease; Dementia, Movement Disorders; Huntington's Disease.

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Obsessive-Compulsive Disorder

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Glossary

Cognitive-behavioral therapy – A form of psychotherapy that helps a patient to identify and address maladaptive patterns of thoughts, feelings, and behaviors.

Compulsions – Overt or covert rituals, escape strategies, and avoidance behaviors that serve to decrease the distress associated with an obsession.

Exposure and response prevention – A form of cognitive-behavioral therapy in which a patient with OCD participates in repeated sessions of prolonged contact with fear-inducing stimuli while simultaneously preventing compulsions.

Habituation – The natural reduction of a physiological fear response over repeated sessions of prolonged contact with fear-inducing stimuli.

Obsessions – Intrusive thoughts, impulses, or images that elicit distress and are inconsistent with one's beliefs, values, or self-image.

OC-spectrum – A hypothesized family of psychiatric disorders which are similar to OCD.

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) – An etiological theory of OCD in which streptococci infections purportedly elicit an autoimmune attack of the basal ganglia.
Yale-Brown obsessive compulsive scale (Y-BOCS) – A clinician-rated instrument that assesses the nature and severity of OCD.

History and Definition

Obsessive–compulsive disorder (OCD) has been described consistently since the seventeenth century and initially, was conceptualized from a religious perspective. Obsessions and compulsions were considered products of the devil and thus, required religious intervention (e.g., exorcism). Scientific understanding of OCD did not start until the nineteenth century, when early characterizations of the disorder suggested that individuals with OCD could not resist the obsessions but had insight into the unreasonable nature of their symptoms. Further theoretical understanding of the disorder developed from early case studies, such as several accounts by Sigmund Freud (e.g., *Rat Man*), who formulated a psychodynamic theory of OCD that has evolved and persisted to date in many professional circles.

The twentieth century saw great strides in the understanding of psychopathology as a result of behavioral research, leading to theoretical advances in understanding the development and maintenance of phobias from a classical and operant conditioning perspective. In the early part of the century, O.H. Mowrer introduced a model of phobia maintenance in which certain behaviors are rewarded because they result in escape from feared stimuli and decrease or preclude a fear response. This model of phobia maintenance naturally was extended to the understanding of OCD; that is, compulsions serve to decrease the distress elicited by obsessions, thus, negatively reinforcing the compulsions and increasing their frequency. Other important strides in the understanding of OCD occurred later on in the twentieth century when biological, cognitive, and neuropsychological models of psychopathology emerged.

Currently, the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV) provides a commonly used taxonomic definition of OCD. Defining OCD using a taxonomic approach has elicited several lines of research on how best to carve OCD phenomena at their joints. One growing area of research examines the heterogeneity of OCD in an attempt to split the condition further by defining discrete OCD subtypes or dimensions. A second line of research aims to lump OCD with similar conditions into an OC-spectrum.

More traditional subtype research has attempted to define OCD subtypes based on categorical differences, such as the presence or absence of comorbid tics. Most of the latest research, however, has focused on exploring symptom dimensions in an effort to define specific OCD subtypes. While the evidence regarding the number and type of dimensions is still inconclusive, preliminary data suggest that four symptom themes appear consistently across studies. One of the themes relates to fears and rituals that involve checking for or avoiding contamination. The second consistent OCD dimension concerns symmetry, a distressing sense of imperfection, and an impulse to straighten or arrange. The third reliable dimension is defined by hoarding symptoms, which is characterized by fears of needing to save items and rituals of collecting seemingly valueless items. The fourth less consistent dimension of OCD concerns a variety of checking compulsions and harm, sexual, or religious intrusive thoughts or images.

While many investigations have attempted to split OCD phenomena into subtypes or dimensions, other lines of research have attempted to lump them with other similar conditions into an *OC-spectrum*. The spectrum has many potential overlapping DSM-IV conditions, including somatoform disorders (e.g., body dysmorphic disorder, hypochondriasis), impulse control disorders (e.g., trichotillomania), eating disorders (e.g., anorexia nervosa), tic disorders (e.g., Tourette's disorder), personality disorders (e.g., obsessive–compulsive personality disorder), dissociative disorders (e.g., depersonalization disorder), paraphilias (e.g., fetishism), and pervasive developmental disorders (e.g., Asperger's disorder). Typically, these disorders have been lumped together because of similarities in a variety of domains, including symptom overlap, demographics, etiology, course, and treatment response. There is currently debate in the scientific community regarding the status of an OC-spectrum and the specific disorders that comprise this category.

One disorder within the OC-spectrum, Tourette syndrome, is a movement disorder characterized by multiple motor tics and one or more vocal tics. OCD and Tourettes can be challenging to differentiate, especially when a tic-related OCD subtype is also considered. However, evidence suggests some differentiating characteristics. Compared to the individuals with tic-free OCD, those with Tourettes or tic-related OCD are more likely to report specific types of obsessive–compulsive symptoms, such as touching or tapping rituals, hoarding, symmetry compulsions, and self-injurious behaviors. In contrast, those with tic-free OCD report more physiological anxiety and OCD-related cognitions associated with the stereotyped movements. That is, those with Tourettes typically report an urge that immediately precedes and elicits a tic, but those

with OCD typically indicate that compulsions are triggered by anxiety stemming from an obsession.

Etiology and Clinical Correlates

With the exception of genetic factors, cognitive, neuroanatomical, and neuropsychological factors might best be considered clinical correlates of OCD until further research is conducted. With respect to genetics, family studies over many decades have suggested strong familial patterns of OCD symptoms. In addition, twin studies of the concordance rates of OCD in monozygotic and dizygotic twins have provided estimates of the influence of genes on the phenotypic expression of the disorder. The differential concordance rates suggest a range of 27–65% for the influence of genes, with pediatric samples demonstrating a higher range. Research findings from segregation analyses, candidate gene studies, and genetic linkage studies are mixed, but there is some evidence that has implicated specific inheritance patterns for OCD symptoms, particular genes involved in the serotonergic and dopaminergic pathways in the brain, and a location on chromosome 9p that is associated with a glutamate transporter.

While evidence concerning the pathophysiology of OCD remains inconclusive, research has implicated several brain regions. In particular, research in this area has suggested impairment in the corticostriatal–thalamic circuit. This brain circuit includes the orbitofrontal cortex, caudate nucleus, anterior cingulate cortex, and thalamus. This circuit has many hypothesized functions, including the integration of sensory information, voluntary bodily movements, modulation of social behavior, and higher-level cognitive skills that include planning and inhibition of responses. Other brain regions have been implicated in OCD pathophysiology (e.g., corpus callosum), but these two models have received the most attention in the research literature.

Similar to the neuroanatomical research, the neuropsychological research on OCD remains inconclusive. Reviews of the research suggest that those with OCD predominately engage in inefficient approaches to organize information, possibly as a result of focusing mainly on irrelevant details rather than global and contextual features. This organizational strategy may have a negative impact on overall executive functioning, thus accounting for other noted neuropsychological dysfunctions in OCD, including deficits in set shifting and planning abilities. There seems to be less evidence for impairment in attention span, verbal fluency, and aspects of verbal memory.

While a discussion of all of the cognitive models of OCD is outside the scope of this article, it is worth noting the recent work of *The Obsessive Compulsive Cognitions Working Group*, which consists of the world's experts on the cognitive processes of OCD. The research from this group has provided strong evidence for three cognitive dimensions of OCD. The first dimension, labeled *Responsibility/Threat Estimation*, reflects a tendency to overestimate personal responsibility and worry excessively about harm to self or others. A second cognitive dimension, called *Perfectionism/Certainty*, suggests a tendency to maintain rigid and unreasonable standards, as well as demonstrate excessive need for certainty. The final cognitive dimension is called *Importance/Control of Thoughts*, which measures one's overvaluation of thoughts and need for controlling obsessions.

Other epidemiological data suggest a range of risk factors and clinical correlates. Older adolescents appear at-risk for developing OCD, but an inverse relationship may exist between adult age and OCD onset. Growing evidence also indicates an increased risk in females during the postpartum period. Another clinical concomitant includes psychiatric comorbidity, such as other anxiety disorder diagnoses, major depressive disorder, and substance dependence. In addition, the results are mixed with respect to the relationship between OCD and several other factors: IQ, race and ethnicity, and socioeconomic status. Some reliable evidence suggests a direct relationship between the size of a household and the risk for OCD symptoms, implying the possibility of an infection causing OCD. One possible infection theory for OCD is called Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS).

The association of PANDAS and OCD has received growing attention in the research community. According to the theory, antibodies produced by the body to fight *Streptococci* infections purportedly attack the host as a result of the similarity in antigens between streptococci and the basal ganglia. At this time, however, the evidence remains inconclusive. While some case studies and cross-sectional data support a link between strep infections and OCD (as well as tic disorders), causal evidence is yet to be found. Similar lines of research have started to explore other infections, as well, including the role of mycoplasma pneumoniae and the Borna virus.

Epidemiology

Current epidemiological evidence suggests that OCD has a lifetime prevalence rate between 2 and 3% of the general population. Males and females develop the disorder in roughly equal proportions, but there may be gender differences in the age at onset. Males typically develop the disorder at a younger age (i.e., 13–15 years old for male modal onset), while females develop it later in life (i.e., 20–24 years old for female modal onset). While development of the disorder is usually gradual, acute onset is not uncommon. Most reports suggest that the course of OCD symptoms wax and wane over time, but some evidence indicates that 10% of patients with OCD experience a

deteriorating course. With respect to comorbidity, most evidence suggests that 50–75% of OCD sufferers meet criteria for at least one other psychiatric disorder, usually major depressive disorder, other anxiety disorders, or other conditions similar to OCD.

Assessment and Treatment

Diagnosing OCD can be complicated, especially considering the rate of comorbidity and phenomenological overlap with other disorders. The option for a *poor insight* specifier in the diagnosis of OCD can make the differential with psychotic disorders particularly challenging. A trained expert must determine if the obsession reaches delusional intensity, and whether or not the patient can test reality. Another difficult differential exists between OCD and generalized anxiety disorder, which is characterized by excessive worry about realistic issues. The distinction generally involves assessing the intensity and frequency of the thoughts, the realism of the fear content, and the degree to which the patient believes the fears are consistent with his or her beliefs, values, and self-image. While a distinction is sometimes difficult between OCD and autistic disorders, the latter class of disorders typically presents with a range of non-OCD signs and symptoms, as well as a specific and required developmental history. Often, it is difficult to distinguish OCD from other OC-spectrum disorders, but spectrum disorders typically present with a particular theme that usually takes precedence in diagnostic classification.

There are many tools for assessing various aspects of OCD, including diagnostic interviews, clinician-rated measures, and self-report measures. Diagnostic interviews generally consist of a standardized structured or semistructured interview to determine whether or not OCD diagnostic criteria are met. Clinician-rated instruments require a trained expert to judge information about a patient's OCD presentation. One clinician-rated instrument in particular has been considered the gold standard assessment of OCD severity: the Yale-Brown Obsessive–Compulsive Scale (Y-BOCS). The scale contains two parts, including a checklist to determine the current and past obsessions and compulsions, and also a clinician rating of the patient's OCD symptom severity. In addition, there are numerous self-report measures of OCD and its correlates. Some commonly used examples include a self-report Y-BOCS, the Obsessive–Compulsive Inventory-Revised, and the Padua Inventory, and its revised form. Many adjunctive measures evaluate OCD correlates, including cognitive constructs like perfectionism, biological correlates like physiological anxiety, and symptom-specific measures such as hoarding severity.

There are two first-line treatment options for those who suffer from OCD. One is exposure and response prevention (ERP), which is considered the gold standard psychological treatment model for OCD. ERP consists of two parts: (1) stepwise and prolonged exposure to a fear-inducing stimulus to facilitate a natural reduction of the physiological fear response over time (i.e., *habituation* or *extinction*) and (2) simultaneous and purposeful prevention of avoidance strategies, escape plans, or rituals that serve to decrease the fear response during a therapeutic exposure. This procedure is repeated until the stimulus elicits a minimal fear response, and then the model is applied to a different fear-inducing stimulus. Participating in roughly 10–20 ERP sessions is associated with symptom improvement in at least 85% of patients, with 55% reporting considerable improvement; however, these numbers are deceptive, because ~25% of patients refuse to participate in ERP and a roughly equal percentage of patients drop out of ERP once initiated. As a result of these high refusal and dropout rates, many lines of research have attempted to develop additional cognitive-behavioral therapy (CBT) approaches. Examples include cognitive therapy, which focuses on helping the patient directly address the distorted beliefs associated with OCD, and motivational interviewing techniques, which help facilitate the patient's willingness to engage in treatment.

For the other first-line treatment option for OCD, psychopharmacologists suggest the use of serotonin reuptake inhibitors (SRIs), in particular all of the selective SRIs, such as fluoxetine, paroxetine, and sertraline. They also reported evidence for clomipramine, a tricyclic antidepressant that affects serotonin reuptake. Evidence suggests that SRIs elicit a favorable response in 40–60% of OCD patients, but they are also associated with high rates of relapse following their discontinuation. While the selective SRIs appear more effective than tricyclic antidepressants (except clomipramine), no specific selective SRI is more or less effective than its counterparts. When patients do not respond to monotherapy, SRIs often are augmented with typical or atypical neuroleptics. While the evidence is mixed concerning any added benefit of combining psychological and psychopharmacological interventions (e.g., CBT plus an SRI), some experts recommend the use of this joint approach. One promising combination of psychopharmacology and psychotherapy concerns the use of D-cycloserine, a partial agonist that affects a specific type of glutamatergic receptor in the brain, to expedite the habituation process during ERP.

Nontraditional medical techniques also might benefit those with OCD. Evidence for neurosurgery suggests that anterior cingulotomy, anterior capsulotomy, subcaudate tractotomy, or limbic leucotomy might benefit patients who have failed multiple trials of medication and CBT. There is promising preliminary evidence concerning transcranial magnetic stimulation and deep brain stimulation, but further research is needed to clarify possible effects further. At this time, these nontraditional approaches are reserved as a last line of treatment.

See also: PANDAS; Serotonin and Tryptophan; Tics; Tics, Complex; Tics, Simple; Tourette Syndrome; Tourette Syndrome: Animal Models; Yale Global Tic Severity Scale (YGTSS).

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Relevant Websites

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http://www.aabt.org/ – Association for Behavioral and Cognitive Therapies.
http://www.nimh.nih.gov/ – National Institute of Mental Health.
http://www.nmha.org/ – Mental Health America.
http://www.nami.org/ – National Alliance on Mental Illness.
http://www.apa.org/ – American Psychological Association.
http://www.psych.org/ – American Psychiatric Association.

Oculomasticatory Myorhythmia

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Glossary

Bruxism – The grinding of the teeth or clenching of the jaw, which may be involuntary (a form of focal dystonia).
Myorhythmia – A hyperkinetic involuntary movement disorder characterized by a tremor of irregular frequency (from 1 to 4 Hz).
Pendular vergence oscillations – Alternating convergent–divergent movements of the eyes that occur at about 1 Hz frequency.

Oculomasticatory myorhythmia (OMM) is characterized by involuntary movements that involve the eyes, the muscles of the face, the muscles of mastication, and the pharyngeal muscles. OMM was first described in 1986 by Schwartz et al. and has since been reported in multiple cases.

The ocular movements are described as convergent–divergent 1 Hz movements, which can be more precisely described as pendular vergence oscillations (PVOs). PVOs of OMM are mostly horizontal and may affect one eye more than the other. OMM is typically associated with supranuclear ophthalmoplegia.

Myorhythmia involves 1–2 Hz movements of the face characterized by contractions of the muscles of mastication as well as other muscles of the face or the pharynx (see **Figure 1**). These movements occur in synchrony with the PVOs and can persist during all sleep phases. There has been a case report of permanent bruxism severe enough to cause tooth abrasions.

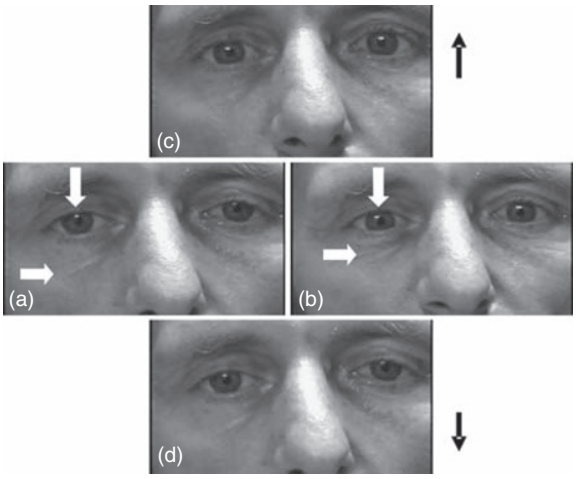

Figure 1 Episodes of divergent (a) and convergent (b) ocular oscillations can be appreciated in primary gaze (the corneal light is displaced laterally from a to b). Note the elevation of the inferior eyelid crease (horizontal arrow, a to b), indicating contraction of the levator labii muscles, synchronous with the convergent ocular movements. Attempts to upgaze (c) and downgaze (d) are ineffective.

OMM, along with the associated oculofacialskeletal myorhythmia (OFSM), which can also involve proximal and distal skeletal muscles, has been found in about 20% of reported cases of central nervous system (CNS) Whipple's disease. The specificity, on the other hand, is 100%, hence making this sign pathognomonic for CNS Whipple's disease.

OMM and OFSM can improve or remit entirely if a patient has been satisfactorily treated for Whipple's disease. Typical treatment is with an antibiotic drug such as trimethorim-sulfamethoxazole, penicillin, doxycycline, or ceftriaxone. With proper treatment, the disease can remit in up to 70% of patients. The relapse rate, however, can approach 40%.

See also: Whipple's Disease.

Further Reading

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Olivopontocerebellar Atrophy

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Glossary

Essick cellbands – Groups of cells in the developing rhombencephalon that migrate in two bands, one of which eventually forms the inferior olivary nucleus and the arcuate nucleus, and the other the pontine nuclei.

Neuronal intranuclear inclusions – Intranuclear inclusion bodies in the neurons that have been reported in SCAs with expanded trinucleotide repeats and are composed of ataxins, ubiquitin, and proteins of the nuclear matrix and proteasomes.

Polyglutamine or polyQ – CAG repeat expansions cause expanded polygutamine stretches; imply that corresponding gene products (e.g., ataxins or atrophin) induce neurodegeneration by means of 'gain of toxic functions.'

Spinocerebellar atrophy – Degeneration of spinocerebellar tracts, posterior white columns and griseum pontis with preservation of inferior olivary nuclei and corticospinal tracts, often the pathological hallmark of inherited SCAs.

Definition, History, and Classification

The term OPCA (olivopontocerebellar atrophy) was introduced by Dejerine and Thomas in 1900 to designate the pathological presentation in a patient with sporadic

adult-onset progressive cerebellar ataxia. In 1891, however, Menzel had reported an autosomal dominant pedigree of OPCA who exhibited a complex clinical picture including progressive cerebellar ataxia, spasmodic dysphonia, lower limb rigidity, dysphagia, and dystonic neck posture.

The sporadic case described by Dejerine and Thomas ('Vais D.V.', Dejerine Laboratory, Paris, reviewed by Berciano) featured progressive ataxic gait, dysarthria, impassive face, hypertonia, hyperreflexia, and urinary incontinence beginning at the age of 53. Autopsy 2 years later showed an advanced degeneration of the basis pontis, inferior olives, middle cerebellar peduncles (MCP), and to a lesser degree inferior cerebellar peduncles. There was severe atrophy of Purkinje cells, more marked in the cerebellar hemispheres than in the vermis. Neither the basal ganglia nor substantia nigra are mentioned. According to the authors, OPCA would be a nonfamilial disease to be included among primary cerebellar degenerative disorders. While confirming the reported olivopontocerebellar lesions (**Figure 1**) and the absence of apparent lesions of the putamen, it was not possible to establish whether or not the substantia nigra had degenerated. This finding would have been of great interest because the patient may have had incipient parkinsonism; in fact, this clinicopathological study probably represents the first description of multiple system atrophy (MSA).

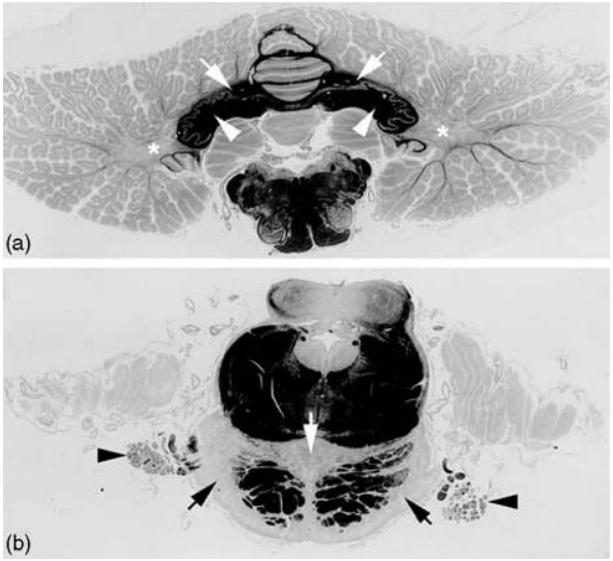

Figure 1 Olivo-ponto-cerebellar lesions in the case reported by Dejerine and Thomas. Both transverse sections are stained using the Weigert–Pal method. (a) This section through medulla and cerebellum shows demyelination of the olivo-cerebellar fibers and the cerebellar white matter (asterisks) with preservation of fibers surrounding (arrows) and exiting (arrowheads) the dentate nuclei. (b) This section through the upper half of the pons, at the emergence of trigeminal nerves (arrowheads), shows demyelination of pontocerebellar fibers (arrows); note that corticospinal and corticopontine fibers stand out due to complete disappearance of transverse pons fibers. Reproduced from Berciano J, et al. (2006) Olivopontocerebellar atrophy: Toward a better nosological definition. *Movement Disorders* 21: 1607–1613.

In 1954, Greenfield proposed a pathological classification of the ataxias, where OPCA was divided into two forms: sporadic (Dejerine–Thomas type) and familial (Menzel type).

For almost a century clinicopathological studies in hereditary ataxias contributed to a confused nosology as it ignored the fact that genetic heterogeneity affects not only the clinical picture but also the pathological features, making the classification difficult within reported families with inconsistent pathological findings. There was a pressing need to find a new classification, a task achieved by Harding culminating in a series of exceptional contributions to the field of hereditary ataxias. In 1983, she proposed to start from genetic and clinical features which are, certainly, the tools used by neurologists in clinical practice. Along these lines, she proposed a clinicogenetic classification (**Table 1**), which was soon universally accepted.

Table 1 Harding's clinicogenetic classification of the hereditary ataxias and paraplegias

I. Congenital disorders of unknown aetiology
II. Ataxic disorders with known metabolic of other cause
III. Ataxic disorders of unknown aetiology
  A. *Early onset cerebellar ataxia (usually before 20 years)*
    i. Friedreich's ataxia
    ii. Early-onset cerebellar ataxia with retained tendon reflexes
    iii. With hypogonadism ± deafness and/or dementia
    iv. With myoclonus (Ramsay Hunt syndrome, baltic myoclonus)
    v. With pigmentary retinal degeneration ± mental retardation and/or deafness
    vi. With optic atrophy ± mental retardation
    vii. With cataracts and mental retardation (Marinesco–Sjögren syndrome)
    viii. With childhood-onset deafness and mental retardation
    ix. With congenital deafness
    x. With extrapyramidal features
    xi. X-linked recessive spinocerebellar ataxia
  B. *Late-onset cerebellar ataxia (onset usually after 20 years)*
    i. Autosomal dominant cerebellar ataxia with optic atrophy/ophthalmoplegia/dementia/extrapyramidal features/amyotrophy (probably includes Azorean ataxia) (ADCA type I)
    ii. Autosomal dominant cerebellar ataxia with pigmentary retinal degeneration ± ophthalmoplegia and/or extrapyramidal features (ADCA type II)
    iii. 'Pure' autosomal dominant cerebellar ataxia of later-onset (over 50 years) (ADCA type III)
    iv. Autosomal dominant cerebellar with myoclonus and deafness (ADCA type IV)
    v. Periodic autosomal dominant ataxia
    vi. 'Idiopathic' late-onset cerebellar ataxia
IV. Hereditary spastic paraplegia
  A. 'Pure' spastic paraplegia
  B. Complicated forms of spastic paraplegia

In the last decade this clinicogenetic classification has been modified with the molecular genetic advances; in fact, hereditary ataxias and paraplegias now comprise around 80 *loci*, 29 of them belonging to autosomal dominant cerebellar ataxia (ADCA), and designated as SCA1 to SCA29 (from *spinocerebellar ataxia*, numbers indicating the chronological order of discovery of locus linkage). In 14 of these syndromes the underlying mutations are known. Seven SCA subtypes (SCA1, SCA2, SCA3, SCA6, SCA7, SCA17, and dentatorubral-pallidoluysian atrophy (DRPLA)) are caused by CAG trinucleotide expansions in the respective genes. OPCA might be the pathological hallmark in every subgroup of Harding's classification except for Friedreich's ataxia (FA), ADCA III, and 'pure' hereditary spastic paraplegia. According to neuroimaging studies (see below) or pathological findings, OPCA is the usual pathologic substrate of SCA1, SCA2, SCA7, SCA12, SCA13, and DRPLA; furthermore, mild OPCA may also occur in SCA3, though spinopontine atrophy is the most common pathological picture in this setting.

Pathogenesis

OPCA is a type of primary neuronal degeneration of the spinocerebellar systems, namely, a form of sporadic or hereditary neurodegenerative disorder. The recent molecular advances in the field of hereditary ataxias have demonstrated that degeneration of olivopontine and cerebellar systems may occur in a vast number of genetic defects, including SCAs caused by polyglutamine (or polyQ or CAG trinucleotide repeat) expansions.

Major insights into the molecular pathology of the trinucleotide repeat neurodegenerative diseases have been attained over the past decade. For OPCA associated with SCA caused by CAG repeat expansion in the coding region of a gene, the functions of the affected proteins (ataxin-1 for SCA1, ataxin-2 for SCA2, ataxin-3 for SCA3, ataxin-7 for SCA7, and atrophin for DRPLA) are still unknown. Expanded polyQ repeats can form insoluble aggregates that are the hallmark of all polyQ diseases. Neuronal intranuclear inclusions (NIIs) characteristically occur. It is generally held that polyQ disorders are due to a toxic gain of function of mutant expanded proteins, though haploinsufficiency remains a tenable possibility in which polyQ domains would alter proteasomal degradation in a malignant manner. The most intriguing possibility is transcriptional dysregulation. PolyQ sequences are relatively hydrophobic and can interact with each other in 'polar zipper' configurations. Many transcriptionally active proteins have polyQ domains, and the expanded sequences resulting from expanded CAG repeats may sequester transcriptionally active proteins and alter cellular functions. This does not necessarily imply that the NIIs are themselves pathogenic agents of neurodegeneration; in fact, NIIs may be epiphenomenal or even protective. The proposed pathogenic cascade of neurodegeneration probably includes protein misfolding, interference with DNA transcription and RNA processing, activation of apoptosis, and dysfunction of cytoplasmic elements. The molecular and cellular bases for the differential vulnerability of olivopontine and cerebellar neurons in SCA polyQ expansion disorders are poorly understood. It has been speculated that expanded polyQ-containing proteins differ in their affinity for different transcriptionally active proteins, and that the intersection of a given protein with an expanded polyQ domain and the repertoire of transcriptionally active proteins expressed by specific populations of neurons may determine regional effects. Animal models of SCA1, SCA2, SCA3, or SCA7 have not as yet reliably reproduced OPCA pathology. This is not the case of MSA, however, where combined mitochondrial inhibition and overexpression of oligodendroglial α-synuclein in a transgenic mouse generates a novel model of MSA demonstrating OPCA and striatonigral degeneration; furthermore, in MSA, degeneration of the olivopontocerebellar system significantly correlates with the frequency of glial (oligodendroglial) cytoplasmic inclusions (GCIs).

Epidemiology

OPCA is not explicitly considered in general epidemiological surveys on spinocerebellar syndromes. In my Community of Cantabria (Spain), the prevalence ratios of ADCA and idiopathic late-onset cerebellar ataxia (ILOCA) were 1.2 and 2.2 cases per 100 000, respectively. Some 60% of patients included in these groups had a cerebellar-plus syndrome and their CT or MRI scans revealed cerebellar and brainstem atrophy, allowing a presumptive diagnosis of OPCA. According to these estimations, prevalence ratio of OPCA is around 2 out of 100 000. In Japan, the prevalence of ILOCA has been established in 12 out of 100 000, with OPCA being the presumptive pathological hallmark in 65% of cases.

Clinical Features and Pathophysiology

In 1982, Berciano gathered together 117 cases of pathologically proven OPCA of which 63 were sporadic and 54 (43 pedigrees) were hereditary with an autosomal dominant transmission in 30 families, autosomal recessive in 7, and uncertain due to lack of information in 6. The mean ages of onset were 28.35 years (standard error of the mean (SEM)), $\pm$1.18 years; range, 2 months to 66 years) for familial OPCA and 49.22 ($\pm$1.64; 0–66) for sporadic OPCA, the difference being significant ($t = 6.43$; $p < 0.001$).

The predominant presentation was progressive gait and limb cerebellar ataxia and dysarthria, which was almost always accompanied by additional noncerebellar symptoms summarized in **Figure 2**.

The fundamental lesions, accounting for gait and limb ataxia and dysarthria, were those localized in the cerebellum and in structures derived from Essick cell-bands: the pontine, inferior olivary, arcuate, and pontobulbare nuclei. These fundamental lesions are accompanied by a variable involvement of other structures (**Figure 3**), which undoubtedly account for the additional noncerebellar symptoms and signs observed (**Figure 2**).

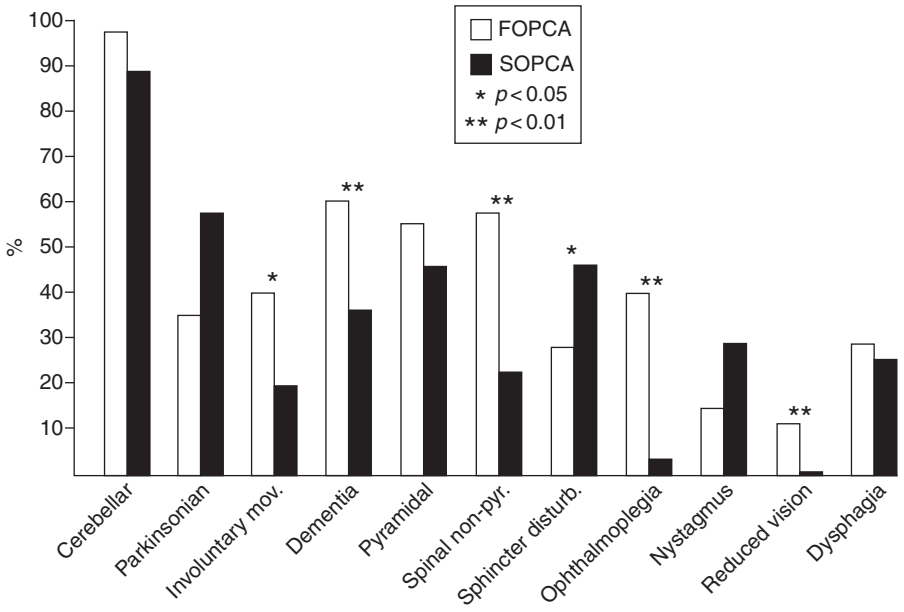

Figure 2 Histogram showing frequencies of symptoms and signs in familial OPCA (FOPCA) and sporadic OPCA (SOPCA). Reproduced from Berciano J (2007) Olivopontocerebellar atrophy (OPCA). In: Gilman S (ed.) *Neurobiology of Disease*, pp. 95–104. London: Elsevier Academic Press.

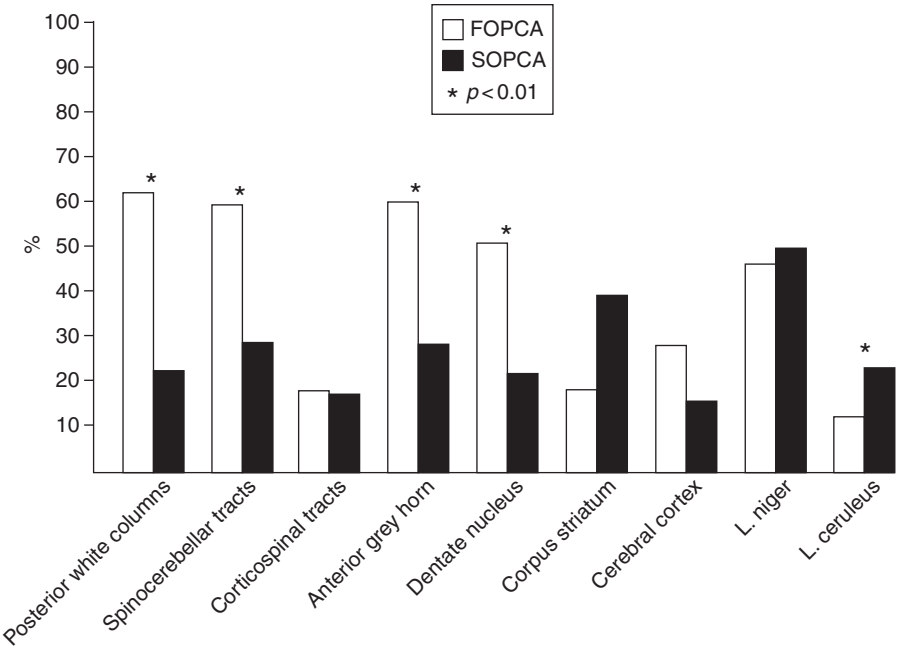

Figure 3 Histogram showing frequencies of the main associated lesions in familial OPCA (FOPCA) and sporadic OPCA (SOPCA). Reproduced from Berciano (2007) Olivopontocerebellar atrophy (OPCA). In: Gilman S (ed.) *Neurobiology of Disease*, pp. 95–104. London: Elsevier Academic Press.

Differential Diagnosis

OPCA may be part of the pathological hallmark of other disorders, namely, mitochondrial encephalomyopathy, hexosaminidase deficiency, adrenoleukodystrophy or sporadic spongiform encephalopathies among others described below. Familial OPCA has been misdiagnosed in some cases of familial prion disorders, either Gerstmann–Straussler–Scheinker syndrome or fatal familial insomnia.

Diagnostic Work-up

Brain CT scan or MRI studies are essential techniques in clinical practice for delineating brainstem and cerebellar atrophy characteristic of OPCA (**Figure 4**). The most sensitive feature differentiating between OPCA and cortical cerebellar atrophy (CCA) appears to be the diameter of the MCP. It is worth noting that besides OPCA, bilateral involvement of MCP may occur in many disorders including fragile X-associated tremor and ataxia syndrome, adrenoleukodystrophy, Wilson disease, and cerebrovascular, inflammatory, or neoplastic processes. Nevertheless, this neuroimaging finding combined with marked atrophy in the posterior fossa is characteristically seen in OPCA (**Figure 4**). In the first year after onset of cerebellar symptoms in OPCA patients, the CT scan may be normal; serial neuroimaging examination is then necessary for detecting infratentorial atrophy. Conversely, there may be brainstem atrophy without clinical correlate. Intermediate and T_2-weighted MR images may show cruciform hyperintensity ('hot-cross bun' sign) of the ventral part of the pons (**Figure 5**), accountable for by demyelination and gliosis of transverse fibers of the pons secondary to atrophy of nuclei pontis. The cruciform hyperintensity may extend

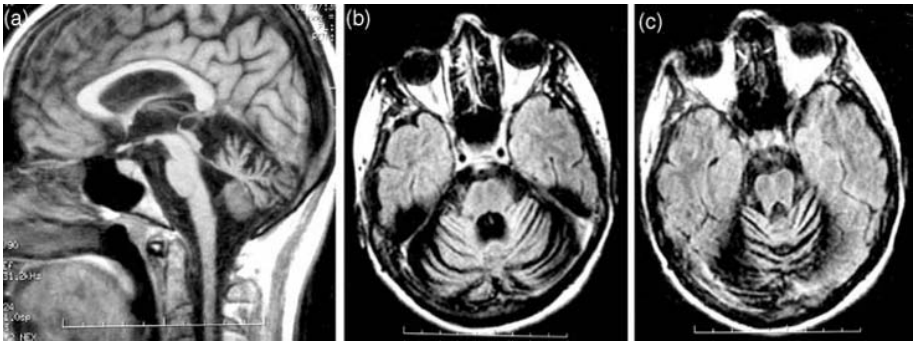

Figure 4 T_1-weighted MR imaging pictures from an SCA2 patient with cerebellar-plus syndrome. (a) Sagittal section showing extensive wasting of the brainstem and cerebellar vermis. (b) Axial section through mid-pons illustrating marked atrophy of the pons and cerebellar hemispheres with enlargement of the fourth ventricle. (c) This higher axial section shows atrophy of the pons and cerebellar vermis. Reproduced from Berciano (2007) Olivopontocerebellar atrophy (OPCA). In: Gilman S (ed.) *Neurobiology of Disease*, pp. 95–104. London: Elsevier Academic Press.

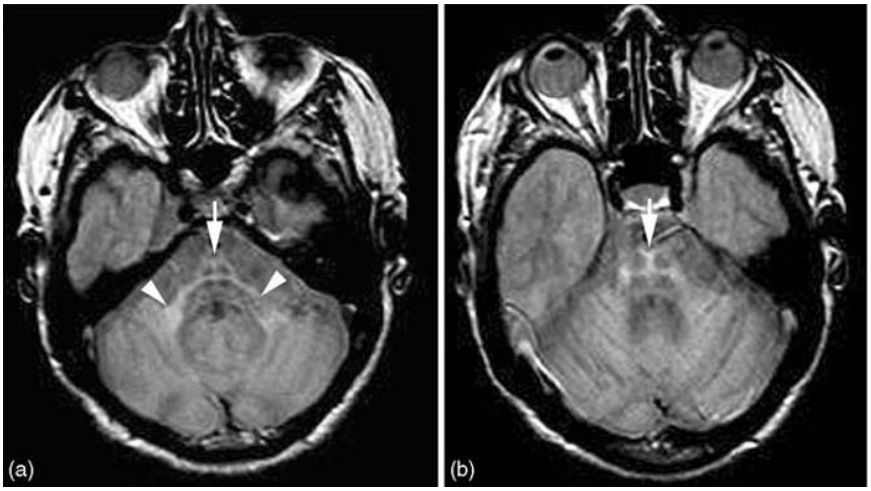

Figure 5 Axial proton-weighted density MRI pictures passing through lower (a) and mid pons (b) from a patient with probable MSA-C. Arrows indicate the presence of hyperintensity of pontocerebellar fibers conforming incipient (a) and fully developed (b) 'hot-cross bun' sign. Note also that signal hyperintensity involves middle peduncles extending to deep cerebellar white matter (a, arrowheads). Reproduced from Berciano et al. (2006) Olivopontocerebellar atrophy: Toward a better nosological definition. *Movement Disorders* 21: 1607–1613.

into MCP, a combination of lesions highly suggestive of OPCA, either sporadic or associated with any SCA.

Positron emission tomography (PET) scans of OPCA patients, as compared with those of normal control subjects, show a clear decrease of local cerebral metabolic rate for glucose (LCMRgluc) within the vermis, cerebellar hemispheres, and brainstem. The cross-validated sensitivity of absolute LCMRgluc as a predictor of OPCA was 82% with a corresponding specificity of 71%. A significant relationship was found between the degree of atrophy and the level of LCMRgluc in the cerebellum and brainstem. Nevertheless, there may be patients with minimal atrophy and substantially reduced LCMRgluc. PET study may therefore be especially useful as a diagnostic test in patients with presumptive clinical diagnosis of OPCA and normal CT or MRI.

Together with olivopontine and cerebellar systems, other neural systems (e.g., pyramidal tracts, spinal anterior horns or spinal posterior white columns) may degenerate, and there may be extracerebellar semiology (e.g., abnormal eye movement or sleep disorders; **Figure 2**). Electrophysiologic techniques are useful to investigate the extracerebellar semiology or the subclinical involvement of extraolivopontine neural systems.

Sporadic OPCA, MSA and ILOCA

The most complex nosologic problem is probably the relation among sporadic OPCA, MSA, and ILOCA. In fact, it has been proposed that MSA and sporadic OPCA are actually one and the same disease. We will briefly analyze the nosology of MSA and ILOCA in relation to OPCA.

MSA is defined as a sporadic neurodegenerative disease that causes a clinical syndrome of extrapyramidal, pyramidal, cerebellar, and autonomic features. The pathological hallmark of MSA is the presence of glial and neuronal inclusions showing pronounced α-synuclein immunoreactivity, on a highly variable topographic histopathological process. Lesions may vary from minimal, just involving the substantia nigra and locus ceruleus, to fully developed OPCA or striatonigral degeneration, with or without atrophy of the intermediolateral columns and Onuf's nucleus. GCIs have rarely been reported in OPCA associated with SCA1 or SCA2, but unlike MSA, they do not exhibit immunoreactivity for α-synuclein. As reviewed in a Consensus Conference, patients should be clinically classified as having MSA-P if parkinsonian features predominate, or MSA-C if cerebellar features predominate. The diagnosis of probable MSA requires a sporadic, progressive adult-disorder, including rigorously defined autonomic failure and poorly levodopa responsive parkinsonism or cerebellar ataxia. Starting from such diagnostic guidelines, a considerable number of classical sporadic OPCA descriptions could be reclassified as examples of MSA-C.

Harding introduced the eponym ILOCA to designate an ataxic disorder of unknown origin in three groups of patients with sporadic and progressive cerebellar ataxia, onset ranging between 30 and 74 years. The first group, with pure cerebellar ataxia, was composed of 12 patients who had greater truncal ataxia compared to limb ataxia and relatively late-onset (mean ± SD, 54.75 ± 10.0 years); Harding related this group to the Marie–Foix–Alajouanine type of CCA. The second group included six patients who had prominent upper limb tremors, both resting and during action (onset, 52.83 ± 9.89 years). The third group comprised 16 individuals with a cerebellar-plus presentation similar to patients previously reported as sporadic OPCA (onset, 45.22 ± 9.43 years). Radiological investigations were limited and neuropathological studies were lacking in Harding's series. Subsequent CT or MRI studies usually showed either cerebellar atrophy with an intact brainstem suggestive of CCA (in patients with pure cerebellar presentation) or combined cerebellar and brainstem atrophy suggestive of OPCA (in patients with cerebellar-plus syndrome). Therefore, in this second subgroup a working diagnosis of sporadic OPCA could be made, though in clinical practice a diagnosis of ILOCA with cerebellar-plus syndrome is preferred.

In Harding's and two further ILOCA series encompassing 35 patients with cerebellar-plus syndromes and extended follow-up, only three cases demonstrated parkinsonism or autonomic failure/urinary dysfunction as required for the diagnosis of probable MSA. Moreover, a substantial number of cases exhibited features not typically seen in MSA, such as dementia, chorea, generalized areflexia, or polyneuropathy. Conversely, in another ILOCA series, all 13 patients with additional extracerebellar symptoms showed parkinsonian features whereas urinary dysfunction was found in only five. Therefore, 16 out of 48 (33%) cases with cerebellar-plus syndrome from these four ILOCA series would fulfill criteria of MSA-C. This reinforces the criterion that not all sporadic OPCA patients (i.e., ILOCA patients with cerebellar-plus syndromes) necessarily have MSA. Intriguingly this percentage is comparable to a recently reported, longitudinal study of 51 sporadic OPCA cases, in which one-quarter of them evolved into MSA-C.

Treatment

Symptomatic treatment is only possible for a selection of clinical manifestations. Levodopa or other dopaminergic agents may provide some benefit for extrapyramidal rigidity or bradykinesia. Urinary disturbances due to detrusor hyperreflexia may be treated with a peripherally acting anticholinergic agent such as oxybutinin (5–10 mg at bedtime) or propatheline. In any case, treatment of either urinary or sexual disturbances should be carried out in close collaboration with an expert in neurourology.

Autonomic dysfunction including constipation, erectile dysfunction, sphincter disturbances, and syncope may require specific treatments. Although numerous reports have discussed the treatment of ataxia, most authors agree that results obtained with a variety of therapies are generally disappointing; in fact, none of the trials reported to date has produced results convincing enough to justify routine use of any drug in OPCA.

Psychosocial support and therapies are most important. Physical, occupational, and speech therapies may be essential to reduce patient's disability and to maintain longer independent functioning. Gait training and assistive devices may help prevent falls.

Acknowledgment

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See also: Ataxia; Hot-Cross Bun Sign; Multiple System Atrophy; Multiple System Atrophy: Animal Models; Spinocerebellar Ataxias Genetics.

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Opioid System

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Glossary

Direct pathway – One of two major routes by which the striatum can influence basal ganglia outputs, from the internal globus pallidus (GPi) and substantia nigra pars reticulata (SNr). The 'direct' pathway is a monosynaptic GABAergic connection.

Indirect pathway – One of two major routes by which the striatum can influence basal ganglia outputs, from the internal globus pallidus (GPi) and substantia nigra pars reticulata (SNr). The 'indirect' pathway or network incorporates poly-synaptic connections through the intermediaries of the external globus pallidus (GPe) and the subthalamic nucleus.

Opiate – Opiate refers to a specific subset of opioids that have an alkaloid structure similar to morphine. Not to be confused with opioid. Endogenous opioids in the brain are not opiates.

Opioid – A substance, natural or synthetic, that produces an action mimicking morphine.

Pharmacology

In the early nineteenth century, the principle active component of opium, morphine, was isolated from the opium poppy, *Papaver somniferum.* The realization that the effects of opium could be mimicked by morphine formed the starting point of opioid pharmacology. However, it had taken until the 1950s to provide a body of evidence to support the existence of receptors to mediate these effects. It had not

been until the early 1970s that opioid receptors in the brain were demonstrated by the binding of high affinity ligands.

The effects of opioid peptides are classically mediated via three receptors, termed μ-, δ-, and κ-opioid receptors. A fourth receptor has been identified which, while not completely fitting classic criteria for opioid receptors, is clearly related. This opioid receptor-like receptor is activated by the peptide nociceptin/orphanin FQ (N/OFQ) and is termed the N/OFQ peptide (NOP) receptor. Opioid receptors fall into the family of G-protein coupled receptors (GPCRs) and have a prototypical seven transmembrane domain organization. Their signal transduction is typically through coupling to Gi and inhibition of adenylyl cyclase activity, thus reducing cAMP levels.

Opioid receptors can be stimulated by a variety of endogenous peptides produced from a range of large molecular weight precursors. Thus, pre-proenkephalin-A (PPE-A) is the precursor for the pentapepide enkephalins, leu- and met-enkephalin. Enkephalins are endogenous ligands for δ-opioid receptors. Pre-proenkephalin-B (PPE-B) is processed to a range of dynorphins of different molecular weights (e.g., dynorphin A and B), α-neoendorphin, β-neoendorphin, and leu-enkephalin. PPE-B-derived peptides are endogenous ligands for δ, μ, and κ subtypes of opioid receptors. Pre-opiomelanocortin (POMC) is a precursor for both opioid and nonopioid peptides and is processed differentially in different tissues. The principle opioid peptide produced from POMC is β-endorphin, an extended form of met-enkephalin that can stimulate μ- and δ-opioid receptors.

Endomorphin-1 and -2, the precursor(s) for which are unknown, activate μ-opioid receptors.

Opioids in the Basal Ganglia

Striatal output neurons employ opioid peptides as cotransmitters with GABA. The use of neuropeptide cotransmitters by neurons equivalent to striatal output neurons is highly conserved across a range of vertebrate species, from reptiles to man. However, in mammals, striatal opioid peptides are segregated with respect to the direct and indirect striatal output pathways. Thus, the indirect pathway projection neurons utilize enkephalins derived from the precursor PPE-A, while the direct pathway employs opioids derived from PPE-B. Opioid peptides are released from striatal output neurons, both from recurrent collaterals within the striatum, and from terminals in the targets of striatal output, for example, the globus pallidus and the substantia nigra.

δ-, μ-, and κ-Opioid receptors are found in high concentrations within the striatum, being localized on GABAergic neurons and on terminals of glutamatergic and dopaminergic afferents. Striatal μ-opioid receptors show a patchy distribution, being more concentrated in striosomes. μ-Receptors are localized presynaptically on dopamine terminals. Stimulation of striatal μ-receptors enhances dopamergic transmission. Striatal κ-opioid receptors localized presynaptically on dopaminergic and glutamatergic terminals, activation of κ-receptors can reduce the release of dopamine and glutamate.

The striatum also contains high levels of endomorphin-1 and -2 and the NOP receptor.

δ-, μ-, and κ-Opioid receptors and NOP receptors are also found in regions receiving input from the striatum. For instance, in the external globus pallidus, the terminals of the indirect pathway express δ-opioid receptors and release enkephalins. These enkephalins can thus act upon the terminals from which they are released and reduce GABA release. With respect to the direct pathway, release of peptides produced from PPE-B can have multiple effects. Thus, α-neoendorphin or dynorphins released from the terminals of the direct pathway in the internal globus pallidus or substantia nigra pars reticulata inhibit basal ganglia outputs, either by inhibiting output neurons directly, by μ-receptor activation, or by reducing glutamate transmission by subthalamic efferents, by κ-receptor activation.

Opioids and Parkinsonism – Mechanisms and Opportunities for Novel Therapies

Striatal opioid peptide function, especially that involving enkephalins, is intimately linked to dopaminergic transmission. Thus, PPE-A mRNA and enkephalin protein levels are elevated in the dopamine-depleted striatum in parkinsonism. Enkephalin via activation of δ-opioid receptors in the GPe reduces GABA release from the indirect pathway. Elevation of enkephalinergic transmission, after dopamine loss in Parkinson's disease, and a consequent reduction in GABA transmission by the indirect pathway, is considered as a compensatory mechanism, that is, an attempt to overcome the loss of functionality resulting from dopamine loss. Enhancement of this endogenous compensatory mechanism has been suggested as a means to alleviate parkinsonian symptoms. In animal models of Parkinson's disease, δ-opioid agonists have antiparkinsonian actions. To date, these actions have not been translated into a clinically available therapy.

In contrast to PPE-A/enkephalins, the levels of PPE-B and one of its major products, dynorphin, are reduced in neurons of the direct pathway in parkinsonism. Reduced stimulation of κ-opioid receptors in the striatum and GPi would enhance glutamate release in these regions. As enhanced glutamate transmission in these regions is a component of mechanism of parkinsonism, κ-opioid-replacement therapy may thus be useful in the treatment of parkinsonian symptoms. Some κ-opioid receptor agonists have been shown to increase locomotion in animal models of Parkinson's disease, but to date, no subtype-selective opioid agonists have been assessed for antiparkinsonian efficacy in Parkinson's patients.

NOP receptor activation reduces dopamine neurotransmission in the striatum. In animals, at least, selective NOP antagonists have antiparkinsonian actions and potentiate the antiparkinsonian actions of levodopa. Further research is required to define how and whether it is possible to combine NOP antagonists with levodopa therapy in a manner to alleviate parkinsonism without worsening motor complications in patients.

Opioids and Dyskinesia – Mechanisms and Opportunities for Novel Therapies

The long-term treatment of parkinsonism with levodopa is associated with the development of motor complications such as levodopa-induced dyskinesia. Such treatment, and dyskinesia, is also associated with an elevation, within the striatum, in the synthesis of both PPE-A and PPE-B and their opioid peptide products. In contrast, dopamine agonists that have less propensity than levodopa to induce dyskinesia do not elevate striatal opioid peptide synthesis. The correlation between elevation of opioid peptide levels and dyskinesia has been interpreted as suggestive of a potential role for opioids in the pathophysiology of levodopa-induced dyskinesia. In this case, opioid receptor antagonists could represent a useful therapeutic approach to dyskinesia. However, data from preclinical and clinical studies are confusing. Non-subtype selective opioid receptor antagonists such as naltrexone or naloxone can either have no effect, or reduce or increase levodopa-induced dyskinesia.

It now seems likely that subtype-selective agents will be required to obtain robust antidyskinetic therapies from an opioid antagonist approach. μ- and δ-Opioid receptor antagonists appear the most interesting candidates, although, to date, no subtype-selective opioid receptor antagonists are available for clinical study.

See also: Basal Ganglia; Direct Pathway; GABA and Movement Disorders; Indirect Pathway.

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Opsoclonus-Myoclonus Syndrome

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Glossary

Ataxia – Incoordination or unsteadiness in regulation of posture and limb movements, due to impaired function of the cerebellum or its connections.

Myoclonus – Sudden, brief, shock-like involuntary movements caused by contraction or inhibition of a muscle or groups of muscles.

Opsoclonus – A disorder of eye motility involving involuntary, chaotic, arrhythmic, large-amplitude, conjugate saccades.

Paraneoplastic disorders – A variety of syndromes affecting any part of the nervous system related to the remote effects of cancer, usually attributed to the action of antibodies formed against tumor antigens.

Definition and History

Opsoclonus–Myoclonus syndrome (OMS) is a rare movement disorder consisting of involuntary eye movements, myoclonus, ataxia, or behavioral disturbances. It may be idiopathic or occur in association with a broad number of underlying disorders. OMS was originally described by Orzechowski in 1913 and has since been known by many names, including Kinsbourne syndrome, dancing eye syndrome, dancing eyes–dancing feet syndrome, myoclonic encephalopathy of infants, infantile polymyoclonia, and opsoclonus–myoclonus–ataxia (OMA) syndrome.

Pathogenesis/Pathophysiology

The pathophysiology and pathological substrate of OMS are not well understood and may vary according to the underlying cause. Most lines of evidence suggest an immune mechanism, including: symptom occurrence in the postinfectious state, documented responses to immunosuppressive therapy, demonstration of B- and T-cell recruitment in cerebrospinal fluid (CSF), and intense lymphocytic infiltration of associated tumors. Autopsy findings have either been normal or demonstrated abnormalities such as brainstem, basilar meningeal, and cerebellar inflammatory infiltrates, Purkinje cell loss, or peridentate gliosis and demyelination. The abnormal eye movements have been suggested to result from impaired interactions between omnipause and burst neurons in the brainstem or disinhibition of cerebellar nuclei have been suggested to cause the abnormal eye movements. Myoclonus may originate from abnormalities in the subcortical–supraspinal pathways connecting the brainstem and cerebellum, as supported by electrophysiological observations.

Epidemiology

OMS is rare, affecting children more than adults, and has largely been described in small series or case reports. Prevalence is not reported.

Clinical Features and Diagnostic Criteria

OMS is usually gradual in onset over several days, but can occur abruptly. Some patients have a prodrome consisting of nausea, vomiting, vertigo, oscillopsia, and gait difficulties. A subset may present with subacute, mild ataxia weeks before developing other symptoms. Despite the limited descriptive terms used in the name of the syndrome, patients may display any combinations of the following clinical signs.

Involuntary Eye Movements

Opsoclonic eye movements are involuntary, chaotic, conjugate, continuous, arrhythmic, multidirectional, large-amplitude saccades, without intersaccadic intervals. Opsoclonus is more prominent with agitation or when attempting to change fixation, may be associated with eyelid flutter or blinking, and can persist during sleep and eyelid closure. Patients can experience visual blurring and oscillopsia. Alternatively, ocular flutter (horizontal bursts of conjugate saccades interrupting gaze fixation) may occur as the primary eye movement abnormality or become apparent after resolution of opsoclonus, possibly representing a subform of opsoclonus.

Myoclonus

Myoclonus occurs mainly with action, typically localized to the head, face, limbs, or trunk, and rarely involving the diaphragm, larynx, pharynx, or palate. The amplitude may vary from larger, violent jerks to very small amplitude, generalized, continuous movements resembling tremulousness (which is termed minipolymyoclonus). Myoclonus and/or ataxia often compromise the ability to stand, walk, or even sit upright.

Ataxia

Ataxia is mainly truncal with varying degrees of appendicular involvement, and can be difficult to ascertain in the presence of severe myoclonus. Some cases have had severe ataxia without myoclonus.

Encephalopathy

Many patients develop a diffuse encephalopathy, ranging from lethargy and confusion to coma. Neurobehavioral and affective disorders also occur, including irritability, anxiety, personality changes, hallucinations, or 'rage attacks.'

Other Symptoms

Children may also have hypotonia, malaise, or psychomotor retardation. Hearing loss, lid retraction, hemifacial spasm, blepharospasm, sleep disorders, vertigo, head tilt or nodding, dysarthria, or mutism rarely occur.

Differential Diagnosis

Many medical and neurological diseases have been associated with OMS and are here grouped under the general disease categories.

Paraneoplastic

Children

OMS is the most common paraneoplastic disorder of childhood, most associated with neural crest-derived tumors. Neuroblastoma is discovered in the chest or abdomen of 50% of pediatric cases, with the neurologic symptoms preceding tumor diagnosis in 50%. Only 2–3% of children with neuroblastoma have OMS. The average age of presentation is 18 months. Anti-Ri/ANNA-2 is the most commonly associated paraneoplastic antibody, and 5–10% may have anti-Hu antibodies.

Adults

Only 20% of adults with OMS have an underlying neoplasm, with older age at onset (>50) as compared to idiopathic cases. Adult paraneoplastic OMS is mostly due to breast, gynecological, and small-cell lung cancers when Anti-Ri or Anti-Hu antibodies are detected. Other rarely associated paraneoplastic antibodies include anti-Yo, anti-Ma2, and amphiphysin antibodies. However, many do not have detectible antibodies. Adult paraneoplastic OMS has also been reported with non-small cell lung cancer, non-Hodgkin's lymphoma, Hodgkin's disease, benign ovarian teratoma, malignant melanoma, neurofibrosarcoma, chondrosarcoma, esthioneuroblastoma, pharyngeal squamous cell carcinoma, or primary malignancies of most organs (pancreas, gallbladder, renal, gastric, ovarian, ovarian duct, uterus, bladder, thymus, or thyroid).

Autoimmune/Demyelinating

OMS has been associated with anti-glutamic acid decarboxylase (GAD), adrenocorticotropic hormone (ACTH), antimitochondrial, acetylcholine receptor, and celiac antibodies. Ocular flutter, myoclonus, and ataxia with positive anti-GQ1b antibodies have been reported. Patients with sarcoidosis, multiple sclerosis, Guillain–Barre syndrome, acute disseminated encephalomyelitis, and HIV-associated immune reconstitution inflammatory syndrome have rarely developed OMS.

Infectious/Parainfectious

As a more common cause in adults, OMS has occurred in conjunction with, or following, various infectious etiologies. Documented infectious agents include viral infections (rubella, mumps, lymphocytic choriomeningitis, varicella-zoster, cytomegalovirus, poliomyelitis, Epstein–Barr, parainfluenza, Hemophilus influenzae, Coxsackie B, human immunodeficiency virus, St. Louis encephalitis, human herpesvirus 6, and West Nile), neurosyphilis, Salmonella typhi, streptococcal infection, Lyme disease, mycoplasma pneumoniae, tuberculosis, psittacosis, and malaria. Whipple's disease may cause a clinical picture similar to OMS, and should be considered in the differential diagnosis.

Drug Toxicity

OMS has occurred as part of toxicity syndromes of numerous drugs, including tricyclic antidepressants, dopamine blocking agents (haloperidol, metoclopramide), recreational drugs (cocaine, phencyclidine, amphetamines), lithium, nicotine, isoniazid, and antiepileptic drugs (phenytoin, diazepam, carbamazepine). Several toxic exposures have caused OMS, including lead, mercury, strychnine, toluene, thallium, and bismuth salts, have caused OMS.

Idiopathic

Workup in up to 50% of cases may yield no identifiable etiology despite an exhaustive search, which more often is the case in younger (<40) adult patients. OMS may represent a transient phenomenon in otherwise normal infants.

Miscellaneous

OMS has been associated with focal intracranial tumors (lymphoma, glioma, pineal, posterior fossa cysts), stroke (thalamic or pontine hemorrhage, vertebrobasilar insufficiency), pregnancy, trauma, post-vaccination, post-infectious encephalitis, metabolic derangements (nonketotic hyperosmolar coma, multiple carboxylase deficiency), allogeneic stem cell transplant, and congenital malformations.

Diagnostic Work-up/Tests

Neoplastic Work-up

An aggressive search for associated neoplasms should be guided by age and individual risk factors, and may include high-resolution CT or MRI imaging of the neck, chest, abdomen, and pelvis. Discovery of suspicious masses may further direct neoplasm-specific workup. Meta-iodobenzylguanidine (MIBG) whole-body scintigraphy may sensitively detect neuroblastoma if other imaging is negative. Directed or broad screening for paraneoplastic antibodies should be considered, although the absence of detectable antibodies does not always rule out a paraneoplastic syndrome.

Brain Imaging

Imaging studies are usually normal, but may reveal evidence for focal brain lesions or other clues to the specific underlying etiology.

CSF analysis

CSF may be normal or show lymphocytic pleocytosis, oligoclonal bands, or elevated protein. Neuroblastoma results in reduced 5-HIAA and homovanillic acid in CSF in conjunction with elevated urine catecholamine levels.

Management

Management is not standardized, and the rarity of OMS has not permitted randomized treatment trials. Therapeutic strategies vary according to identified causative factors and are directed towards symptomatic treatment of the most disabling symptoms. For paraneoplastic disorders, treatment modalities specific to underlying tumor can include chemotherapy, radiotherapy, or surgery. Empiric immunomodulatory therapy is commonly employed, initially with high-dose steroids or ACTH. Resistant or relapsing cases may be treated with combinations of intravenous immunoglobulin (IVIG), plasmapheresis, cyclophosphamide, or azathioprine. Rituximab, an anti-CD20 antibody, has been used in resistant or relapsing cases and is being investigated in open-label trials. Some patients have benefited from the serotonin precursor 5-hydroxy-L-tryptophan, thyrotropin-releasing hormone, or protein A column immunoabsorption. Symptomatic treatment includes trazodone for sleep difficulty or rage attacks, mood-stabilizing medications, anti-myoclonic drugs (clonazepam, valproic acid, levitiracitam, piracetam), or monoamine depleting drugs. Oscillopsia may be treated with propranolol, clonazepam, thiamine, or baclofen.

Prognosis

The prognosis varies depending on the symptoms, promptness of treatment, the presence and type of neoplasm, and individual-specific factors. Children respond more robustly to immune therapy than adults, with partial or complete relief in 80% of patients after 1–4 weeks of treatment. Corticosteroids or IVIG appears to accelerate recovery in adults. Although most patients initially respond to initial therapy, many exhibit persistent neurologic problems such as persistence of movement disorders, sleep difficulty, learning disorders, mood disorders, or neuropsychiatric deficits. Patients may have clinical remissions of any subset of symptoms or waxing and waning of neurologic function, requiring repeat treatment or maintenance therapy. Idiopathic causes typically have a more benign course, although older patients may have residual gait ataxia. Paraneoplastic OMS may have partial or complete remission if the underlying malignancy is treated; if the malignancy remains untreated, outcome is poor regardless of therapy.

See also: Ataxia; Drug-induced Movement Disorders; Eye Movement Abnormalities in Movement Disorders; Myoclonus; Paraneoplastic Movement Disorders.

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Oral Dyskinesia

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Glossary

Oral dyskinesia – Abnormal, involuntary, aimless, repetitive movements affecting the tongue, lips, and jaw.
Oral stereotypies – Repetitive, aimless, patterned movements of the tongue, lips, and jaw.
Oromandibular dystonia – Sustained muscle contractions resulting in twisting repetitive movements and abnormal postures, producing lip retraction and grimacing, tongue rolling and thrusting, jaw closure with trismus, jaw opening or lateral deviation, and jaw jerks, sometimes generating teeth grinding noise (wakeful bruxism) and tremor.
Tardive dyskinesia – Term encompassing a variety of abnormal, involuntary movements following chronic exposure to dopamine receptor-blocking agents (e.g., antipsychotic drugs, antiemetic agents such as metoclopramide), commonly involving the lower facial musculature to justify the label 'orobuccolinguomasticatory syndrome'.

Definition

Oral dyskinesia consists of abnormal, involuntary, aimless, repetitive movements affecting the tongue, lips, and jaw. These movements produce lip pursing, pouting, retracting, smacking, sucking, and licking, tongue writhing and thrusting, and chewing. Compared with extraoral hyperkinetic movement disorders, oral dyskinesia more often results from exposure to an offensive medication or a peripheral condition. Thus, oral dyskinesia should be considered drug induced until proved otherwise, allowing a proper inquiry into the patient drug history to take place. Clinical examination should first proceed without any foreign object in mouth, and should not be restricted to the oral cavity since extraoral findings may point to a specific diagnosis.

Differential Diagnosis

The various forms of oral dyskinesia are classified according to the predominant phenomenology of the manifestations as stereotyped (if patterned and predictable), choreiform, and dystonic in nature. Oromandibular dystonia is recognizable by sustained lip retraction and grimacing, tongue rolling and thrusting, jaw closure with trismus, jaw opening or lateral deviation, and jaw jerks, sometimes generating teeth grinding noise (bruxism). Sensory signals ('geste antagoniste') provided by holding something in the mouth (seed, gum, straw), or a local light touch, may reduce these spasms. A rare form of myorhythmic movements of the jaw and eyeballs may be seen as a distinctive feature of systemic Whipple disease. Oral dyskinesia must be distinguished from motor tics (more sudden, irregularly occurring, and suppressible, sometimes preceded by an urge) and the 'rabbit syndrome' (vertical labial or orofacial resting tremor of the parkinsonian type).

Oral dyskinesia occurs in a variety of brain conditions (**Table 1**), including mental retardation, Rett syndrome, and neurodegenerative conditions such as Huntington's disease. Reported estimates of the incidence of orofacial dyskinesia in antipsychotic-free patients with Alzheimer disease have varied between 10% and 40%. The issue of the occurrence of 'spontaneous' (or unmedicated) oral dyskinesia in normal aging remains blurred, since complete drug history and other dyskinesigenic conditions (e.g., orodental and cognitive status) are often incompletely documented. Lip smacking and chewing may be seen in never-medicated patients with chronic schizophrenia, with prevalence estimates averaging 12%. Other neurological disorders associated with oral dyskinesia include chronic hepatic encephalopathy, infectious or paraneoplastic encephalitis, and subcortical infarcts. Severe lingual dystonia, uncommon in primary dystonias, suggests the presence of a secondary or heredodegenerative cause, such as neuroacanthocytosis, pantothenate kinase-associated neurodegeneration, Lesch–Nyhan syndrome, postanoxic encephalopathy, and drug-induced ('tardive') dystonia. A wide range of medications crossing the blood–brain barrier also causes various types of orofacial dyskinesia, particularly the first-generation antipsychotic drugs (potent dopamine D2 receptor antagonists) and antiparkinsonian medications (chiefly levodopa). Certain drug addictions (amphetamines, cocaine, alcohol) may trigger orofacial dyskinesia.

Oral dyskinesia may also occur in association with certain orodental conditions. Edentulism is a neglected source of stereotyped oral dyskinesia. Orodyskinesia has been documented in 16% of edentulous subjects. The smacking and pursing of the lips, lateral deviation and protrusion of the tongue, and lateral deviation and protrusion of the jaw,

Table 1 Causes of oral dyskinesia

Subtype	*Cause*
Stereotypies	'Spontaneous' (detailed characterization lacking)
Chorea	Stress
Dystonia	Anxious clenching habit
Myorhythmia	Idiopathic
	oromandibular dystonia
	Meige syndrome (with blepharospasm)
	Non-DYT1 primary generalized dystonia
	Task-specific dystonia (e.g., speaking, embouchure instrument playing)
	Episodic focal lingual dystonic spasms
	Drug induced
	antipsychotic drugs (conventional > > atypical)
	antiemetic agents (metoclopramide, prochlorperazine)
	antidepressants
	buspirone
	Lithium
	psychostimulants
	antiparkinsonian drugs
	anticholinergic drugs
	antihistaminic drugs
	H2 receptor blockers
	antiepileptic drugs (phenytoin, carbamazepine, gabapentin, barbiturates)
	Calcium channel blockers (flunarizine, cinnarizine)
	flecainide
	Toxins (ecstasy, cocaine, amphetamines)
	Alcohol dependence syndrome
	Neurodegenerative disorders
	Huntington disease
	neuroacanthocytosis (with 'eating dystonia')
	pantothenate kinase associated neurodegeneration (PKAN)
	neuroferritinopathy
	Wilson disease
	Neurodevelopmental disorders
	schizophrenia (unmedicated)
	Rett syndrome
	Down syndrome
	Joubert syndrome
	Angelman syndrome
	Acquired brain damage
	posttraumatic
	postanoxic encephalopathy
	subarachnoid hemorrhage
	subcortical infarcts (basal ganglia, thalamus)
	Infections
	streptococcus (Sydenham chorea)
	varicella
	syphilis
	Whipple (oculomasticatory myorhythmia)
	Paraneoplastic (anti-Ma2, anti-*N*-methyl-D-aspartate receptor (NMDAR)
	Tumors
	Metabolic conditions
	Lesch-Nyhan syndrome (with self-mutilation)
	Gaucher disease
	chronic acquired hepatocerebral degeneration
	Peripherally induced
	grossly incorrect occlusion
	edentulous dyskinesia
	denture-related dyskinesia (ill fitting)
	posttraumatic
	dental procedure-related dystonia

have been observed. The movements are generally mild in intensity, but a significant fraction of subjects still feel distressed by the condition. These individuals are more likely to wear inadequate or no dentures at all than edentulous subjects without dyskinesia. In those with unstable dentures and oral discomfort, the label 'denture-related dyskinesia' may be justified. The prevalence of this complication is undetermined. Edentulous orodyskinesia may be distinguished from oral tardive dyskinesia (TD) on the basis of excessive aimless movements always restricted to the oral region, never dystonic in nature, and the absence of tongue writhing or thrusting at rest. In rare case reports, peripherally induced dystonia-like activity has followed a routine dental procedure, facial or orodental trauma, or ill-fitting denture or bridge insertion. No direct relation has been found between the severity of the injury and the development of dystonia. Several of these patients have had the onset of their manifestations within 1 week of the procedure. Spreading to other muscle groups, fixed jaw-deviating spasms, and pain have been noted. A coincidence or unmasking effect of a latent movement disorder by the dental procedure cannot be ruled out, as well as a psychogenic disorder.

Pathophysiology

The pathophysiologic mechanisms underlying oral dyskinesia remain unclear. Most forms of oral dyskinesia are of cerebral origin. Transient chemical disruption of inhibitory signaling in the lentiform nucleus of conscious monkeys produced orofacial dyskinesia, and deep brain stimulation of the external globus pallidus caused controlateral chorea in humans. The impact of many offensive medications on dopamine and acetylcholine neurotransmission suggests that these transmitters are implicated in the induction process and expression of oral dyskinesia. The antidyskinetic benefit afforded by the VMAT2 ligand tetrabenazine, a central monoamine depleter, supports this hypothesis. In animal models, the enhancement of striatal dopamine D1 receptor-mediated responses and the striatal activation of the Ras-extracellular signal-regulated kinase 1/2 mitogen-activated protein kinase signaling pathway have been correlated with levodopa-induced dyskinesia. Whether these molecular changes constitute a common neural substrate

for drug-induced dyskinesias and potential targets for future therapy remains undetermined.

The possible contribution of orodental factors such as edentulism should not be ignored, since they not only can generate oral dyskinesia amenable to correction, but also can worsen orofacial TD ratings. In edentulous orodyskinesia proprioceptive defects, due to loss in nerve endings and periodontal ligaments resulting from tooth extractions, have been suggested as a mechanism. However, no change in perioral pain sensory threshold has been documented in edentulous orodyskinesia cases relative to controls. Clinical findings support the view that edentulous orodyskinesia often takes place in a context of inadequate occlusion and overclosed vertical dimension (biomechanical factors associated with denture instability, and reduced facial support). On the other hand, long-standing oral dyskinesias can lead to premature wear and instability of the dentures, damaging gingival and bone structures, causing atrophy and additional prosthetic problems.

Management

The management of involuntary orolingual movements remains difficult. Since the diagnosis essentially relies on clinical assessment, recognition and proper therapy are not always straightforward. The emphasis of management strategies for drug-induced oral dyskinesia should focus on prevention. Early detection of vermicular tongue movements should be immediately reported to the treating physician, and the offensive drug withdrawn if possible. For disabled cases, palliative antidyskinetic treatment with tetrabenazine may be offered, but this is not an option in levodopa-induced dyskinesia. The benzodiazepine clonazepam can be used alone or in combination, but causes dose-dependent somnolence and carries a risk of dependence and tachyphylaxis over time. In dystonic cases, young subjects in particular, benefit may be obtained with an anticholinergic drug (e.g., trihexyphenydil). These oral treatments should in general not be discontinued abruptly to avoid a dystonic storm or a withdrawal syndrome. Intramuscular botulinum toxin administration is an excellent option in orofacial dyskinesia. The genioglossus muscle may be injected in severe tongue protrusion dystonia, but this approach has been rarely described. Severe refractory cases may respond to bilateral deep brain stimulation of the internal globus pallidus.

The potential complications (**Table 2**) caused by oral dyskinesia must be evaluated and treated diligently. In case reports, the insertion of dentures offering proper fit and adjustment of the occlusion has quickly relieved oral movements in edentulous orodyskinesia. Occlusal treatment has also ameliorated oral TD, as well as oral dyskinesia displayed by Down syndrome subjects with orofacial dysmorphology. Since denture retention may be troublesome in the presence of oral dyskinesia, an osteoimplanted mandibular prosthesis has been proposed, but only few isolated cases have been reported. In jaw-closing dystonia responsive to a sensory trick, a simple bite-raising soft device fitting between the molars to prevent jaw closure by a few mm can improve function. This should be introduced early to prevent tooth wear and temporomandibular joint dysfunction.

Table 2 Potential complications resulting from oral dyskinesia

Complications
Tooth wear
Tooth and denture damage
Accelerated bone loss in edentulous patients
Oral pain
Temporomandibular joint degeneration
Mandibular luxation
Friction/biting injuries (tongue, cheek bites)
Speech impairment
Dysphagia
Drooling
Chewing difficulties
Inadequate food intake and weight loss
Breathing difficulties
Displacement/impaired retention of removable dental prostheses
Social embarrassment (unemployment, isolation, depression)

See also: Anticholinergics and Movement Disorders; Antidepressants and Movement Disorders; Botulinum Toxin; Choreiform Disorders; Dopamine Depletors and Movement Disorders; Drug-induced Movement Disorders; Dyskinesias; Dyskinesias: Animal Models; Dystonic Storm; Huntington's Disease; Neuroleptics and Movement Disorders; Tardive Syndromes.

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Oxidative Stress and Movement Disorders

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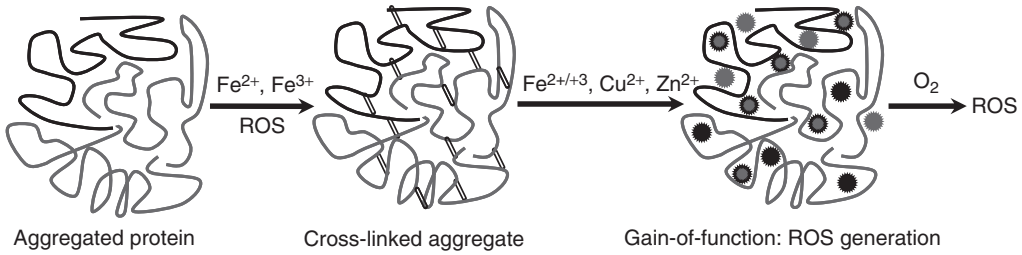
Glossary

Complex I deficiency – The mitochondria generate ATP via chemical coupling of a gradient of protons to ATP synthesis. A gradient of protons (between the outer mitochondrial membrane and the inner mitochondrial membrane) is generated by the transport of electrons from Complex I to IV. Abnormalities of complex I in PD lead to a buildup of electrons (which are passed on to oxygen to generate superoxide) and a decreased proton gradient leading to decreased ATP.
Free radical – Stable molecules contain two paired electrons of opposite spin in one or more of their outer most orbitals. Radicals contain an unpaired electron in their outer most orbitals. They are called 'free,' because they are stable enough for independent existence. Radicals move around the cell, looking for electrons to steal from cellular constituents such as lipid, protein, or DNA and thereby leave the target irreversibly altered.
Glutathione – An endogenous tripeptide, γ-glutamyl-cysteinyl-glycine, that is present in brain and peripheral tissues in concentrations approaching millimolar. It is a versatile antioxidant that along with enzymes such as glutathione peroxidase and glutathione reductase protects neurons. Of note, glutathione is one of the earliest known changes in Parkinson's disease – its levels are decreased.
Oxidative stress – Operationally defined as an imbalance between oxidants (free radicals) and antioxidants in the cell in favor of oxidants and above a threshold that leads to damage or death of a cell.
Superoxide dismutase – Superoxide is produced as a result of an addition of one electron to oxygen. Superoxide is produced as a consequence of many reactions, particularly as a byproduct of oxygen utilization in the mitochondria to generate ATP. Superoxide is thus a free radical that is produced as a consequence of normal metabolism. Mitochondrial dysfunction in PD leads to increase superoxide production.

Prototypic neurodegenerative movement disorders include Parkinson's disease (PD) and Huntington's disease (HD). Both the disorders are linked to inherited mutations resulting in accumulation of the damaged proteins or their wrongly processed variants. However, sporadic neurodegenerative conditions are also associated with accumulations of misfolded proteins and their aggregates resulting in the endoplasmic reticulum (ER) stress. The ER has a quality-control function with these proteins; only correctly folded proteins are excreted from the ER, while unfolded or misfolded proteins are degraded via ER-associated protein degradation, which is mediated by the ubiquitin–proteasome system. The accumulation of unfolded or misfolded proteins in the ER is one of the major causes of ER dysfunction. Downstream of these events, metal-catalyzed oxidation leading to oxidative stress has been implicated as a common final pathway of injury (**Scheme 1**). Despite the rarity of the familial forms of PD and HD, the identification of the genes and their defects has fueled our understanding of the pathogenic mechanisms,



Scheme 1 Widely accepted hypothetic gain-of-function transformation of cross-linked aggregates of misfolded proteins. Confirmed for AD, PD, ALS, and supposed for HD.

which include ubiquitin–proteasome system malfunction, oxidative stress, and mitochondrial dysfunction.

Oxidative stress can be operationally defined as an imbalance of cellular oxidants and antioxidants in favor of oxidants. However, cellular oxidants and the injuries they perpetrate are not an undifferentiated whole. Rather distinct oxidants act in distinct cell types and subcellular locations to trigger a continuum of responses from adaptation to apoptosis to necrosis. Here, we provide a 30 000 foot view of oxidative injury in the nervous system, as it relates to movement disorders and from this hope to build a conceptual framework for understanding how changes in redox balance can mediate dysfunction in the CNS.

Oxidative Stress: Inescapable Component of Mitochondrial Respiration

Mitochondria as a Major Source of Superoxide under Normal Conditions

Neurodegeneration is directly modified by cell aging. Some theories invoke the mitochondria as the major site of generation of deleterious free radicals that promote aging. The chemistry of reactive species that could result in oxidative damage under normal physiological conditions is the same for any cell. The major species in cells is superoxide radical produced as a byproduct of the mitochondrial respiration, in particular by Complex I and III of the respiratory chain. Complex III breaks 2e reducing equivalent into two single-electron reducing equivalents inside the membrane (Q-cycle), and the resulting quinone radical reacts with oxygen, giving rise to superoxide radical. This side reaction is known as 'mitochondrial leakage' and comprises up to 3–4% of the total oxygen consumption. If in a lifetime, we consume nearly 60 000 L of oxygen per kg weight, it means that we produce ~2000 L superoxide per kg weight. What happens to the released superoxide and how does cell handle the consequent 'oxidative' load?

Antioxidant/Antiaging Mechanisms: Superoxide Scavenging

In both cytosol and mitochondria, superoxide is scavenged and converted into hydrogen peroxide and oxygen by superoxide dismutase (SOD), although the nature of SOD in mitochondria and cytosol is different (MnSOD and CuZnSOD). The formed hydrogen peroxide is further decomposed into water with the help of catalase or reduced by the glutathione peroxidase/glutathione system. Very recent studies show that thioredoxin reductase/thioredoxin system is also capable of reducing hydrogen peroxide to water.

There are a number of theoretical reasons why the nervous system in general and neurons in particular are under the biggest load of oxidative stress under basal conditions. Neurons have a very high metabolic rate in order to meet the demands of electrical signaling. Specifically, our brain uses 20% of the total oxygen consumed, although brain is only 2% of the body weight. An expected corollary of high oxygen utilization is 10-fold higher level of radical production. Paradoxically, despite higher radical production, catalase is absent in brain mitochondria. This is not the case for heart mitochondria.

Given the higher level of radical production and the absence of catalase in brain mitochondria, what are the mechanisms at play inside neuronal mitochondria to neutralize the formed hydrogen peroxide and to keep oxidative damage to tolerable levels? In addition to glutathione peroxidase, the only other known system that neutralizes hydrogen peroxide is that of thioredoxin and peroxiredoxin. Reduced thioredoxin provides peroxiredoxin with reducing equivalents to reduce hydrogen peroxide to water. Oxidized thioredoxin is reduced back by mitochondrial thioredoxin reductase, selenocysteine flavo-dithiol oxidoreductase. Why mitochondrial catalase is absent in neurons is not well understood, but could be related to signaling functions of peroxide in neurons that are not necessary in other tissues. The absence of catalase from neuronal mitochondria places the burden of neutralizing hydrogen peroxide generated in mitochondria squarely on the shoulders of the thiol-based detoxification systems, particularly glutathione, thioredoxin, and periredoxin. A causal role for mitochondrial peroxide in aging was supported by the generation of transgenic mice that overexpress catalase in the nucleus, the peroxisome, and the mitochondria. Significant extension of lifespan was seen only in animals in which catalase was overexpressed in the mitochondria. The extension of lifespan was associated

with improvement in cardiac function, decreased development of cataracts, and diminished mitochondrial DNA mutations. It is unclear to what extent the increased lifespan reflected improvements in brain function.

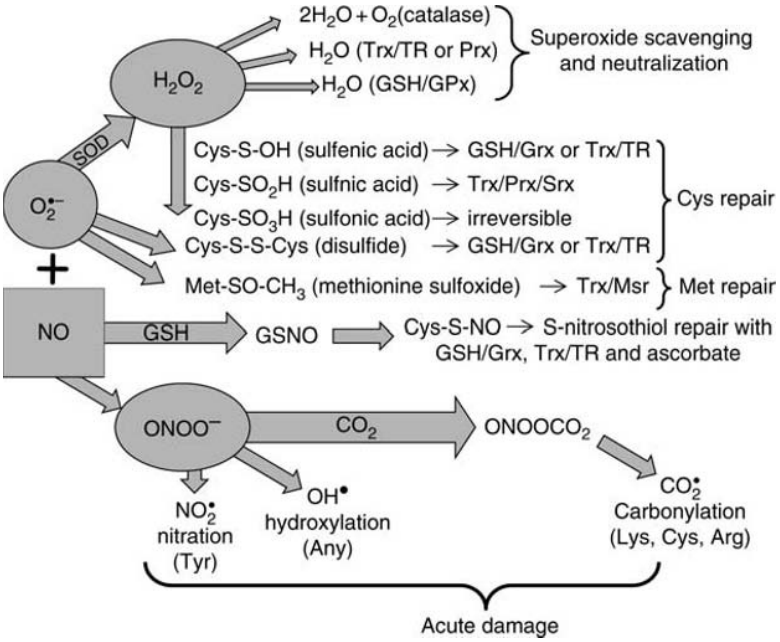
Antioxidant/Antiaging Mechanisms: Repair of Oxidized Residues

Unscavenged radicals are thermodynamically driven to oxidize cellular constituents including protein cysteines and methionines. These critical amino acid residues can be reduced back only with the help of specialized enzyme systems (**Scheme 2**). Cysteines are reduced back with glutaredoxin-glutathione system, and methionines are reduced back with methionine sulfoxide reductase (MSR) system. The MSR system includes two enzymes, only one of which belongs to the same enzyme class as glutathione reductase and thioredoxin reductase.

The glutaredoxin-glutathione enzyme system has beneficial effects on the functional activity of a number of proteins, including the thiol-containing mitochondrial Complex I, the inhibition of which was caused by administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a neurotoxin that produces PD-like symptoms in primates, including humans. Interestingly, glutathione depletion is an early feature of PD and appears to be disease specific. The depletion of glutathione may explain defects in Complex I function found in sporadic forms of PD.

MSR, another important enzyme in repair of proteins, is proposed to play a central role in neurodegeneration and aging. Genetically engineered organisms overexpressing the enzyme live longer. On the contrary, the reduced or suppressed activity of the enzyme results in shortened life span, hippocampal degeneration, and increased sensitivity to oxidative stress. The enzyme can repair oxidized methionines and restore the function of many important proteins, for example, calmodulin. MSRs act on oxidized calmodulin and repair all the eight methionine sulfoxide residues initially present in the inactive protein.

As mentioned earlier, neuronal mitochondria protect themselves against hydrogen peroxide formed inside the matrix solely with the thiol-dependent enzyme systems. Moreover, repair systems also largely depend on reduced thiols (see above). In many cases, the catalytically important enzyme thiols were shown to be protected against oxidative damage by glutathionylation. Glutathionylation is a posttranslational, reversible redox modification of proteins by thiol/disulfide exchange. Indeed, glutathione used to be a dominant theme in brain neurodegeneration, and it was only recently that the significance of thioredoxin-based systems has been fully appreciated. Measurements of NAD(P)H-dependent thiol reducing activity in



Scheme 2 ROS/RNS generation and neutralization reactions & systems: Upper level: Superoxide scavenging reactions catalyzed by superoxide dismutase (SOD), catalase, thioredoxin reductase (TR), peroxiredoxin (Prx), and glutathione peroxidase (GPx) and mediated by thioredoxin (Trx) and glutathione (GSH). Center: Oxidation states of cysteine and methionine and their repair; glutathione repairs most of the oxidative modifications by glutathionylation followed by its removal with glutaredoxin (Grx) system; methionine is repaired with methionine sulfoxide reductase (Msr)/Trx system; sulfonic acid modification is irreversible, while sulfinic acid can be repaired with the use of a recently characterized ATP- and Mg2+-dependent enzyme, sulfiredoxin (Srx), which is capable of reducing the sulfinic form of peroxiredoxin. Lower level: peroxynitrite-generated radicals cause largely non-repairable damage to proteins, DNA and lipids.

brain mitochondria show that glutathione reductase and thioredoxin reductase are equally important. Thiol-dependent systems of hydrogen peroxide neutralization and subsequent repair by themselves are targets for oxidative modification, and this obviously creates a threshold of oxidative damage that can be handled by neuronal mitochondria. Once reached, it results in mitochondria failure and the subsequent cell death by either apoptotic or necrotic pathways.

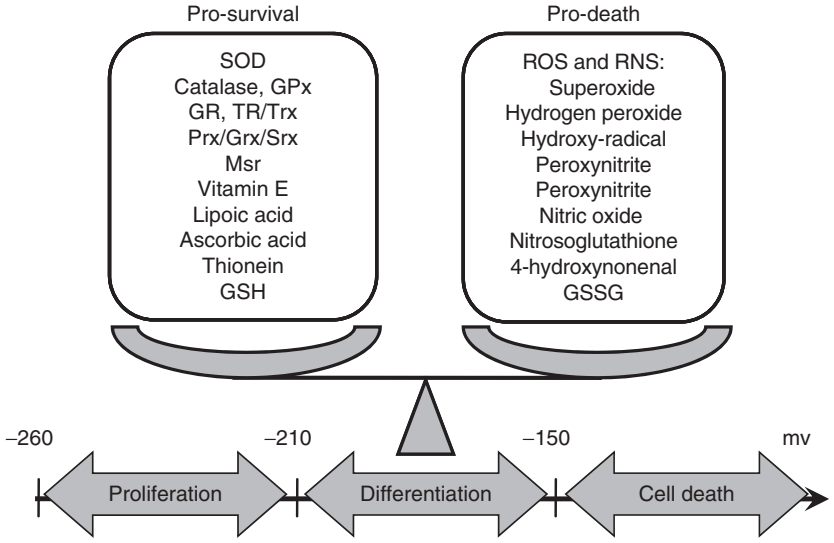
Oxidative Stress and Aging

Chronic Oxidative Stress and Ischemia

The delicate balance existing under normal conditions between oxidant production and antioxidant defensive mechanisms (**Scheme 3**) can be either slowly shifted with aging or disturbed at once upon acute injury. The 'slow acting' factor is a progressive mitochondrial malfunction, which originates mainly from the damage of the mitochondrial DNA: the superoxide released by mitochondria is directed both 'in' and 'out' of the mitochondrial inner membrane, and therefore, is capable of damaging mitochondrial DNA, matrix proteins, inner membrane proteins, and lipids. The progressive 'oxidation' eventually results in mitochondrial inability to utilize oxygen efficiently and makes them less competitive with respect to other intracellular processes consuming oxygen, particularly those controlling the ratio between aerobic and anaerobic respiration. Aging cells are more and more dependent on mitochondrial respiration, and consequently are less prepared for the increased risk of ischemia. Paradoxically, ischemia results in the increased production of ROS and excessive damage upon reperfusion. The master regulator of the hypoxic adaptation, hypoxia-inducible factor (HIF), has been recently shown to activate one of the key antioxidant proteins in mitochondria, metallothionein-3. HIF is a widespread transcription factor activating a battery of genes including those involved in glucose uptake and metabolism, extracellular pH control, angiogenesis, erythropoiesis, and mitogenesis, acting to enhance the cell survival ability. More and more new genes are found to be regulated by HIF. Tyrosine kinase receptor B (TrkB) for Brain-derived neurotrophic factor (BDNF) is also a HIF target implicating HIF in the regulation of neurotrophin signaling. The most exciting finding was the upregulation of tyrosine hydroxylase, the rate-limiting enzyme in the synthesis of dopamine, by HIF. However, the link between hypoxia and mitochondrial biogenesis activator PGC-1α as well as the mechanism of hypoxic upregulation of mitochondrial uncoupling protein-3 is still controversial.

The predominant O_2-dependent regulation of HIF-1α is mediated by posttranslational mechanisms, among which hydroxylation of Pro564 (HIF-1α is the major regulator and is catalyzed by nonheme iron αKG-dependent dioxygenases known as the HIF prolyl hydroxylases (HIF prolyl hydrodxylases isozymes 1–3). Deficiency or inhibition of PHD1 induces hypoxia tolerance in skeletal muscle by reprogramming basal metabolism through activation of HIF-2α – > Pparα – > Pdk4 (pyruvate dehydrogenase kinase isozyme-4, restricts entry of glycolytic intermediates into TCA cycle), although no direct link between HIF-2α and Pparα has been established.

PHD3 only recently gained full attention because of two major findings. First, PHD3 was shown to accumulate



Scheme 3 Delicate balance between pro-death and pro-survival factors determines the cell fate *in vivo*. For the cultured nerve cells, the depletion of intracellular redox potential (shown as that for GSSG/GSH couple) below a certain level determines whether the cells will differentiate or die.

with age in different tissues. Age-associated changes in PHD3 expression inversely correlate with the expression of HIF-target gene macrophage migration inhibitory factor (MIF), which was described to be involved in cellular HIF-mediated antiaging effects. In a recent study, evidence was provided that HIF-1 plays a critical role in delaying the onset of senescence in rodent cells via transcriptional activation of MIF and thereby inhibition of the p53-mediated pathway. It is worth mentioning here again that PHD3 in mice has a mitochondria-targeting leader sequence and that PHD3 seems to be most flexible PHD isoform regarding stimuli-induced change in expression.

Second, PHD3 was found to form subcellular aggregates. The most intriguing finding was that PHD3 inhibition prevented it from forming aggregates. The PHD3 aggregates were dependent on microtubular integrity and contained components of the 26S proteasome, chaperones, and ubiquitin, thus demonstrating features that are characteristic of aggresome-like structures. Forced expression of the active PHD3 induced the aggregation of proteasomal components and activated apoptosis under normoxia. The apoptosis was seen in cells prone to PHD3 aggregation and the PHD3 aggregation preceded apoptosis. The data demonstrate the cellular oxygen sensor PHD3 as a regulator of protein aggregation in response to varying oxygen availability. Given the fact that PHD3 expression is upregulated with aging, it may actually contribute to the reduced cell tolerance to hypoxia-reoxygenation and other pathological scenarios of oxidative stress.

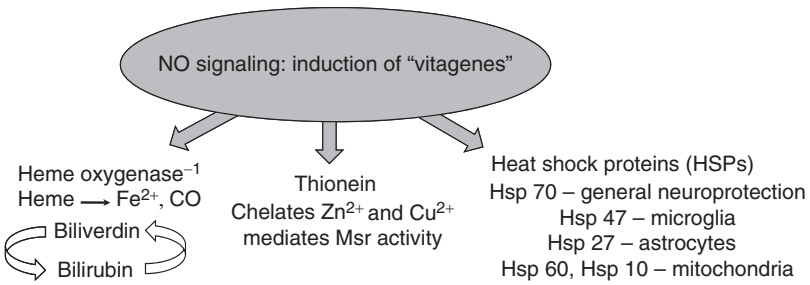
Acute Oxidative Stress

The neurotoxins (rotenone, MPTP) and neurotoxic animal models of PD renewed interest in possible environmental causes of PD. The most common form of neurodegeneration occurs after an acute injury. The causes of neuronal injury are many and include trauma, DNA damage from radiation, chemotherapeutic agents, exposure to environmental neurotoxins, and others. Acute neuronal damage involves a complex combination of processes including excitotoxicity, inflammation, necrosis, and apoptosis. The adaptive response to tissue damage includes the activation of transcription factors such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and others to switch on the inflammation response to limit damage and promote repair.

Excitotoxicity

Excitotoxicity is a particularly important event that initiates acute neurodegeneration. Accumulation of glutamate within the synaptic cleft leads to Ca^{2+} influx via hyperactivation of *N*-methyl-D-aspartate receptors, voltage-gated Ca^{2+} channels, and nonspecific cation conductances. The latter non-specific cation channels are represented by the recently discovered transient receptor potential (melastatin) (TRPM) ion channels, among which TRPM7 and TRPM2, shown to be permeable for Ca^{2+} and inhibited by gadolinium, appear to play a critical role in anoxic cell death.

Excess Ca^{2+} via ionotropic glutamate receptors results in the initiation of neurotoxic signaling cascade by activating calmodulin and neuronal NO synthase (nNOS). Current opinion holds that the intracellular redox state is the critical factor determining whether in brain cells NO is toxic or protective (**Scheme 4**). NO is known to signal the induction of heme-oxygenase-1, which is considered as a prosurvival enzyme. It degrades heme yielding ferrous iron, CO, and biliverdin, which cycles between the oxidized and reduced form, bilirubin. The latter exhibits strong antioxidant properties. Biliverdin reductase is present in brain in large functional excess, suggesting that such redox cycling amplifies antioxidant effects of heme-oxygenase expression. On the other hand, NO also reacts with glutathione, generating nitrosoglutathione, which is able to modify and thus inactivate protein thiols. However, the most dangerous species, peroxynitrite, is generated via the direct interaction of superoxide radical and NO, a comparatively stable and harmless molecule. Peroxynitrite is extremely reactive and capable of nitrating tyrosine residues in proteins (**Scheme 2**). A downstream effect of peroxynitrite production is the activation of TRPM channels. Molecular deletion of TRPM2 or TRPM7 channels renders neurons resistant to hypoxia/aglycemia. Whether



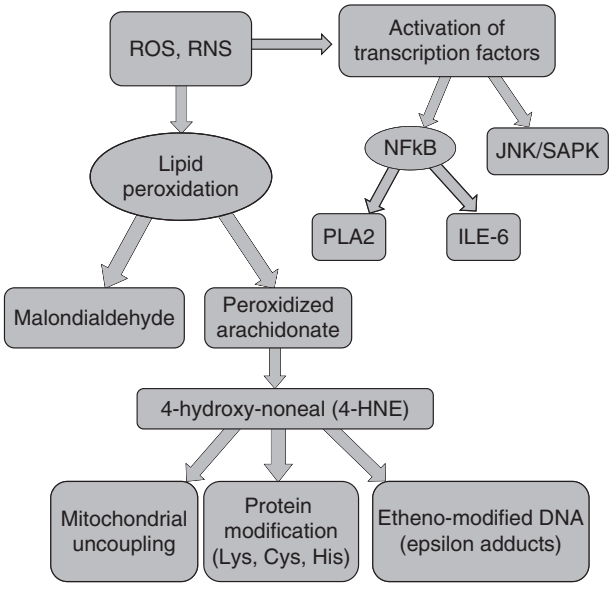
Scheme 4 Pro-survival role of NO: induction of synthesis of (a) heme oxygenase, which provides cells an antioxidant bilirubin/biliverdin/biliverdin reductase system; (b) thioneins, which chelate metal ions and in addition can mediate/enhance methionine sulfoxide reduction by Msr and Trx; and (c) heat shock proteins.

peroxynitrite induces activation of TRPM channels via nitration of its critical components or some upstream modulatory protein is unclear. Protein nitration has been shown to take place in brain injuries and some but not all neurodegenerative diseases.

Superoxide and especially peroxynitrite-induced modification of the metallothionein thiols results in the release of zinc. Neurodegenerative diseases are characterized by a mobilization of intracellular zinc. The latter was shown to mediate NO-induced neuronal death by directly affecting mitochondrial respiration through inhibiting Complex III. In addition, it has recently been shown that zinc is capable of entering mitochondria and directly inactivating lipoamide dehydrogenase, the terminal enzyme of major multienzyme energy-producing complexes, as well as glutathione reductase and thioredoxin reductase. The inactivation is irreversible, and only the newly synthesized proteins transported into mitochondria may compensate for the damage (**Scheme 5**). Thus, acute oxidative damage resulting in massive release of intracellular zinc will cause the mitochondrial failure and cell death.

Inflammation

Oxidative stress can directly or indirectly initiate an inflammatory cascade. Collective evidence from many recent studies suggests that increased phospholipase A2 activity plays a central role in acute inflammatory responses in the brain as well as in oxidative damage associated with AD, PD, and multiple sclerosis. PLA2 contributes to the pathogenesis of neuroinflammation by attacking neural membrane phospholipids to yield arachidonic acid and lysophospholipids. These are subsequently metabolized to a variety of proinflammatory lipid mediators such as prostaglandins, leukotrienes, thromboxanes, and platelet activating factor. Arachidonic acid metabolism is also one of the major sources of oxidative damage (**Scheme 6**). Arachidonic acid undergoes catalytic oxidation by cyclooxygenases 1 and 2, and in addition, can react with superoxide or peroxynitrite to generate one of the most potent modifying agents, 4-hydroxy-2-nonenal (HNE). The latter can modify lysine, cysteine, histidine residues in proteins and can bind to free amino acids and deoxyguanosine. Immunostaining for HNE-modified proteins shows that such modification is characteristic of acute oxidative stress, occurring during brain and spinal cord injury.

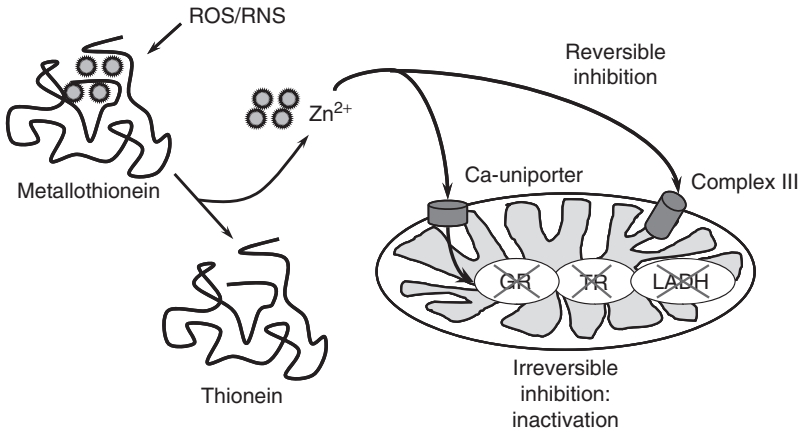


Scheme 5 4-hydroxy-nonenal: the most damaging product of lipid peroxidation. Phospholipase A2 (PLA2) inhibitors were shown to be neuroprotective.

Inflammation is characterized by the increased deposition of iron. Iron, especially in the ferrous or unbound form, is able to catalyze the formation of free radicals and could be a cause of neuronal injury. Depletion of antioxidants in the brain and rise in iron-dependent oxidative stress and monoamine oxidase B (MAO B) activity are key characteristics of aging that contribute to the onset of neurodegenerative disorders. MAO B is a mitochondrial flavin-dependent enzyme that catalyzes oxidative deamination of neurotransmitters and exogenous arylalkylamines. MPTP, an impurity in synthetic heroin, being activated by MAO B, gives a widely used chemically induced model of PD.

1-methyl-4-phenylpyridinium (MPP^+), the toxic product of MPTP conversion, increases superoxide formation by suppressing activity of NADH dehyrogenase (Complex I) and increasing leak of electrons to oxygen. Superoxide is then available to attack Fe/S cluster proteins such as aconitase. Destabilization of cytosolic as well as mitochondrial aconitase results in an increase in iron regulatory protein-1 (IRP-1), an RNA-binding protein that signals cellular iron deficiency. This leads to the paradoxical and maladaptive increase in iron in the cell. The mechanisms underlying iron cellular toxicity are only beginning to emerge. A representative trend in neuroprotective drug development is to combine an iron chelator and a MAO inhibitor in the same compound. Iron chelators have recently been shown to have the ability to induce adaptive gene expression via the stabilization of factors such as HIF-1. HIF is a heterodimeric transcriptional complex that mediates the induction of more than 70 genes involved in hypoxic compensation including vascular endothelial growth factor (VEGF) and Epo.

Activated neutrophils and macrophages generate widespread secondary damage at the traumatic site by releasing cytokines and free radicals. They produce inducible NO synthase and NAD(P)H oxidase (Phox) generating nonmitochondrial superoxide, both the enzymes cooperate to generate peroxynitrite and thus, expose cells to further oxidative damage. In addition to peroxynitrite, leukocytes possess myeloperoxidase, which generates hypochlorite



Scheme 6 Zn-induced damage to mitochondrial enzymes of energy production and antioxidant defense.

from hydrogen peroxide and chloride anion. Hypochlorite is a strong oxidizing agent capable of chlorinating protein residues and oxidizing membrane lipids. In all cases of rodent neurodegeneration, medications reducing inflammatory responses were shown to exhibit beneficial effects on the disease progression.

Apoptosis

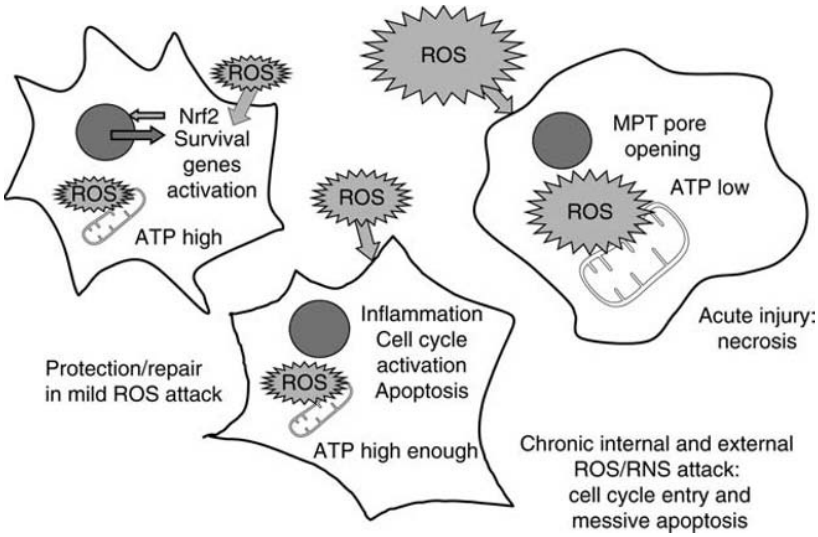
The discovery that oxidative stress can trigger a program of cell death in neurons with features of apoptosis was significant in several aspects. First, it showed that oxidative stress does not always result in random and disordered cell damage. Second, it demonstrated the possibility of free radical triggering an endogenous program of cell suicide.

Oxidative stress has been shown to activate a host of downstream signaling pathways leading to apoptosis. In some schemes, c-Jun N-terminal kinases (JNKs) signaling pathway resulting in Bax translocation, cytochrome c release, and apoptosis. In other schemes, Erk activation or PARP activation leads to translocation of apoptosis inducing factor and caspase-independent cell death. Oxidative stress has been implicated in the activation of cell cycle resulting in cell death, although two studies in which oxidative stress has been induced by downregulating antioxidant defenses failed to demonstrate a protective effect of cell cycle inhibitors.

The superoxide released by mitochondria is directed both 'in' and 'out' of the mitochondrial inner membrane and, therefore, is capable of damaging mitochondrial DNA, matrix proteins, inner membrane proteins, and lipids, and cytosolic proteins and nuclear DNA. With respect to DNA damage, more than 1000 DNA damaging events occur in each mammalian cell every day from replication errors and cellular metabolism. To cope with the deleterious consequences of DNA lesions, cells are equipped with efficient defense mechanisms to remove DNA damage by DNA repair pathways, control cell cycle progression, and eliminate damaged cells via apoptosis. The complicated network of DNA repair mechanisms includes base excision repair, transcription-coupled repair, global genome repair, mismatch repair, homologous recombination, and nonhomologous end-joining damage. Evolution has overlaid the core cell cycle machinery with a series of surveillance pathways termed cell cycle checkpoints. Checkpoints in proliferating cells tightly control progress through the cell cycle; cells may be arrested at any of the checkpoints and either DNA will be repaired or cells will die by apoptosis. It appears that apoptosis induced by oxidative damage may be promoted by multiple pathways, both cell cycle dependent and independent. The determining factor for the pathway(s) induced is an area of active exploration (**Scheme 7**).

Nature of Aggregated Deposits in Neurodegenerative Diseases

PD is a common neurodegenerative disorder affecting 1% of the population over the age of 65. Clinically, PD generally presents with bradykinesia, resting tremor, muscular rigidity, and postural instability. PD is a heterogeneous disease, and the majority of the cases appear to have sporadic origins. The disease is characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta, as well as the presence of Lewy body inclusion in these cells. At least 20% of Parkinson's cases are familial. Ten different genetic loci have been linked with familial PD, and the genes responsible for PD at these loci include α-synuclein and dardarin/LRRK2 associated with dominantly inherited PD, and parkin, DJ-1, and PINK1 causing recessively inherited PD. α-synuclein readily aggregates and is a major fibrillar component of Lewy bodies. Aggregation of α-synuclein is enhanced with tissue transglutaminase: Lewy bodies in PD patients are positively immunostained with antibodies recognizing isodipeptide bonds, a marker of tissue transglutaminase cross-linking. Phosphorylation also promoted



Scheme 7 Cell fate depends on the level of oxidative stress.

α-synuclein aggregation. Culture cells overexpressing α-synuclein generate reactive oxygen species. One mechanism by which aggregated synuclein leads to ROS generation in PD is via trapping trace metals into the aggregates. These metals can then easily accept electrons from reducing substances such as superoxide or glutathione and transfer them to oxygen to form superoxide radical.

Two types of disruptions of the DJ-1 gene have been identified in PD patients. One is a deletion of several of its exons, which abolishes the production of the DJ-1 protein. The other disruption is a single point mutation giving rise to the L166P mutant at the protein level, which destroys DJ-1 dimeric structure. The monomer apparently loses its antioxidant properties and redistributes from cytosol to the mitochondria and nucleus.

DJ-1 inactivation promotes α-synuclein aggregation state in a cellular model of oxidative stress.

Polyglutamine diseases, the CAG trinucleotide repeat/polyglutamine diseases, are characterized by the occurrence of protein aggregates within neurons. The most well-characterized among 10-known diseases of this origin are HD, dentatorubral and pallidoluysian atrophy (DRPLA), spinal and bulbar muscular atrophy, and multiple forms of spinocerebellar ataxia. Each disease is caused by a distinct gene product with expanded polyglutamine repeats.

HD: The hallmarks of this genetic disorder are a progressive chorea combined with dementia. Historically, the lurching madness was mistaken for possession by witchcraft (some of the Salem witches burnt in 1693 may have actually had HD). It is caused by a single, dominant gene, that is, only one copy is sufficient to cause the disease unlike most genetic disorders which are recessive, that is, two 'bad' copies are needed to cause the disease. The average onset is from 35 to 40 years. Huntingtin is a large (350 kDa) protein of unknown function; once the polyglutamine tail crosses the threshold of 38 residues, the mutant begins to form aggregates. The latter precipitate in cytosol and also form nuclear inclusions. The mechanisms by which huntingtin aggregates launch the disease are still disputable. It is supposed to be a gain of function event. It is documented that mutant huntingtin can interfere with gene expression that is associated with adaptation to oxidative stress or mitochondrial dysfunction. Thus mutant huntingtin may be directly toxic to mitochondria and this toxicity may be sustained by mutant huntingtin's suppression of compensatory gene expression. While defects in energy metabolism are widely documented in human HD and associated animal models, the only evidence for oxidative stress is oxidative DNA damage.

DJ-1 in Focus: Linking Antioxidant Defense, HIF Prolyl Hydroxylase, and ER Stress

DJ-1 antioxidant activity is still a mystery. DJ-1 contains an active cysteine 106 (see **Fig. 1**) which redox cycling is indispensable of DJ-1 functioning. The adjacent His 126 and Glu 18 residues may form a putative active site (see **Fig. 1**).

Cytoprotective binding of DJ-1 to apoptosis signal-regulating kinase-1 (ASK1) depends on the central redox-sensitive Cys-106 and may be modulated by peripheral cysteine residues. ASK1 is a member of the mitogen-activated protein kinase family, which activates c-Jun N-terminal kinase and p38 in response to a diverse array of stresses such as oxidative stress, ER stress, and calcium influx. In the past decade, various regulatory mechanisms of ASK1 have been elucidated, including its

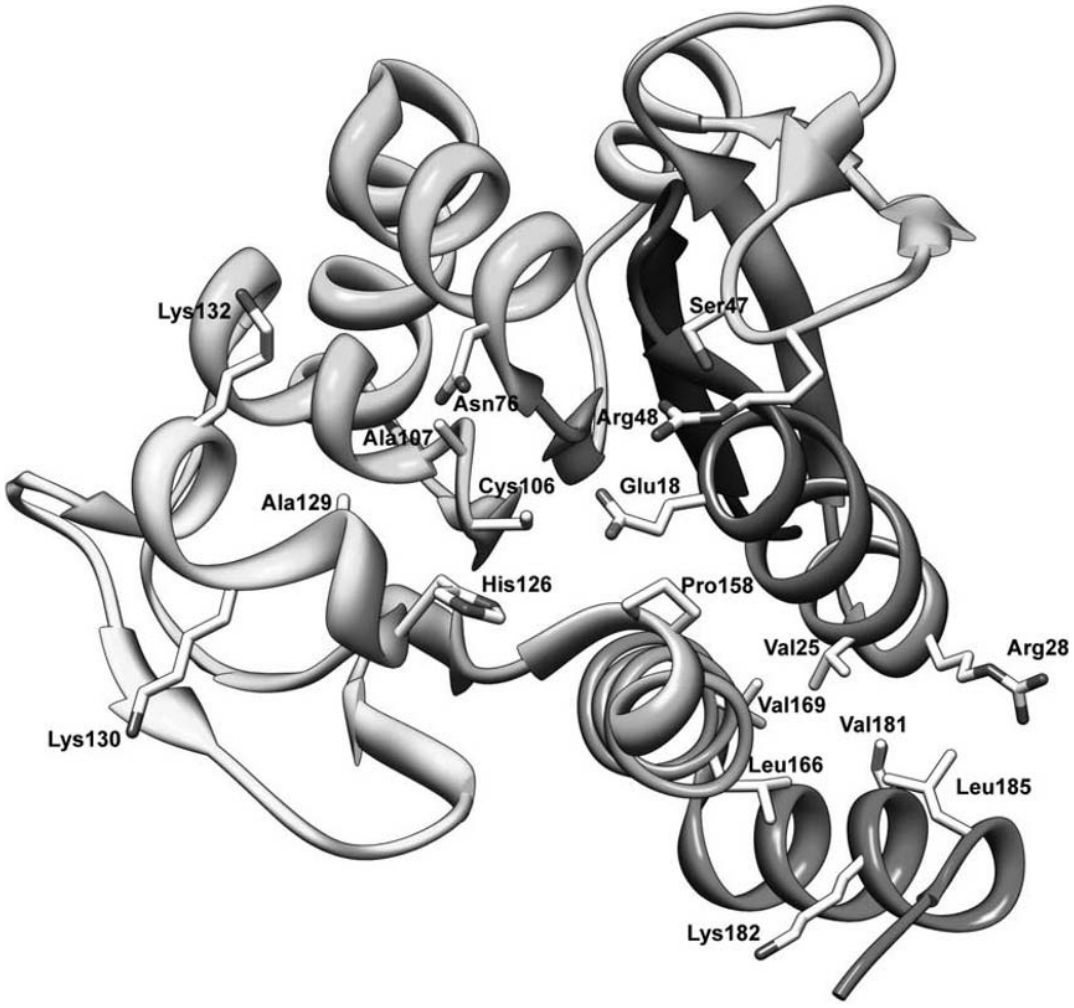


Figure 1 Redox active cyseine 106 and neighborous His126 and Glu18 residues may form a putative active site in DJ-1.

oxidative stress-dependent activation. Recently, it has emerged that ASK family proteins play key roles in cancer, cardiovascular diseases, and neurodegenerative diseases.

DJ-1 is required for the activity of Nrf2 (nuclear factor erythroid 2-related factor), a master regulator of response to oxidative stress. Nrf2 is a member of the cap'n' collar family of basic leucine zipper transcription factors that regulate the expression of many antioxidant pathway genes. Nrf2 is maintained at basal levels in cells by binding to its inhibitor protein, Keap1. Keap1 is a BTB (Broad complex, Tramtrack, Bric-a-Brac) domain-containing protein that targets Nrf2 for ubiquitination by Cul3, leading to its constitutive degradation. Upon exposure to oxidative stress, xenobiotics, or electrophilic compounds, Nrf2 protein is stabilized and translocates to the nucleus. There, it forms heterodimers with other transcription regulators, such as small Maf proteins, and induces the expression of antioxidant genes. Nrf2 drives the expression of detoxification enzymes, such as NAD(P)H quinone oxidoreductase-1, heme oxygenase-1, thioredoxin reductase, and other enzymes that generate antioxidant molecules, such as glutathione. DJ-1 is indispensable for Nrf2 stabilization by affecting Nrf2 association with Keap1, an inhibitor protein that promotes the ubiquitination and degradation of Nrf2.

Finally, DJ-1 was identified as the regulatory subunit of a 400-kDa RNA-binding protein complex and its presence inhibits the binding of RNA by the complex. It is worth emphasizing that the large subunit of RNA polymerase II, Rpb1, has been very recently shown to behave as a substrate for hydroxylation (P1465) by HIF prolyl hydrodxylase-1 (PHD1), in response to low-grade oxidative stress.

Neuroprotection Strategies: Problems and Perspectives

By the time the patient is diagnosed as having a neurological illness, extensive neuronal damage has usually

already occurred. Consequently, there is a great need for the discovery of biomarkers that would allow earlier diagnosis and intervention. Common features among neurodegenerative diseases, that is, genetic mutations, protein misfolding and aggregation, mitochondrial dysfunction, and apoptosis have implications for disease prevention and development of effective therapies. Despite common final pathways, it is unlikely that a single drug or targeting a single mechanism will be sufficient to halt neurodegenerative processes.

Chronic neurodegeneration is age-related, and thus, delay in biological aging will decrease the occurrence of age-related diseases with resulting prolongation of a healthy life span. Available evidence suggests that to delay aging one has to maintain healthy mitochondria and reduce oxidative stress. One of the proposed approaches is to maintain or recover the activity of the so-called vitagenes. The positive effect of heme-oxygenase is linked to the production of bilirubin and biliverdin (already mentioned), which administration after the first few weeks of life in the doses slightly above normal levels resulted in cytoprotective effects.

Another approach to activating vitagenes is administration of nutritional antioxidants. Curcumin, the most prevalent nutritional and medicinal compounds used by Indian populations, has the potential to inhibit lipid peroxidation, and efficiently neutralize reactive oxygen and nitrogen species. It has been recently shown that curcumin inhibits NF-κB activation and induces heme-oxygenase-1. Caffeic acid phenethyl ester, an active component of propolis, has been shown to induce hemeoxygenase-1 in astroglial cells. Gene induction in both the cases occurs through the antioxidant response element (ARE), and this led to the conclusion that the increased expression of genes regulated by the ARE may provide CNS with protection against oxidative stress. Indeed numerous studies have supported a role for ARE activators in the prophylaxis against acute and chronic neurodegenerative conditions.

Antiinflammatory and antiapoptotic treatments will have also shown benefit for many forms of neurodegeneration, although it is also becoming clear that the parts of the inflammatory response must be maintained to facilitate repair.

A recent development in chelators involves the design and synthesis of multifunctional drugs that have the ability to bind iron, inhibit a particular enzyme, and exhibit antioxidant properties (free radical scavengers). Metal, and in particular, iron chelation therapy has been proposed as a way of reducing the level of redox active metals in neurodegenerative diseases. The green tea catechin, EGCG, which is known for its iron-chelating and antioxidant properties, the antibiotic iron chelator clioquinol, and intracerebroventricularly injected desferal (DFO) are potent neuroprotective agents. Obviously, iron chelation targets not only unbound iron and that in the aggregated deposits, but also, more significantly, iron-dioxygenases such as HIF prolyl hydroxylase. The latter is emerging target for neuroprotection although HIF may be not the only substrate of this enzyme. More than 70 genes of putative nonheme iron oxygenases have been identified in the human genome, but only a number of them have the physiological functions ascribed. An assumption on the uniqueness of an inhibitory action of a particular drug selected among others may be wrong, if only one enzyme candidate has been tested. The best example is probably EGCG, which targets HIF prolyl hydroxylase, MAO B, and MICAL, a flavin monooxygenase implicated into axonal guidance and highly homologous to MAO B. The recently discovered M30 as an antioxidant/chelator/MAO inhibitor was also shown to stimulate neurite outgrowth and thus may actually target MICAL as well.

Conclusion

Therapies targeted at reducing oxidative damage in the nervous system must achieve several goals in order to be effective. First, they must interdict pathological oxidant interactions without affecting physiological signaling by radicals. Over the past two decades, peroxide and nitric oxide were shown to play the role of messengers in the nervous system. Antioxidants that inadvertently abrogate these signaling functions would not be desirable. Second, antioxidants or alternatively effective repair strategies must be augmented in distinct cell types and subcellular compartments. Oxidative and nitrosative stress are not an undifferentiated whole and are mediated by distinct species produced in distinct cellular compartments and distinct cell types. The great challenge has been to divine a multimodal strategy that inhibits a cassette of targets without the expected toxicity that arises as the specificity of the therapy decreases. We propose that understanding endogenous homeostatic pathways for protecting against oxidative and nitrosative stress is the way forward. These homeostatic pathways involve the activation of preexisting proteins as well as de novo gene expression. Small molecules that activate homeostatic responses to oxidant stress are expected to reap large therapeutic benefits. Evidence that such an approach is effective and safe continues to emerge from preclinical studies. The ultimate proof will be the demonstration of neuroprotection in a human clinical trial. Such success will also provide long overdue evidence supporting a role for oxidative damage in human neurological disease.

See also: Complex I Deficiency; Dopamine; Mitochondrial Dysfunction; Monoamine Oxidase Type B Inhibitors; Nitric Oxide; Parkinson's Disease: Genetics; Proteasome Function in Movement Disorders.

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Painful Limbs Moving Extremities (PLME)

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Historical Note and Typical Variant

The syndrome 'painful legs and moving toes' (PLMT) was initially described by Spillane et al., when in 1971 they described six patients manifesting spontaneous causalgic pain in at least one lower limb and involuntary foot and toe movements. The movements and pain typically affected one side, subsequently spreading to the contralateral side. Resolution on one side in case of bilateral localization of the symptom onset was possible, whereas reduction of pain in some cases or increase in others occurred following voluntary inhibition of movements. Moreover, an increase in the amplitude of the movements was linked to exacerbation of pain and the severity of pain tended to correlate with the amplitude of movements. Since the periodic involuntary movements may affect both the upper and lower limbs, the term painful limbs/moving extremities (PLME) has been subsequently suggested for this movement disorder.

Pathogenesis of PLME

Despite that a rather simplistic approach to the pathophysiologic mechanism underlying PLME involves hyperexcitability of peripheral nerve fibers, several studies have suggested that central region may be the source of the complex patterns of muscle activities. However, the level of central involvement is currently under debate. In any case, it should be mentioned that most of the proposed pathogenetic mechanisms have been proposed based on studies of single cases or small case series.

As previously mentioned, peripheral nervous system (PNS) damage, including peripheral nerve, plexus, or spinal root lesions, can induce PLME. Lesions in the PNS may rarely evoke semirhythmic or rhythmic involuntary movements of the limbs without pain, which is one of the cardinal symptoms of PLME. Peripheral nerve lesions are able to influence the normal interrelation between the afferent information and the motor system. Alterations in afferent sensory information with subsequent reorganization of segmental or suprasegmental efferent motor activity and more specifically, structural damage of somatosensory pathways caused by injury of A delta and C fibers may be responsible for the genesis of involuntary movements.

Kinesiologic electromyography (EMG) pointed toward a common central oscillator for finger movements in PLME affecting both sides. In the latter study, somatosensory-evoked potential testing showed a marked attenuation of N20 potential recorded from the left somatosensory cortex, while paired transcortical magnetic stimulation of the left motor cortex suggested failure of cortical facilitation, thereby suggesting that the central oscillator responsible for finger movements is located above the level of the spinal cord.

Likewise, a central mechanism has been proposed by a similar case study, involving sensory-evoked potentials, back-averaging, cerebral MRI, and functional MRI. Nevertheless, cortical involvement was rather improbable due to the different levels of afferent and efferent pathways involved. Moreover, the functional MRI findings strongly argued against a cortical origin, as a reduction of activity in the motor cortex region of interest upon tactile stimulation compared with rest condition was not present. The authors proposed that the inhibitory effect of the sensory stimulus on both pain and movement could be viewed as a gating mechanism, tactile information acting on neuronal networks at a spinal cord level, inhibiting the transmission of pain to upper centers and acting on interneurons implicated in the genesis of the involuntary movement. On the other hand, the movement generator was localized below the spinal cord: a finding in keeping with previously published data suggesting that separate oscillators in the segmental interneuron pool of different spinal areas may drive individual movements in PLME.

Whether the level of dysfunction that produces alteration of the motor behavior is the spinal interneuron or

other supraspinal centers remains to be clarified. However, the coexistence of peripheral and central nervous system disorders increase the likelihood of abnormal sensory motor integration. The phenotypic variability and numerous associations of PLME point toward a complex etiology, involving purely central or a combination of peripheral and central cause at different levels (spinal and/or supraspinal).

Peripheral trauma remains the most accepted predisposing factor for the development of PLME. The development of dystonia secondary to peripheral trauma ('peripheral dystonia') supports this view and may well explain the potential cooccurrence of PLME with focal limb dystonia.

Clinical Characteristics of Syndrome

Characteristics of Pain

Pain and involuntary movements can occur simultaneously. However, although the reverse sequence may occur, pain usually precedes the involuntary movements and is rarely distributed to a specific peripheral or segmental dermatomal pattern. Ectopic and/or ephaptic excitation in damaged peripheral nerves may generate abnormal impulse transmission in peripheral sensory and sympathetic nerves, which afterward leads to a reorganization of the central processing of sensory information. This reorganization could be responsible for the spread of pain over areas that are not limited to a specific dermatomal distribution.

Pain is diffuse, burning, crushing, aching, or throbbing in character, varying in severity between patients from a constant discomfort to an intractable condition. Position does not influence pain, which could spread from one limb to the other, while its severity may increase with activity.

Cooccurrence of PLME with alterations of cutaneous sensation, such as hyperpathia and allodynia, is not uncommon and this fact supports the view of an analogy between PLME and complex regional pain syndrome type 2.

Characteristics of Finger Movements

Movements are spontaneous and purposeless, consisting of complex sequences of slow (1–2 Hz) involuntary, writhing, and wriggling movements of flexion–extension and/or abduction–adduction of at least one finger or toe flexion, extension, abduction, and adduction. Movements cannot be reproduced by unaffected persons or on unaffected sides in unilateral cases. The movements of each toe are independent of those of the others, in a pattern that is intermittent or continuous in the awake state and usually disappears at sleep. Voluntary inhibitory effort may temporarily suppress movements, while they may increase after mechanical stimulation or after consumption of a caffeine-containing drink.

Clinical Phenotypes of PLMT

PLME can also be identified as a syndrome with additional variants, that is, unilateral or involving only arms, only legs, or both arms and legs. Sole affectation of the upper limbs is rarely described. Painless arms/moving fingers (PAMF) is a rare variant of the PLME syndrome characterized by slow involuntary movements of the fingers without pain. To our knowledge, literature contains very few PAMF cases. PAMF cases are usually bilateral and are associated with PNS injuries or coexisting peripheral and central nervous system involvement.

Associations of PLME

Despite that several cases are idiopathic, associations with PLME can occur with central and/or PNS conditions. PLME has been suggested to be induced following entrapment neuropathy, that is, carpal tunnel syndrome, following viral central nervous system infections, due to deficiency in circulating adenosine levels, following ischemic stroke and Wilson's disease. Moreover, other conditions that have been previously linked to PLME include spinal cord or cauda equina injury, posterior nerve roots, lumbar and sacral radiculopathy, peripheral neuropathies, hypertrophic mononeuritis, alcoholic neuropathy, and traumatic lesions involving soft tissue and bone in the foot. PLME has been also reported to occur as a side effect of treatment with neuroleptics, anticholinergics, vincristine, cytarabine, and metronidazole.

More recently, PLME has also been reported in Hashimoto's disease. Basal ganglia abnormalities and central lesions have been topographically associated with PLME. In any case, peripheral tissue, nerve root, or dorsal column damage secondary to herpes zoster or HIV infection and trauma are the most common precipitant factors of PLME, thus pointing toward an overlap between PNS damage and movement disorder in the context of PLMT.

Diagnostic Tests

Despite that several methods, including clinical examination, laboratory, neurophysiological, and neuroimaging studies, are currently used to diagnose PLME, none of the tests is sensitive enough for or specific to this syndrome, mainly because they lack continuity. In the majority of cases, clinical examination, nerve conduction studies (NCS), EEG pattern, and cerebrospinal fluid assay reveal no abnormalities, excepting cases with PLMT and peripheral or entrapment neuropathies, where clinical examination and NCS are abnormal.

Concerning the neuroimaging studies, spine MRI, or computed tomography (CT) are mostly used to rule out PLME syndrome secondary to common vertebral abnormalities, such as stenosis and disc degeneration. In fact, neuroimaging reveals only mild findings in these cases, whereas myelography usually shows minor and nonspecific changes. Unlike that, literature contains very few reports of cases in which irritation of neuronal tissue was shown on nerve biopsy, it is widely accepted that nerve biopsies in the context of PLME are usually normal.

It has been previously reported that EMG studies may reveal abnormalities. However, it should be mentioned that they lack continuity. Schoenen et al. described two distinct EMG patterns that have been related to different causes, including a pattern of short, erratic, low-amplitude discharges in foot and leg muscles, and a complex alternating pattern of long-duration high-amplitude bursts in antagonistic muscles. In the first pattern, the physiopathologic mechanism was suggested to act in the periphery, while in the second pattern the resultant cause was of central origin, implying a more general disturbance of sensorimotor control in the context of an overlap of both peripheral and central cause. On the other hand, others support that the movements are generated by long-duration bursts of activity, comprising normal motor units and normal recruitment patterns.

Finally, taking into consideration that symptoms of PLMT may worsen during periods of psychologic stress, the implication of the sympathetic nervous system in generating PLME has been also previously suggested. Therefore, the activation of sympathetic nervous system through the Valsava or cold pressor tests may have a diagnostic role. However, since others have reported opposite results, further study is warranted before definite conclusions about the potential involvement of sympathetic nervous system in the syndrome of PLMT can be drawn.

Differential Diagnosis of PMLE

There are several conditions that have to be ruled out before a firm diagnosis of PLME is to be made. Restless leg syndrome (RLS) is one of these conditions. However, in RLS, pain and movements are related to the sleep–wake cycle and are relieved by lower limbs movement or walking. Additionally, the spontaneous toe movements in PLMT are different from the voluntary fidgeting movements that diminish the distress of RLS.

The characteristics of PLME may resemble those of segmental myoclonus and epilepsia partialis continua. The main difference of PLME and spinal segmental myoclonus is the lack of pain in the context of the second entity. On the other hand, as opposed to PLME, EEG changes are present in epilepsia partialis continua, whereas loss of reciprocal innervation is seen in epilepsia partialis continua and not in PLME syndrome.

On the basis of the association with traumatic events and the presence of Sudeck's atrophy, there have been previously suggested similarities between PLMT and reflex sympathetic dystrophy. However, common vasomotor or trophic changes occurring with reflex sympathetic dystrophy or its kindred causalgia are lacking in the context of PLMT. Additionally, there are also reports describing causalgia and involuntary limb movements (spasms of amputation stumps or 'jumpy stumps') after the occurrence of a severe trauma to the affected limb. Finally, there might occur a link between posttraumatic dystonia and PLME syndrome and therefore posttraumatic dystonia has as well to be excluded.

Treatment Options in PLME

To date, there is no effective prophylactic treatment against PLME and treatment is merely symptomatic. The armamentarium of pharmacological agents commonly used for the symptomatic treatment of PLME include oral medications such as baclofen, clonazepam,carbamazepine, tricyclic antidepressants, β-blockers, and corticosteroids. However, disappointingly, there are a few reports of success and only modest symptomatic relief was observed after the administration of such treatment schedules. In some patients with PLMT, the pain can be severe and unbearable, failing even high doses of opioids.

Additionally, in the 1980s, Progabide, a γ-aminobutyric acid (GABA) receptor agonist has been previously used with some measure of success. More recently, Gabapentin, a novel anticonvulsant having an effect on voltage-dependent Ca^{2+} channel currents at postsynaptic dorsal horn neurons, has been proposed as being able to be effective against PLMT syndrome through peripheral or central nervous system effect, modulating an abnormal sensory processing in the spinal cord.

The use of botulinum toxin type A injections has been previously reported as being able to provide benefit in a single case of the PAMF variant of PLMT. Treatment with Botulinum toxin type has been reported to result in both pain relief and the improvement of involuntary movements due to reduction of muscle spindle discharge leading to a decreased activity of gamma loop and central sensitization; antisympathetic, antiglutamergic, and antiinflammatory effects; and the inhibition of local pain neurotransmitters.

Among nonpharmacological approaches, the use of lumbar neural blocks has been commonly reported in PLME, providing transient relief in about 50% of patients. Repeated or continuous lumbar epidural block provided some degree of symptomatic benefit to PLMT patients. However, symptoms recurred subsequently after treatment. In any case, lumbar epidural block may be considered as the

treatment of choice if pain is due to the involvement of posterior nerve roots and peripheral nerves.

Literature contains a case report of successful use of epidural spinal cord stimulation against the symptoms of PLME. Epidural spinal cord stimulation is a useful treatment for a variety of painful conditions, including neuropathic pain, pain in peripheral vascular diseases, complex regional pain syndrome, failed back surgery, and angina pectoris. Finally, in a single report, unilateral painful hand and moving fingers significantly improved (movement and pain) following tactile stimulation with a glove.

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Paired Pulse TMS

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Glossary

CBI – Cerebellar inhibition; inhibition of motor cortex due to stimulation of the contralateral cerebellum.
CS – Conditioning stimulus; stimulus given prior to the test stimulus and is designed to the response to test stimulus.
ICF – Intracortical facilitation; facilitation of the motor cortex by a subthreshold conditioning stimulus delivered 8–30 ms before a test stimulus.
IHI – Interhemispheric inhibition; inhibition of the motor cortex produced by stimulation of the contralateral motor cortex at interstimulus intervals between 6 and 50 ms.
LAI – Long latency afferent inhibition; inhibition of the motor cortex by contralateral median nerve stimulation ~200 ms earlier.
LICI – Long interval cortical inhibition; inhibition of the motor cortex by suprathreshold conditioning stimulus to the motor cortex ~50–200 ms earlier.
LIHI – Long interval interhemispheric inhibition; IHI at long intervals of ~40 ms.
M1 – Primary motor cortex.
MT – Motor threshold; the lowest stimulus intensity capable of eliciting small motor-evoked potentials.
SAI – Short latency afferent inhibition; inhibition of the motor cortex by contralateral median nerve stimulation ~20 ms earlier.
SICF – Short interval intracortical facilitation; facilitation of the motor cortex by two suprathreshold to threshold second stimuli at ISIs of 1.1–1.5 ms (SICF-1), 2.3–3.0 ms (SICF-2), and 4.1–5.0 ms (SICF-3).
SICI – Short interval intracortical inhibition; inhibition of the motor cortex by a subthreshold conditioning stimulus delivered 1–6 ms before a test stimulus.
SIHI – Short interval interhemispheric inhibition; IHI at intervals of 8–12 ms.

Definition and History

The use of paired transcranial magnetic stimulation (TMS) to study cortical inhibition and facilitation was first described by Kujirai et al. in 1993. Many other protocols have since been described. Paired TMS involves delivering two TMS pulses at different interstimulus intervals (ISI) to study the physiology of intracortical circuits. The first pulse is known as the conditioning stimulus (CS) and the second as the test stimulus (TS). Motor cortical excitability is usually calculated as the ratio of motor evoked potential (MEP) amplitude or the area produced by CS followed by TS to that of TS alone. The cortical circuits activated depend on the stimulus intensities (different thresholds for different circuits), ISI, area of stimulation, and coil orientation (activation of specific neuronal populations is sensitive to current direction). The different protocols can be broadly classified as shown in **Figure 1**. The methodology and properties of these protocols and the findings in several common movement disorders are summarized in **Table 1** and are discussed below.

Parkinson's Disease (PD)

Short interval intracortical inhibition (SICI): Several studies found reduced SICI in resting PD patients in the off state and normalized in the medication state. However, some studies reported normal SICI and reduced SICI may be due to increased facilitation rather than reduced inhibition. Active SICI appeared unchanged in PD. Since SICI is reduced prior to and during voluntary movement, reduction of SICI in PD may be a compensation for bradykinesia to make movement easier, and may explain the normal active SICI.

Long interval cortical inhibition (LICI): Some studies found increased and others found decreased rest LICI in PD. Active LICI was found to be increased. These abnormalities normalize with dopaminergic medications. The opposite findings for SICI and LICI may be because LICI inhibits SICI.

Intracortical facilitation (ICF): In advanced PD, ICF was reduced.

Interhemispheric inhibition (IHI): IHI was reduced in PD patients without mirror movement, especially at long ISIs of 20–50 ms.

Short and long interval afferent inhibition (SAI & LAI): In PD, SAI was found to be normal in patients off medications but levodopa administration reduced SAI. In contrast, LAI is reduced in PD and is unaffected by medications.

Effects of deep brain stimulation (DBS): Internal globus pallidus (GPi) DBS may increase SICI in patients off medications. Subthalamic nucleus (STN) DBS increased SICI in PD patients on and off medications, similar to the effects dopaminergic drugs. GPi and STN stimulation have different effects on cortical circuits and may be related to their different clinical effects. STN DBS normalized both SAI and LAI in PD patients.

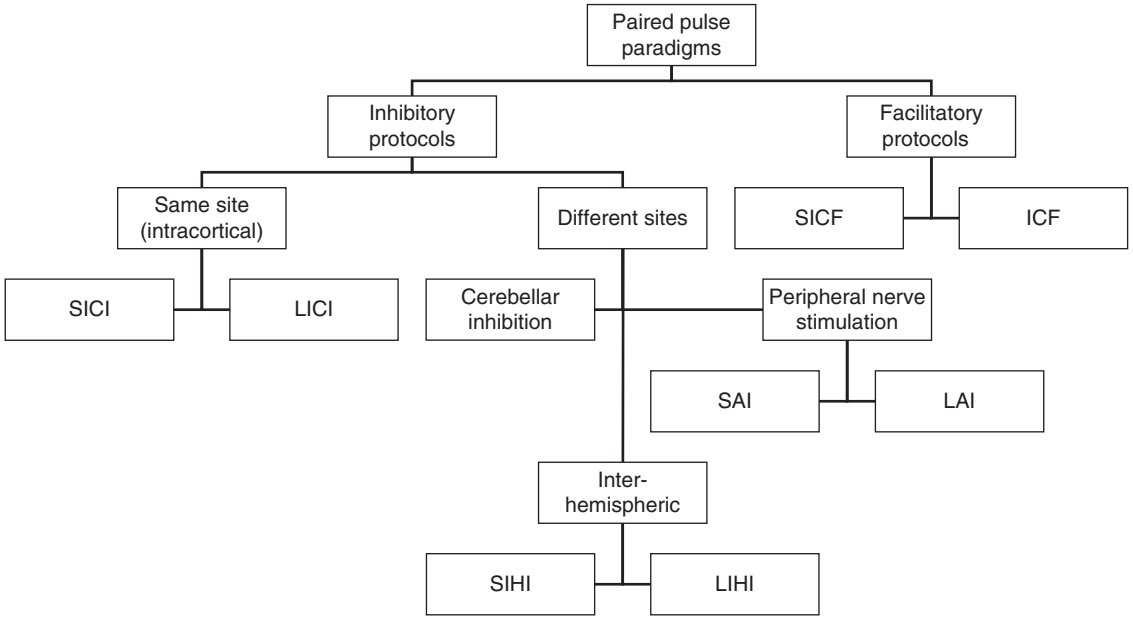

Figure 1 Classification of different paired pulse paradigms. CBI, cerebellar inhibition; ICF, intracortical facilitation; LICI, long interval intracortical inhibition; LIHI, long interval interhemispheric inhibition; LAI, long latency afferent inhibition; SAI, short latency afferent inhibition; SICI, short interval intracortical inhibition; SICF, short interval intracortical facilitation; SIHI, short interval interhemispheric inhibition.

Table 1 Summary of the properties of different forms of cortical inhibition and facilitation and their findings in several common movement disorders

	SICI	*LICI*	*SICF*	*ICF*	*SIHI*	*LIHI*	*CBI*	*SAI*	*LAI*
Method									
Conditioning stimulus/S1 for SICF	Subthreshold TMS	Suprathreshold TMS	Suprathreshold TMS	Subthreshold TMS	Suprathreshold TMS	Suprathreshold TMS	Cerebellar stimulation	Median nerve stimulation	Median nerve stimulation
Test stimulus/S2 for SICF	Suprathreshold TMS	Suprathreshold TMS	Subthreshold TMS	Suprathreshold TMS	Suprathreshold TMS	Suprathreshold TMS	Suprathreshold TMS	Suprathreshold TMS	Suprathreshold TMS
Interstimulus interval (ms)	1–6	50–200	1.0–1.5, 2.3–3.0, 4.1–5.0	8–30	8–12	~40	5–7	~20	~200
Proposed neurotransmitter/ receptor	$GABA_A$? dopamine	$GABA_B$	?Glutamate (↓ by $GABA_A$)	Glutamate	?	$GABA_B$	?	ACh ↑ by $GABA_A$	?
Findings in movement disorders									
Parkinson's Disease	↓ or ↔	↑ or ↓	?	↔	↔	↑	?	↔(↓ on meds)	↓
Dystonia	↓	↓ or ↑	?	↔	↓	?	?	↔	↓
Cerebellar degeneration	↔	↑	?	↓	?	?	↓	?	?
Huntington's disease	↓	↓	?	↑or ↓	?	?	?	↔	?
Myoclonus	↓	↓ (PME)	?	↔	↓	↓	?	↓	↓
Essential tremor	↔	↔	?	↔	?	?	?	?	?

ACh, acetylcholine; CBI, cerebellar inhibition; ICF, intracortical facilitation; GABA, γ-aminobutyric acid; LICI, long interval intracortical inhibition; LIHI, long interval interhemispheric inhibition LAI, long latency afferent inhibition; SAI, short latency afferent inhibition; SICI, short interval intracortical inhibition; SICF, short interval intracortical facilitation; SIHI, short interval interhemispheric inhibition; PME, progressive myoclonic epilepsy; ↓, decreased; ↑, increased; ↔, no change; ?, unknown.

Dystonia

SICI: SICI is decreased in resting hand muscles in upper limb dystonia, blepharospasm, cervical dystonia, Dopa-responsive dystonia, asymptomatic carriers of the DYT1 gene as well as in psychogenic dystonia. Therefore, intracortical inhibition is reduced when patients with dystonia are at rest and not expressing symptoms, in unaffected body parts and in asymptomatic gene carriers. The modulation of SICI by voluntary movement is also impaired in focal hand dystonia (FHD).

SAI and LAI: In FHD, LAI is diminished whereas SAI is normal. Other studies showed altered responses to sensory stimuli and surround inhibition. In a study of sensorimotor integration, focal muscle vibration reduced SICI in healthy subjects but not in writer's cramp patients. Patients with musician's cramp patients exhibited reduced SICI in both vibrated and nonvibrated muscles. These findings suggest different underlying pathophysiology for these types of FHD.

LICI: Resting LICI is reported to be normal in writer's cramp, and decreased in a group of mixed dystonia subjects and in psychogenic dystonia. LICI during voluntary activity was found to be decreased in writer's cramp but increased during slight contraction in a mixed group of dystonic subjects.

ICF: ICF was found to be normal or slightly increased in dystonia.

Chorea

SICI and ICF: In symptomatic Huntington disease (HD), SICI was reduced while ICF was enhanced in one study. SICI and ICF changes were related to clinical rating of chorea, but not to HD severity. However, in another study of chorea due to various etiologies (including HD), the time course and amount of SICI were normal. A more recent study observed decreased ICF and only a tendency for reduced SICI in HD. ICF correlated with the functional capacity scores of the Unified Huntington Disease Rating Scale (UHDRS). These different results may be due to different underlying diseases, disease stages, and study methods.

Tourette Syndrome

Several studies demonstrated reduced SICI in Tourette syndrome (TS). In untreated TS patients, SICI thresholds measured with a range of conditioning intensities were similar to controls, but at higher intensities, SICI was recruited more gradually than controls. Reduced intracortical inhibition may release involuntary movements in TS.

Myoclonus

SICI: SICI is reduced in various conditions associated with myoclonus such as progressive myoclonic epilepsy (PME) and juvenile myoclonic epilepsy (JME). Reduced SICI in cortical myoclonus likely represent impaired GABAergic inhibition that may be a mechanism of myoclonus, whether of epileptic origin or not. Interestingly, reduced SICI was associated with the spread of cortical hyperexcitability, suggesting that reduced inhibition may facilitate the spread of cortical activity responsible for the jerk. Recently, reduced SICI and normal ICF were also observed in familial cortical myoclonic tremor with epilepsy, a condition characterized by postural and action tremor, myoclonus, epilepsy, and cognitive impairment with autosomal dominant inheritance.

LICI and ICF: LICI was found to be normal in patients with JME, but reduced in patients with PME. ICF was normal in most cases of myoclonus.

SAI and LAI: Patients with PME had MEP facilitation rather inhibition following peripheral nerve stimulation.

IHI and IHF: Patients with benign myoclonic epilepsy had increased IHF and reduced IHI, which may play a role in the spread of myoclonic activities. TMS studies also provided evidence for cortical involvement of myoclonus in corticobasal degeneration, consistent with hyperexcitability of the sensorimotor cortex.

Essential Tremor

TMS studies showed normal cortical excitability in essential tremor (ET) and primary writing tremor.

Ataxia

SICI and ICF: SICI is normal in various forms of ataxias whereas ICF was reduced, which may be due to the reduced excitatory drive from deep cerebellar nuclei. Interestingly, ICF was reduced in spinocerebellar ataxia (SCA) 2 and SCA3, but not in Friedreich's ataxia, SCA1, or SCA6, suggesting that reduced ICF may be linked to the genotype. However, ICF did not correlate with the disease severity.

Conclusions

Paired pulse TMS techniques demonstrated abnormalities of SICI, LICI, ICF, SAI, LAI, and IHI in patients with movement disorders (**Table 1**). The most consistent finding is the reduction of SICI reported in dystonia and cortical myoclonus. A limitation for using SICI in

diagnostic workup is that SICI can be abnormal in different types of movement disorders. In addition, the variability of SICI can be high and SICI measures often overlap between patients and normal subjects. Paired pulse studies are, therefore, not of sufficient specificity to distinguish different movement disorders. However, the study of cortical inhibition and facilitation using paired TMS had provided important information on the pathophysiology of different movement disorders.

See also: Ataxia; Brainstem Reticular Myoclonus; Cortical Myoclonus; Cortical Tremor; Dystonia; Electromyography (EMG); Huntington's Disease; Motor Evoked Potential; Myoclonus; Myoclonus, Animal Models; Myoclonus, Epileptic; Myoclonus-Dystonia/Essential Myoclonus; Palatal Myoclonus; Palatal Tremor; Parkinson's Disease: Definition, Diagnosis, and Management; Postural Tremor; Primary Orthostatic Tremor; Propriospinal Myoclonus; Rest Tremor; rTMS; Single Pulse TMS; Spinal Segmental Myoclonus; Tourette Syndrome; Tremor; Tremor, Essential (Syndromes); Tremor, Essential: Genetics; Tremor, Holmes.

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Palatal Myoclonus

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Glossary

EPT – Essential palatal tremor (rhythmic movements of the soft palate, usually with an ear click).
PT – Palatal tremor (rhythmic movements of the soft palate).
SPT – Symptomatic palatal tremor (rhythmic movements of the soft palate, and often other brainstem innervated or extremity muscles).

Definition and History

Palatal myoclonus is a rare movement disorder consisting of brief and rhythmic movements of the soft palate. It was described in 1886 by Spencer. Initially, it was most commonly referred to as 'palatal myoclonus,' but at the First International Congress of Movement Disorders in 1990, it was renamed 'palatal tremor.' The difficulty in phenomenological classification is due to the combination of tremor and myoclonus characteristics of the palatal

movements. The movements are less 'shock-like' and more regular and continuous than that are typically seen in myoclonus. The frequency of the tremor is highly variable among different patients and may vary within a single individual, illustrating the atypical features of the tremor.

There are two different forms of palatal tremor: essential palatal tremor (EPT) and symptomatic palatal tremor (SPT). In EPT, palatal tremor and ear clicks are the sole clinical manifestations of the disorder, whereas in SPT, tremor may involve facial, ocular, and extremity muscles. Ear clicks are usually absent. The underlying cause of EPT remains largely elusive, whereas in SPT, very often a causative lesion can be demonstrated in the dentato-olivary tractus, leading to olivary pseudohypertrophy. Early references of such hypertrophy already date from 1887 from Thomas and Marie and Guillain and subsequently from van Bogaert and Bertrand in 1928.

Pathogenesis and Pathophysiology

About 75% of PT cases are considered symptomatic (SPT) because of structural lesions of the brainstem or the upper cerebellar peduncle (within the Guillain–Mollaret triangle) with subsequent hypertrophic olivary degeneration. Microscopically, the neurons of the inferior olive are enlarged with cytoplasmic vacuolation. Hypertrophy develops ~3 weeks after the lesion, and symptoms start after a variable time delay from 2 to 49 months. Multiple causes for the structural lesions have been described, but in the majority of cases, a vascular lesion can be demonstrated. Multiple sclerosis, metastatic and astrocytic tumors, syringobulbia, and trauma have been occasionally reported as other causes.

The development of SPT after disruption of the dentato-olivary tract is thought to result from a reduction in inhibitory GABAergic input from the dentate nucleus and a successive increase in synchronization of the olivary neurons, leading to an autonomously working olivary oscillator. This is supported by the persistence of PT during sleep and the observation that the rhythm of SPT does not change after a masseter or blink reflex stimulus. The abnormal rhythm of the olivary oscillator is carried through the inferior cerebellar peduncle to the contralateral cerebellar hemisphere and subsequently interferes with the cerebelloreticular systems, leading to the rhythmic activity of brainstem muscles.

In 25% of PT cases, a structural lesion cannot be identified and PT is classified as 'essential' (EPT). However, 'essential' PT differs from other 'essential' movement disorders that are idiopathic, often familial, disorders with well-defined natural histories. In the case of EPT, 'essential' is better considered to be synonymous with 'isolated', meaning that tremor occurs in the absence of other neurological symptoms. The pathophysiological mechanism in EPT is unknown. EPT is clearly not a simple functional variant of SPT, because the palatal muscles that are activated in the two conditions are different. EPT is considered to be a heterogeneous disorder with a considerable proportion of EPT cases having 'voluntary' control over the movements. This voluntary control may be the result of a special skill to open and close the Eustachian tube, which has been reported in scuba divers. On the other hand, a psychogenic origin must be suspected in EPT patients with voluntary control over the palatal movements, especially in the context of other features, suggesting a psychogenic origin.

Epidemiology, Clinical Features, and Diagnostic Criteria

Prevalence data of PT are lacking. In literature, a few hundred cases have been described. The male:female ratio is about 1:1 with a male preponderance in SPT. Age of onset ranges from 4 to 74 years. The movements in PT may be uni- or bilateral and completely or only partially rhythmic (irregular). In EPT tremor ceases during sleep, whereas in SPT tremor may persist. The muscle involved in EPT is the tensor veli palatini, which is innervated by the fifth cranial nerve and is supposed to induce the ear clicks because of the opening of the Eustachian tube by its contraction. Other muscles restricted to the oropharyngeal region may be involved. Ear clicks are often the only complaint, but may be very distressing. In SPT, the levator veli palatini muscle, which is innervated by the ninth and tenth cranial nerves is responsible for the movements of the soft palate. Frequently, extrapalatal muscles are involved, including ocular and extremity muscles. Typically, additional signs of cerebellar or brainstem dysfunction such as ataxia or nystagmus are present in SPT and are the major cause of discomfort and disability.

Differential Diagnosis

As outlined above, PT is phenomenologically classified as tremor. Associated brainstem or cerebellar symptoms separate SPT from EPT (**Table 1**). Some EPT patients can suppress the palatal movements by changing neck position or by digital pressure behind the mastoid, which could be considered as sensory tricks. This may suggest that EPT is a pure dystonic tremor. PT patients may have an urge to perform the movements and are able to voluntarily suppress the movements for a few seconds, suggesting that EPT is a tic disorder. However, continuous rhythmic movements are seldomly described as a form of tic. The diagnosis of psychogenic PT must be considered in the presence of red flags for a psychogenic movement disorder (**Table 2**)

Table 1 Characteristics of SPT and EPT

	SPT	*EPT*
Cause	Cerebrovascular disease, degenerative, multiple sclerosis, trauma causing a lesion in the dentato-olivary pathway	Unknown
Presenting symptom	Usually not ear click	Ear click
Other symptoms	Ataxia, dysarthria or nystagmus	None
Muscles involved	Levator veli palatini and frequently extrapalatal	Tensor veli palatini and/or adjacent muscles
Presence in sleep	Often	Rarely
MRI	Olivary hypertrophy causative lesion	Normal

Table 2 Red flags suggesting a psychogenic origin of PT

Distractibility
Variability
Involvement of extrapalatal muscles clinically distinct from those seen in SPT
Emotional trigger (acute onset)
Trivial trauma preceding onset
Response to verbal suggestion or hypnosis
Response to nonphysiological treatment or placebo
Long lasting benefit from short-acting drugs (prolonged submission after a single treatment with botulinum toxin
Presence of other psychiatric features

Source
Zadikoff C, Lang AE, and Klein C (2006) The 'essentials' of essential palatal tremor: a reappraisal of the nosology. *Brain* 129: 832–840.

Diagnostic Work-up

In SPT, magnetic resonance imaging (MRI) of the brain frequently shows a hyperdense signal of the ventral upper medulla, that is olivary pseudohypertrophy, on T2-weighted or proton density images. Sometimes, the causative lesion in the dentato-olivary tract can also be demonstrated. In EPT, no structural abnormalities are shown on brain MRI. Laboratory findings are normal. Brainstem reflex patterns may be studied but usually do not give additional information for the diagnosis in clinical practice. Neurophysiological studies, including entrainment, may be helpful in the diagnosis of psychogenic PT.

Management and Prognosis

PT is generally considered a lifelong disorder although in rare cases spontaneous remissions have been reported. Treatment is based on anticonvulsants or sedatives with often disappointing effects. Single cases have been described with a favorable response to clonazepam, trihexyphenidyl, or valproate. Surgical therapeutic options have been tried, but none with reproducible results. Injections with botulinum toxin have been successful in a few published case series, and it is considered the treatment of first choice by some physicians.

See also: Palatal Tremor.

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Relevant Websites

www.movementdisorders.org – Movement Disorder Society.

Palatal Tremor

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Glossary

Guillain–Mollaret triangle – The pathway interconnecting the dentate nucleus of the cerebellum, the red nucleus of the midbrain, and the inferior olivary nucleus of the medulla.

Definitions

Palatal tremor (PT) and palatal myoclonus (PM) are the same entity. Although initially always called myoclonus, the consistent rhythmicity has spawned the 'tremor' description. That said, other segmental myoclonus is rhythmic, PT does not oscillate around a point, which

tremor normally does, and the quick myogenic bursts are consistent with myoclonus. We will subsequently refer to this entity as tremor but rhythmic myoclonus may be a more accurate description. PT is observed as upward or lateral deviation of the soft palate. The frequency usually ranges from 0.5 to 3 Hz. Patients may or may not feel the movements, and occasionally they are painful or result in subjective respiratory difficulty or dysphagia. The cycle of PT is not reset by stimulation of trigeminal afferents nor does Valsalva maneuver consistently affect the rhythm or frequency.

Differential Diagnosis

The differential diagnosis for involuntary palatal movements is minimal, but includes tics (usually not rhythmic), myokymia (more continuous), fasciculations (not rhythmic), and psychogenic/volitional cases. PT is considered uncommon but formal epidemiology is lacking. PT is also segregated into essential or primary (EPT) when the PT occurs in isolation without evidence of other neurological problems or cause, and secondary or symptomatic (SPT) when PT occurs as part of a larger illness. SPT is more common than EPT.

Primary versus Secondary PT

The cause of EPT is not known, and some postulate multiple pathophysiologies. One concordant pair of monozygotic twins has been reported. One case of EPT and epilepsy demonstrated serum autoantibodies directed against glutamic acid decarboxylase. No actual pathology has been identified.

In contrast, SPT results from lesions within the dentato-rubro-olivary pathway 'Guillain–Mollaret triangle' (**Figure 1**). Other CNS anatomy is occasionally reported. Stroke, hemorrhage, neoplasm, abscess, arteriovenous malformations, ectatic arteries, and trauma are the most common etiologies. Usually, the SPT presents weeks to a year after the original insult. Other subacute and less-localized 'lesions' have also been associated with SPT. Reported causes include heat stroke (associated with Purkinje cell loss), Hashimato's encephalopathy with antithyroid antibodies, celiac disease (associated with cerebellar ataxia), IgM M-protein that specifically bound to GM1 in the inferior olive nucleus (ION) and dentate nucleus, Alexander's disease in children and adults, epilepsy partialis continuum, and neuroferritinopathy.

Clinically, there are several differences between EPT and SPT (**Table 1**). Because EPT mostly involves the Guillain–Mollaret triangle, which opens the eustachian tube, it is classically associated with ear clicking that may even be audible to others. A separate tinnitus is also occasionally reported although some literature reports clicking and tinnitus synonymously. Auditory acuity is usually normal. In many cases these auditory symptoms are the most disabling feature. EPT is almost always bilateral and stops during sleep.

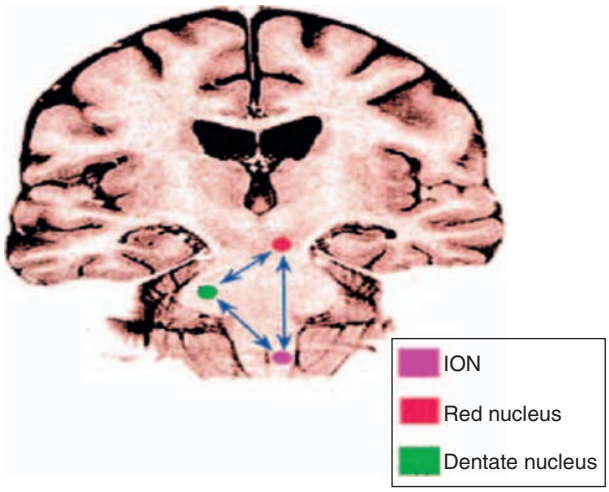

Figure 1 Dentato-rubro-olivary pathway, 'Guillain–Mollaret triangle.'

Table 1 Comparison of primary (Idiopathic) PT and secondary (Symptomatic) PT

	Essential PT	*Symptomatic PT*
Muscle	Tensor Veli Palatini (elevates)	Levator Veli Palatini (elevates)
Cranial Nucleus	V	VII and IX
Ear clicks	Yes	No
Inferior olive hypertrophy	No	Yes
Side	Always bilateral	Unilateral or bilateral
Age	Younger age	Older age
Sleep	Variable persistence during sleep	Persists during sleep

Modified from Deuschl et al.

SPT may be unilateral or bilateral, is not usually associated with clicking, may persist during sleep, and may involve extrapalatal anatomy. Synchronized ocular, facial, platysmal, neck/shoulder, and even arm myoclonus are reported with SPT. The ocular movements are variably described as ocular bobbing, pendular nystagmus, or ocular myoclonus. The extrapalatal anatomy may spread over time. In the absence of underlying neurological symptoms from an underlying lesion or extrapalatal anatomy, SPT may be relatively asymptomatic. Cases are often identified on examination in follow-up after patients had presented with a stroke or some other underlying pathology.

The most striking feature of SPT is the inferior olivary nucleus degenerative hypertrophy (IOHD) observed on T2 MRI and pathological examination (**Figure 2**). Most cases of SPT demonstrate this, and the anatomy correlates

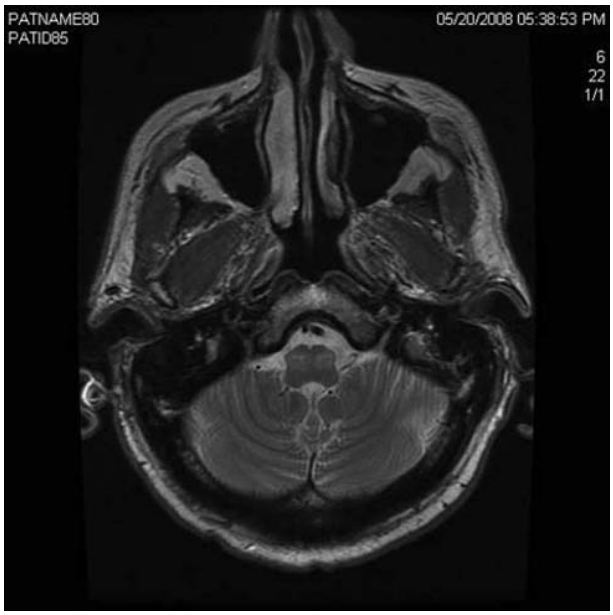

Figure 2 MRI showing modest bilateral degenerative hypertrophy of the inferior olive.

with the clinically involved side when unilateral. Radiographic IOHD precedes the development of SPT in most cases but both may resolve over months to years.

Radiographic IOHD does not necessarily result in SPT. One 12-patient series evaluating IOHD on MRI after a clinical insult to the Guillain–Mollaret triangle found only a single case of clinical SPT. The lesions resulting in IOHD (9 unilateral and 3 bilateral) were in the contralateral dentate nucleus (8), ipsilateral central tegmental tract (5), and contralateral superior cerebellar peduncle (2). The IOHD occurred within 3 weeks in the one case, and the radiographic signal intensity often lessened over years. Another series reported that 8 out of 16 subjects with IOHD and brainstem lesions had PT, appearing 1–2 months after insult in 7 out of 8 cases.

Pathologically, IOHD demonstrates marked neuronal loss in the inferior olivary nucleus (ION), gliosis, and degeneration of both the myelin and the axons of efferent fibers from the olivary neurons. Electromicroscopy shows numerous round, homogeneously electron-dense granules located within expanded cisternal profiles of rough endoplasmic reticulum (RER). These granules may consist of proteinaceous secretion of the RER. Other electron microscopic features of neurons of the hypertrophied olive are neurofilamentous hyperplasia, vacuoles of intermediate and large (up to 15 μm) size, and prominent intracytoplasmic protrusions by boutons containing dense core vesicles. Mitochondria also strikingly proliferate in the reactive astrocytes.

Although somewhat speculative, the ION abnormality is thought to result from loss of inhibition from cephalid structures. This results in toxicity and cell death within the ION. The remaining cells show increased activity and their output may subsequently damage cerebellar structures in some cases. In support of this, a 2-[18F]fluoro-2-deoxy-D-glucose PET study of six SPT and one EPT showed increased metabolic activity in the ION compared to controls. Functional MRI in one case of EPT also revealed increased putaminal activity, thought to result from disinhibition. Another study evaluating IOHD found that the dentate nuclei opposite of the affected ION showed mild-to-moderate shrinkage of the normal low-signal areas and increases in signal intensity on T2-weighted images in 4 of 5 patients. The cerebellar cortices on the same sides as the involved dentate nuclei showed atrophic changes in 4 of 5 patients.

Palatal Tremor/Ataxia Syndrome

Many patients with SPT have mild ataxia on examination. This is seen contralateral to the IOHD in unilateral cases. However, a subset of patients demonstrate an unexplained progressive ataxia associated with a variety of eye movement abnormalities and radiographic IOHD. Familial cases, possibly Alexander's disease, have been reported. Imaging may also demonstrate cerebellar atrophy, which is hypothesized to result from altered signaling from the IO. No specific treatments for the ataxia exist.

Treatment

Treatment for PT should only be initiated if the movements or ear clicking are problematic. There are no large treatment series or controlled trials to guide treatment decisions. A variety of pharmacologic interventions are occasionally effective, but results often lessen over time. SPT may respond better to pharmacotherapy, although small case series and reports often do not distinguish between them. Clonazepam and other benzodiazepines, high-dose piracetam (24–36 g per day), opioids, anticholinergic medications, baclofen, lamotragine, carbamazepine, phenytoin have been reported to improve PT. Sumatriptan transiently improved one case of EPT.

Volitional mouth movements and neck postures that presumably affect the eustachian tube and individually fitted dental appliances may improve the ear clicking. Botulinum toxin injected into the tensor veli palatini or levator veli palatini improves some cases of PT. This can be a delicate procedure, typically using only 2.5–10 units per side to minimize the risk of dysphagia. Unilateral injections are better tolerated. Radiofrequency ablation improved subjective clicking and observed movements in one case.

See also: Myoclonus.

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www.movementdisorders.org – Movement Disorder Society.

Pallido-Nigro-Luysian Degeneration

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Glossary

Hallervorden-Spatz syndrome – is a genetic disorder associated with brain iron accumulation. The features include dystonia, dysarthria, pigmentary retinopathy and characteristic MRI changes. Mutations in the gene encoding pantothenate kinase 2 underlie this disorder, now referred to as pantothenate kinase-associated neurodegeneration or PKAN.

Progressive supranuclear palsy (PSP) – is a pathologically defined, primary neurodegenerative disease characterized by motor disturbance, postural instability, cognitive dysfunction and eye movement abnormalities.

Supranuclear eye movement control – There are six extraocular mucscles innervated by the three cranial nerves, 3, 4, and 6. These control simple eye movements. The complex and precise array of eye movements that secure clear vision result from the supranuclear eye movement control centers that provide the oculomotor system the ability to maintain a target upon the fovea of the retina.

Definition and History

Pallido-nigro-luysian degeneration (PNLD) is a rare sporadic neurodegenerative disorder of adult age. PNLD has also been called as 'pallido-nigro-luysian atrophy (PNLA).' The term 'pallido-luysian atrophy' was used by Van Bogaert to report two patients with chorea and ballism; this term should not be confused with PNLD. The term 'progressive pallidal atrophy' (Progressive Pallidumatrophie in German) was used by Jellinger to include both pure pallido-nigro-luysian atrophy and extended forms of PNLA. The extended forms represent PNLA associated with degeneration of other systems. Neurodegenerative changes in the pallido-nigro-luysian system may be seen in association with other established condition such as motor neuron disease. It is not clear whether or not these extended forms can be included in the entity of PNLD. Also, the term 'pure pallidal degeneration' was used to report a patient with marked bradykinesia and dystonic posture in the neck and the trunk with marked pallidal degeneration without neuronal loss in the nigra and the subthalamic nucleus. Hunt also used the term 'progressive atrophy of the globus pallidus' for a patient with tremor dominant young onset parkinsonism.

But at that time, 'globus pallidus' included striatum as well; actually he described putaminal neuronal loss in his patient. These conditions should not be confused with PNLD. PNLD is rare but is a clear clinical and pathologic entity different from other system degenerations.

Pathology and Epidemiology

The core pathologic feature of PNLD consists of simple atrophy of the substantia nigra, globus pallidus, and the subthalamic nucleus (**Figure 1**). The substantia nigra shows severe depigmentation. Both segments of the globus pallidus show severe neuronal loss, fibrous astrocytosis, and loss of myelinated fibers (**Figure 2**). Argyrophilic neurons can be seen in the nigra, globus pallidus, midbrain tegmentum, and the pons and accumulation of tau protein can be demonstrated when immunohistochemical staining is used; however, neurofibrillary tangle formation is absent or rare, and even if present, its distribution is not typical of progressive supranuclear palsy (PSP). Spheroids may be seen but mainly in the globus pallidus and they are of the foamy type. In addition, some of the pathologically proven PSP cases show predominant involvement of the pallido-nigro-luysian system. In PNLD, usually neurofibrillary tangles and tufted astrocytes, which are pathologic hallmarks of PSP, are absent; another difference from PSP is the absence of grumose degeneration in the dentate nucleus of the cerebellum in PNLD; such pathologic differences discriminate PNLD from PSP. Iron may accumulate in the internal segment of the globus pallidus, but not so prominent as in Hallervorden–Spatz syndrome or pantothenate-associated neurodegeneration (PKAN). There is no epidemiological study on the prevalence of PNLD.

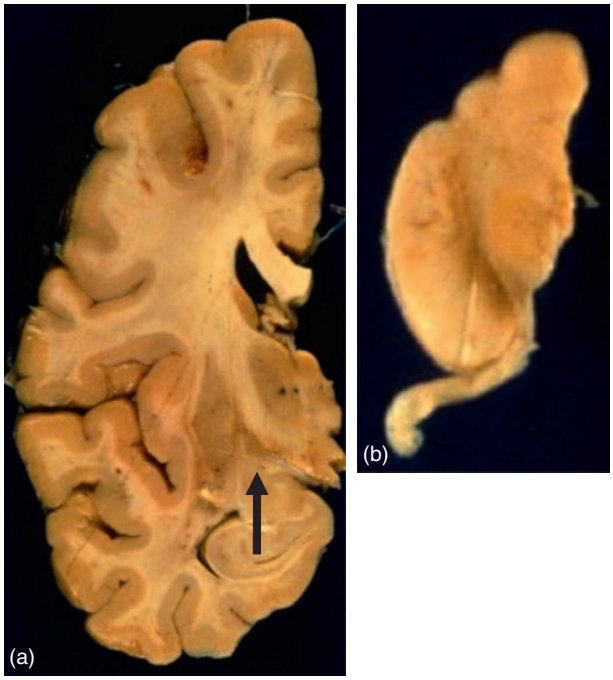

Figure 1 Macroscopic finding of the globus pallidus (a) and the substantia nigra (b). The globus pallidus looks smaller than normal indicating the atrophy (arrow). Marked depigmentation is seen in the substantia nigra.

Clinical Features and Diagnostic Criteria

The core clinical feature is parkinsonism consisting of bradykinesia, rigidity, postural instability, and rest tremor in some patients. The age of onset is usually between mid-fifties and mid-sixties. Initial symptom is either rest tremor or bradykinesia in one hand or gait disturbance starting on one side. Initial symptom can be frozen gait and start hesitation or palilalia. Supranuclear vertical gaze paresis, dystonic features, dysarthria, dysphagia, cognitive impairment, or muscular atrophy may set in some patients during the course of the disease. Clinical features mimic Parkinson's disease (PD) or PSP.

Diagnostic Work-up/Tests and Differential Diagnosis

Neuroimaging of PNLD is not specific. Atrophy of the midbrain tegmentum and the dilatation of the third ventricle, which are characteristic features of PSP, are not seen in PNLD. The eyes-of-the tiger pattern, which is a characteristic MRI finding of PKAN is not seen. Brain MRI can be essentially normal. No report is available on cardiac metaiodobenzyl guanidine (MIBG) scintigraphy in autopsy-proven PNLD; but I would assume MIBG uptake would be normal in PNLD. Cardiac MIBG diminishes in Lewy body PD and dementia with Lewy bodies (DLB) and in some advanced cases of multiple system atrophy (MSA).

Differential diagnosis includes PD, MSA, PSP, corticobasal degeneration (CBD), adult onset Hallervorden–Spatz syndrome, vascular parkinsonism, and drug-induced parkinsonism. Differential diagnosis of PD and DLB is usually not difficult. PD-patients respond to dopaminergic treatment and cardiac MIBG uptake is diminished. Differential diagnosis of PSP is at times not easy. Clinical features are similar, but supranuclear gaze paresis is usually absent or

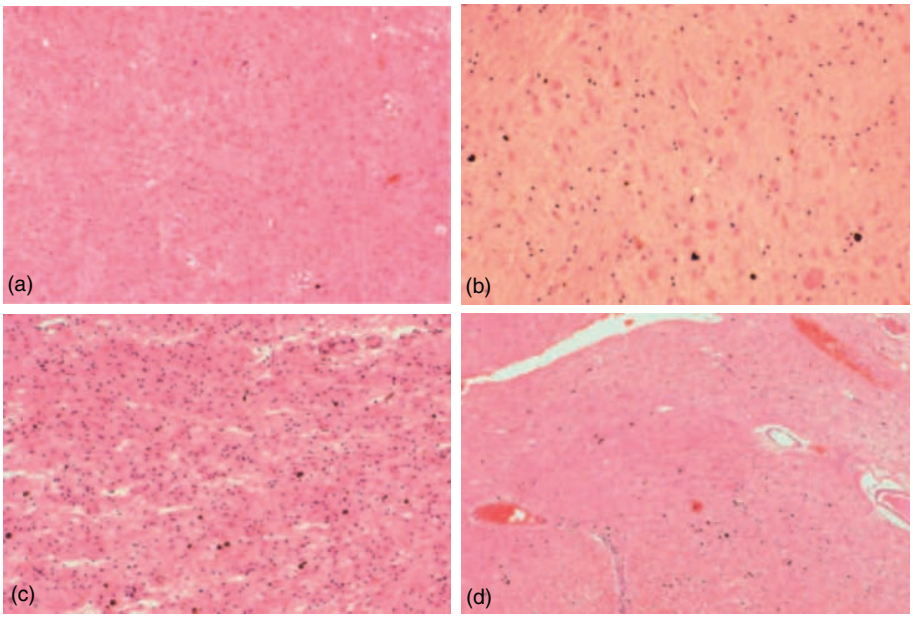

Figure 2 Histology of the internal segment of the globus pallidus (a), the external segment of the globus pallidus (b), the substantia nigra (c), and the corpus Luysi. Marked neuronal losses are seen in these structures, but no Lewy bodies or neurofibrillary tangles are seen. A few spheroids are seen in the external segment of the globus pallidus (c).

mild in PNLD. But some PSP patients show normal ocular movements, and in such case, differential diagnosis is almost impossible. There are cases where differentiation from PSP is difficult even after postmortem examination.

Management and Prognosis

No established treatment is available for PNLD. Dopaminergic drugs for the treatment of PD should be tried in PNLD, but usually the response is limited.

See also: Corticobasal Degeneration; Dementia with Lewy Bodies; Hallervorden–Spatz Syndrome (PKAN); Parkinson's Disease: Definition, Diagnosis, and Management; Parkinsonism: Vascular; Progressive Supranuclear Palsy; Supranuclear Eye Movement Control.

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Pallidotomy for Parkinson's Disease

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Glossary

Dyskinesias – Involuntary movements provoked by levodopa.

Definition and History

In January 1985, Lauri Laitinen in Umeå, Sweden, inaugurated the renaissance of surgical treatment for Parkinson's disease (PD) by resurrecting 'Leksell's posteroventral pallidotomy (PVP)' published by Svennilson et al. in 1960. Following his publications of its results in 1992, pallidotomy experienced a worldwide spread. A few years later, pallidotomy became the first evidence-based surgical procedure for PD, and the first modern surgical procedure for PD with published outcome beyond 5 years and with documented improvement of the quality of life. Since the end of the 1990s, deep brain stimulation (DBS), especially DBS in the subthalamic nucleus (STN) has become the dominant surgical procedure for PD. However, pallidotomy remains an alternative surgical procedure, although very rarely performed nowadays. This chapter summarizes the rationale and indications for pallidotomy. Its effects and side effects are detailed, and some reasons for the decline of its use in surgical treatment for PD are described.

Rationale for Pallidotomy

When Leksell performed his pallidotomies in the 1950s, and moved his target progressively further posterior and ventral in the pallidum, treatment with levodopa was not available then, and there were no animal models. The PVP was a result of the surgical serendipidity, and the observation that the outcome was better led to more posterior and ventral pallidotomy lesion being made. Aditionally, when Laitinen rediscovered Leksell's PVP, nobody knew what its effect on levodopa-induced dyskinesias (LID) would be. Clinical observation and serendipidity confirmed, again, the excellent effect of PVP on LID. The information about the pallido-thalamo-cortical circuitry, obtained later on through experimental studies on nonhuman primate models of PD, confirmed the clinical observations and experience of Leksell and Laitinen, that is, the posteroventral pallidum was 'sensorimotor' and that a stereotactic lesion in that area could alleviate not only the cardinal symptoms of PD, but also the LID.

The animal model of PD can be summarized roughly as follows: dopamine deficiency in the putamen provokes (through a γ-aminobutyric acid (GABA)ergic direct pathway to the globus pallidus internus (GPi) and an indirect GABAergic and glutamatergic pathway through external pallidum and STN) a pathological pattern of (over)activity of the GPi, which provokes an inhibition of the initiation of movements by inhibiting the thalamocortical circuitry. This inhibition may account for the development of akinesia, rigidity, and probably tremor in PD. The dyskinesias seen in PD patients after long-term levodopa treatment may be mediated by an underactivity of the STN leading to a pathologically decreased pattern of activity of the GABAergic pallidothalamic projections. As a result, glutamatergic thalamocortical projections exhibit abnormally increased firing patterns, leading to the initiation of choreoathetotic and dystonic movements, that is, dyskinesias. Therefore, a lesion in the posteroventral sensorimotor part of the globus palldus internus GPi may contribute to decrease the pathological pattern of neuronal activity of the GPi and a 'normalization' of the thalamocortical activity, accounting for symptom improvement.

Indications for Pallidotomy

Patients suffering from L-dopa sensitive PD symptoms, with motor fluctuations, ON–OFF phenomena, and dyskinesias, and who have a preserved cognition, may benefit from PVP. There is an impact profile of PVP: dyskinesias respond best; rigidity and tremor do mostly respond, while the effect on akinesia, and especially gait freezing is clearly less robust. A second contralateral pallidotomy should not be performed routinely. It may be performed at least 6 months after the first one, if absolutely needed, and only if the first pallidotomy has been without side effects, and has been verified to lie entirely within the posteroventral pallidum without involving the internal capsule. Bilateral staged pallidotomies may increase the risk for dysarthria, dysphonia, and cognitive decline.

Surgical Procedure

The surgery starts with stereotactic visualization of the pallidal target and its surroundings using dedicated MRI sequences. The author uses a proton density, 2 mm thick

axial, and coronal scans, enabling visualization in the individual patient of internal and external pallidum, lamina medullaris, putamen, internal capsule, and optic tract (**Figure 1**). Hence, there is no need to relate the position of the brain target to third ventricle landmarks and stereotactic atlas.

At surgery, one can use microelectrode recording (MER) techniques for physiological confirmation of the target, prior to performing the lesion, but these techniques may harbor increased risks of bleeding without guarantee of increased accuracy in hitting the target and in confining the lesion to the intended structure.

The present author does not use MER. At surgery, impedance recording is used to differentiate between grey matter, white matter, and CSF space. Impedance recording, macrostimulation, and lesioning are carried out with a noninsulated electrode tip of 2 mm in length and 1.5 mm in diameter. The main aim of stimulation is not primarily to elicit a block of the symptoms (like tremor arrest during thalamic stimulation) but to avoid internal capsule and optic nerve. If stimulation (500 μs, upto 5 mA at 100 Hz or 1000 μs upto 10 mA at 6 Hz) does not give rise to undesirable reactions (capsular, optic, mental), 2–4 radiofrequency lesions, 2 mm apart, are produced with 75–80 °C during 60 s, using a 1.5 mm thick electrode with a 2 mm long noninsulated tip. The effect of a successful pallidotomy is often visible on the operating table. Movements such as cycling with the leg and finger taps are faster than those before the lesioning. To confirm the lesion's location, a thin slice MR scan is done, preferably weeks or months after surgery when the perilesional edema has resolved (**Figure 1**).

Side Effects of Pallidotomy

Pallidotomy may provoke worsening of memory, injury to optic tract, paresis, depression, stroke, drooling, confusion, dysarthria, and dysphonia. Some side effects of pallidotomy may become evident only days or weeks after surgery. As for one of the most feared risks of this surgery, bleeding in the brain, the Toronto group provided the following details: in 1959 patients from 85 papers from 40 centers in 12 countries, MER was used in 46.2% and

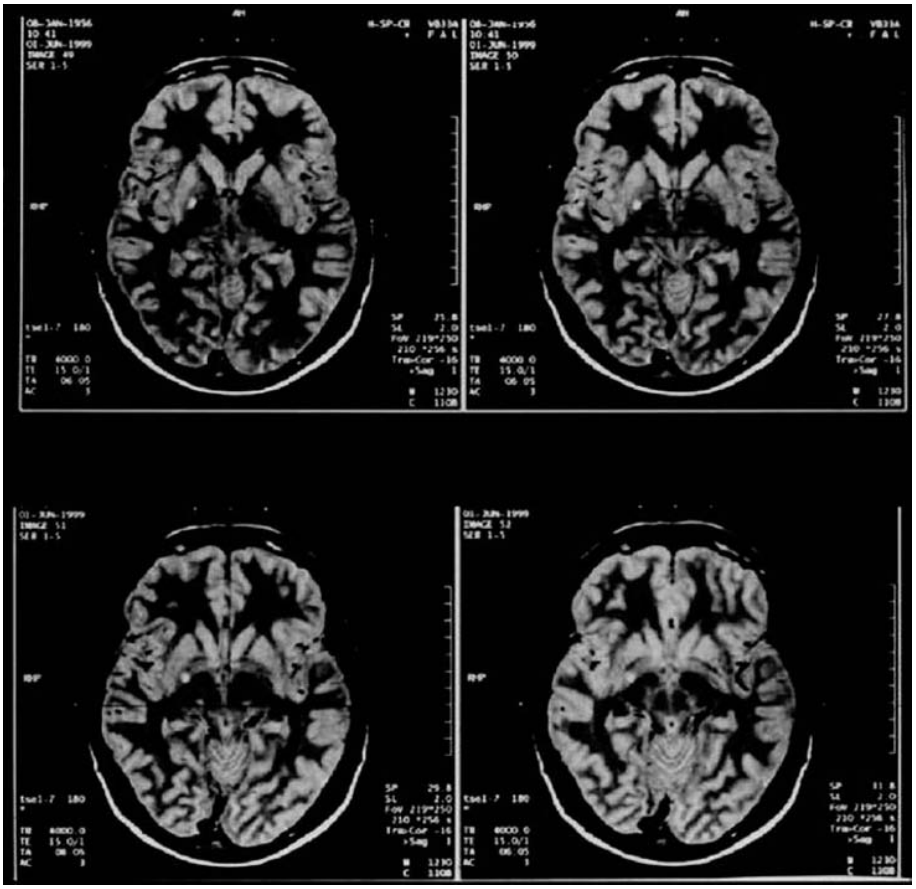

Figure 1 Stereotatic MRI using a proton density sequence performed 1 year after surgery: four contiguous axial 2 mm thick scans showing subdivisions of the pallidii, and a right-sided pallidotomy confined to the posterior and ventral internal pallidum.

macrostimulation in 53.8% of the patients. Cerebral hemorrhage occurred in 2.7% of MER patients and in 0.5% of macroelectrode patients. Overall complications occurred in 26% of MER patients and in 19.2% of macroelectrode patients.

Results

The results of pallidotomy depend on the symptoms that are assessed. The degree of improvement of the symptoms, dyskinesias excepted, may be variable. Following pallidotomy, 'ON–OFF' fluctuations may still occur; however, the 'ON' periods generally last longer and provide better mobility without dyskinesias, and the 'OFF' periods usually are not as profound and as long-lasting as the periods before surgery. The most consistent finding in the literature is that pallidotomy exerts its main effect on contralateral limb dyskinesia/dystonia, rigidity, and tremor, in that order, and least on gait freezing and other axial symptoms. Although the percentages of improvement in various aspects of the Unified Parkinson's Disease Rating Scale (UPDRS) reported in the literature were rather disparate, this disparity was not between reports from MER groups versus non-MER groups, but within either group, as has been shown by Starr et al. in their comprehensive survey on the effects of unilateral pallidotomy. In general, pallidotomy provides a 20–30% improvement on the motor part of the UPDRS, at 6–12 months after surgery. At longer follow up, results are inconsistent among authors with exception for long-lasting effect on tremor and especially on dyskinesias.

What Future for Pallidotomy?

In 2001, Mahlon DeLong defended pallidotomy, arguing that it is less expensive than DBS, without need for battery replacement or time consuming adjustment of stimulation parameters, and is without risk of infection and hardware problems. Recently, Gross also advocated that pallidotomy should remain in the surgical armamentarium for treatment of PD. Pallidotomy is safe and allows continuation or even increase of dopaminergic medication without fear for dyskinesias. It is well tolerated even by elderly patients, with few of the nonmotor side effects inherent to STN DBS. It is readily accessible for patients living far away from movement disorders centers or in areas and countries lacking means for sophisticated expensive healthcare. It is certainly not as safe as DBS if performed bilaterally, but even when unilateral, evidence shows that it is still by far better for patients with advanced PD than medications alone. For pallidotomy to remain a viable surgical alternative, the new generation of DBS-oriented movement disorder neurologists should be aware of its indications and its documented effects. Additionally, the new generation of functional neurosurgeons should learn – or relearn – the skills of performing proper stereotactic lesions in the pallidum. In experienced hands, it has been shown that a unilateral pallidotomy does not harbor more risks than DBS.

See also: Dyskinesias; Parkinson's Disease: Definition, Diagnosis, and Management.

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PANDAS

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Glossary

Chorea – Irregular, changing movements that flow between body areas, with unpredictable timing, and an asymmetrical and asynchronous pattern.
Cytokines – Protein molecules secreted by cells that influence and regulate the immune system.
Compulsions – Repetitive, purposeful behaviors usually performed in response to an obsession, or according to certain rules, or in a repetitive fashion.
Obsessions – Recurrent ideas, thoughts, or impulsions that intrude on conscious thought.
Tics – Involuntary, sudden, rapid, repetitive, nonrhythmic stereotyped movements or vocalizations.

Introduction

The number of proposed poststreptococcal movement disorders continues to expand from the archetype of Sydenham's chorea (SC) to a list that now includes tics, Tourette syndrome (TS), obsessive–compulsive disorder (OCD), dystonia, myoclonus, Parkinsonism, opsoclonus myoclonus, and paroxysmal dystonic choreoathetosis. In each, it is hypothesized that symptoms result from a Group A β-hemolytic streptococcal (GABHS) activation of the adaptive immune system. The proposed mechanisms include the induction of antibodies that in turn cross-react against neuronal tissue (molecular mimicry) and the production of secreted proteins that mediate and regulate immunity and inflammation (cytokines and chemokines). For most of these disorders, however, required criteria to confirm a pathogenic role for the immune system (see **Table 1**) have not been firmly established or accepted.

In 1998, Swedo and colleagues proposed that SC was not the only immune-mediated central nervous system (CNS) manifestation of GABHS and described their diagnostic criteria for Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infection (PANDAS). In this report, based on 50 cases recruited from a nationwide search, they suggested that a systematic clinical evaluation of children with OCD and tic disorders, including TS, defined a homogeneous subgroup in which symptoms were associated with a streptococcal infection (**Table 2**). Boys were affected more frequently than girls (ratio 2.6:1) and the mean age of onset for tics was 6.3 years and OCD 7.4 years. In general, children were normal prior to the explosive symptom onset, and tics, typically motor, were noted in 80%. The primary obsessive–compulsive behavior focused on contamination concerns with hand washing/cleaning. Numerous psychiatric comorbidities were noted, including separation anxiety, emotional lability, bedtime rituals, and oppositional behaviors. Confirmation of GABHS infection was found in 72% of patients, with 42% having definitive infection.

In subsequent reports, proponents have clarified several requirements. For example, diagnosis necessitates atleast two exacerbations of neuropsychiatric symptoms with distinct intervening periods of remission during which throat cultures and antistreptococcal antibody titers are negative. Explosive tic exacerbations are defined as the simultaneous appearance of several different motor and phonic tics with an intensity that causes parents to seek immediate medical attention. Acute recurrences must begin simultaneously with a positive throat culture or within 7–14 days after the infection. Lastly, choreiform movements that are included in the movement disorder repertoire of PANDAS have been further defined as fine piano-playing finger movements.

Even with these criteria, the existence of PANDAS is controversial, with advocates and opponents taking firm positions on either side of the clinical issue. Support for

Table 1 Criteria for establishing a pathogenic role for autoantibodies

1. Identification of autoantibodies
2. Presence of antibodies at the pathologic site
3. Induction of symptoms with autoantigens
4. Passive transfer of the disorder to animal models
5. Positive response to immunomodulatory therapy

Table 2 PANDAS criteria

1. Presence of OCD and/or tic disorder (based on Diagnostic and Statistical Manual criteria)
2. Prepubertal age at onset (between 3 years of age until start of puberty)
3. Sudden 'explosive' onset of symptoms and a course of sudden exacerbations and remissions
4. Temporal relationship between symptom onset and exacerbations and GABHS infections
5. The presence of neurologic abnormalities including tics, hyperactivity, and choreiform movements during exacerbations.

PANDAS is derived from the description of additional cohorts; familial studies showing that first degree relatives of children with PANDAS have higher rates of tic disorders and OCD than found in the general population; expanded expression of a trait marker for susceptibility in rheumatic fever (the monoclonal antibody D8/17) in individuals with PANDAS; and MRI volumetric analyses of 34 children with PANDAS showing that the average size of the caudate, putamen, and globus pallidus, but not thalamus or total cerebrum, was significantly greater in PANDAS than in healthy children. No correlation between basal ganglia size and symptom severity was observed.

Critics of PANDAS as a nosological entity emphasize that the diagnostic criteria established for PANDAS are potentially confounded by several factors: phenotypic variability commonly associated with tic disorders, such as a normal fluctuation in the frequency and severity of symptoms or exacerbation of tics by stress, fatigue, and illness; the finding of 'sudden, abrupt' onsets and/or recurrences of tics in non-PANDAS subjects; suggestions that first degree relatives with tics and OCD indicate a familial disorder (i.e., TS) rather than a tendency to PANDAS; the absence of cardiac abnormalities and other systemic manifestations; and the lack of a precise definition for associated neurological conditions (i.e., the presence of chorea indicating the diagnosis of SC not PANDAS).

Streptococcal Infection

A recently published American Heart Association report on rheumatic fever emphasized several important points: GABHS pharyngitis is clinically difficult to differentiate from pharyngitis due to other pathogens without a throat culture; antistreptococcal antibody titers (antistreptolysin O (ASO) and antideoxyribonuclease B) reflect past, not present, immunological events and cannot be used to determine whether an individual with pharyngitis and even a positive throat culture is truly infected or merely a streptococcal carrier; streptococcal antibody titers are often misinterpreted due to the failure to recognize that normal levels of these antibodies are higher among school-age children than among adults.

Epidemiological studies of PANDAS have produced conflicting results. In a case control study in children, patients receiving their initial diagnosis of TS, tic, or OCD were more than twice as likely to have a prior streptococcal infection in the 3 months before the onset of symptoms. This observation, however, is in contrast to a case control study using a very large primary care dataset that showed no increased exposure to streptococcal infections in individuals with OCD, TS, or tics. Some investigators have shown higher ASO titers in adult TS subjects as compared to controls; however, there was no association between levels of ASO titers and clinical symptoms. In other studies, no association was detected between streptococcal markers and tics or OCD in pediatric or mixed pediatric/adult populations. No significant difference was seen in ASO titer when comparing children with OCD-alone and OCD plus PANDAS. As noted, longitudinal laboratory data, rather than studies that use only a throat culture or only a single antistreptococcal titer, are necessary to confirm the presence of a previous GABHS infection. Lastly, in a longitudinal study of PANDAS subjects, only 6 of 65 documented exacerbations were associated a streptococcal infection.

D8/17 Antibody

As most children who get GABHS infections do not develop PANDAS, it has been theorized that an inherent genetic vulnerability may play a role. The monoclonal antibody D8/17, directed against B-cells, is a known susceptibility marker for rheumatic disease, including SC. Children with PANDAS were highly positive for the D8/17 marker (85%) as compared to healthy children (17%). An elevated expression of D8/17 is also seen in children with TS and/or OCD, although D8/17 positivity alone did not predict an increased rate of tics or OCD. In contrast to prior studies, a prospective longitudinal study using flow cytometry to quantify B-lymphoctyes expressing a known marker for GABHS infection (D8/17) found no clear relationship between new GABHS infections or amplification of B-lymphocyte populations relevant to new GABHS infections, amplification of B-lymphocyte populations relevant to GABHS infections, or tic symptom exacerbations.

PANDAS: An Autoimmune Disorder?

Background Issues

Mechanistically, if bacteria are not immediately eliminated by the innate immune response, antigens are carried by macrophages to lymph nodes. Presentation of these antigenic fragments to their cognate CD4+ T cells triggers their differentiation into either helper T_1 or T_2 cells, thus initiating the adaptive immune response. Activated T_1 cells secrete cytokines IL-2 and interferon-γ (INF-γ) which work to activate macrophages and cytotoxic T-cells. The cellular immune system is further enhanced by factors that stimulate acute phase reactions (tumor necrosis factor-α, TNF-α) and serve as chemotactic agents for T cells (regulated on activation, normal T expressed and secreted, RANTES) and macrophages (monocyte chemotactic protein-1, MCP-1). Activated helper T_2 cells secrete cytokines IL-4,-5,-6, and-10 and also trigger the proliferation and differentiation of B cells and plasma cells

that secrete immunoglobulins (humoral system). If two antigens share an identical epitope or if two different epitopes have similar shapes and charges, it is possible that an antibody produced against a GABHS epitope could cross-react with neuronal tissue, through the process of molecular mimicry (see **Figure 1**).

Autoantibodies

If serum antineuronal antibodies (ANAb) contribute to the pathogenesis of PANDAS, it would be hypothesized that individuals with these disorders should have elevated autoantibodies in their serum which cross-react with components of the CNS and, in particular, with brain regions thought to be involved in the generation of tics/OCD. To test this hypothesis, investigators have used three approaches to measure antinuclear antibodies: enzyme-linked immunosorbent assay (ELISA), Western immunoblotting, and indirect immunofluorescence (IF).

Several studies have measured ANAb in children with PANDAS, usually on single-point-in-time samples unrelated to the presence of a GABHS infection or the timing of clinical exacerbations. Results in these studies have been inconsistent and controversial. Several investigators have suggested, based on ELISA or immunoblotting, that this cohort is readily differentiated from a variety of disease controls. For example, analysis of antibodies by Western immunoblotting identified significantly more reactive bands at 60, 45, and 40 kDa in poststreptococcal subjects. These antigens were subsequently defined as the neuronal glycolytic enzymes pyruvate kinase M1, a doublet of nonneuronal- and neuronal-specific enolase, and aldolase C, respectively. In contrast, other researchers, using ELISA and immunoblotting against a variety of brain epitopes, were unable to distinguish PANDAS subjects from children with TS or controls. Immunoreactivity suggested neither diagnostic specificity at previously reported molecular weights nor to their putative antigenic proteins.

Few studies using the IF methodology of Husby have been published in children with PANDAS. In one, approximately two-thirds of 22 children and adolescents with this disorder had positive detectable staining at a 1:10 serum dilution, as did a small number of TS cases possessing positive putative antibodies determined by immunoblotting assays. In contrast, in a study comparing 30 cases of PANDAS, TS, and controls, using double staining with anti-glial fibrillary acidic protien (GFAP) (glial) and anti-microtubule associated protien-2 (MAP2) (neuronal) to establish localization of the IF, no association was identified between IF positivity or localization and the diagnosis of PANDAS or TS. Further, IF reactivity did not correlate with tic severity, titers of antistreptococcal antibodies, the presence of immunoblot reactivity against human caudate, or the putative antigens pyruvate kinase M1 and aldolase C.

Three reports, using pediatric OCD as the primary inclusion factor, have identified disparate alterations of immunoreactivity against striatal tissues. In one, immunoblotting showed the presence of antibasal ganglia antibodies in 42% compared with 2–10% in pediatric autoimmune, neurological and streptococcal control groups; reactive immunoblot bands were more common in the OCD cohort at 40, 45, and 60 kDa. In a second study, immunohistochemistry failed to differentiate cases from controls, but immunoblotting identified two proteins at molecular weights of 55 and 86 kDa in some prepubertal-onset OCD patients. Lastly, a third study showed no differences among groups for immunohistochemical staining and ELISA. Immunoreactivity against hypothesized putative specific antigens (α and γ-enolase, aldolase C, and pyruvate kinase M1) did not differentiate PANDAS, though more cases than controls had bands against caudate at 27, 36, and 100 kDa.

In order to avoid the multiple unknowns associated with single-point-in-time investigations, a multicenter longitudinal study provided the opportunity to evaluate the association of immune factors to clinical symptomatology and to changes at the time of a GABHS infection. In brief, using quantitative measures of autoantibodies obtained by three separate methodologies, ELISA, and immunoblotting against three brain regions as well as putative specific antigens, and competitive inhibition with lysoganglioside, investigators confirmed the presence of autoantibodies in children with PANDAS, but were unable to identify definitive increases in ANAb or an association with clinical worsening, with or without a GABHS infection. Hence, this study was consistent with the findings of others who reported that the presence of antineuronal antibodies at 40, 45, and 60 kDa detected against basal ganglia do not predict a specific tic phenotype, phenomenology, severity, or duration.

Another requirement for determining an autoimmune disease is the demonstration that the passive transference of antibodies to an unaffected host elicits the disease state. The microinfusion of sera from children with PANDAS into rodent striatum did not change the number of observed motor stereotypy behaviors.

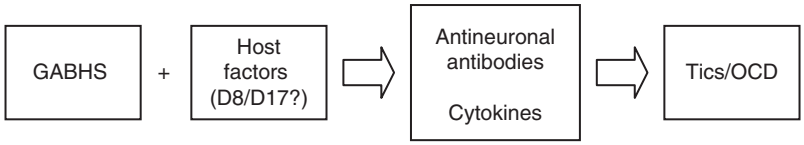

Figure 1 Proposed pathophysiologic mechanism underlying PANDAS.

Cytokines

Although much of the focus has been on autoantibodies, pathophysiological mechanisms could involve immune abnormalities associated with cytokines or lymphocyte dysfunction. Cytokines IL-4 and-10 are elevated in the cerebrospinal fluid (CSF) of about 30% of patients with acute SC. Quantification of serum proinflammatory cytokine levels suggest that elevations in IL-12 and TNF-α accompany tic exacerbations in TS but not PANDAS patients. Serial analyses of cytokines in longitudinal study showed no meaningful differences between PANDAS groups, with or without exacerbation associated with streptococci, and no definite increases during exacerbations. The lack of validity of serum cytokine measurements as accurate predictors of activity in the CNS has been noted in the literature.

Lysoganglioside G_{M1}

In SC, investigators have identified a monoclonal antibody that has specificity not for a brain protein, but for *N*-acetyl-β-D-glucosamine (GlcNAc), a streptococcal surface antigen, plus mammalian lysoganglioside G_{M1} and G_{M1} ganglioside. In a study of 15 patients with PANDAS, a competitive-inhibition ELISA assay showed that serum IgG reacted with lysoganglioside G_{M1} and GlcNAc in 73% of subjects. In a longitudinal study, 50% of PANDAS subjects had a positive competitive-inhibition assay in at least one serum sample, but only one showed values that correlated with clinical exacerbation. Other recent studies focusing on the specific target site of the autoantibodies in rheumatic fever have suggested β-tubulin, a molecular mimic of the Group A streptococcal carbohydrate epitope, GlcNAc. Sera from children with PANDAS are currently being evaluated for tubulin binding.

Regulatory T Cells

Children with TS have significantly decreased numbers of regulatory T cells (CD4+, CD25+). Regulatory T cells are thought to prevent autoimmunity by potently inhibiting both CD4+ and CD8+ T lymphocytes. These cells are reduced in other autoimmune diseases such as multiple sclerosis.

Future Perspectives

PANDAS is an intriguing diagnosis with a unique acronym. Much debate, however, exists pertaining to the validity of the condition as a distinct etiology for tics or OCD. To date, none of the five criteria supporting a role for the immune system in PANDAS have been satisfied unequivocally. Whereas it appears that an infection, be it viral or bacterial, can exacerbate tics, there exists no consistent evidence of an autoimmune process as the underlying pathophysiological mechanism in either TS or PANDAS. Given that confirmation of the concept of a postinfectious autoimmune tic/OCD disorder would have broad neurobiological, epidemiological, and treatment implications, research efforts continue to focus on the PANDAS as a potential model of neurological illnesses.

Treatment

In rheumatic fever, the reduction of recurrences by antibiotic prophylaxis against GABHS was an important factor in confirming a pathogenic association with streptococci. In a double-blind, placebo-controlled crossover trial with oral penicillin (250 mg penicillin V) undertaken to prevent recurrences of PANDAS, no significant change in severity of either obsessive–compulsive or tic symptoms occurred between the active and placebo arms. However, because an acceptable level of streptococcal prophylaxis was not achieved, no firm conclusions were possible. One study has shown that penicillin and azithromycin decreased streptococcal infections and neuropsychiatric symptoms, but several investigators have raised concerns about serious shortcomings in study design and suggested that the results be interpreted with great caution.

Indirect support for an immune hypothesis is derived from a single study showing that a small number of patients with PANDAS responded to immunotherapy with intravenous immunoglobulin (IVIG) and plasmapheresis (PEX). Twenty-nine children with PANDAS recruited from a nationwide search were randomized in a partially double-blind fashion (no sham apheresis) to an IVIG, IVIG placebo (saline), and PEX group. One month after treatment, the obsessive–compulsive symptoms were reduced by 58% and 45% in the PEX and IVIG groups, respectively, compared with only 3% in the IVIG control. In contrast, tic scores were significantly improved only after PEX treatment, with reductions of 49% (PEX), 19% (IVIG), and 12% (IVIG placebo). In this study, however, there were several methodological concerns: the small number of subjects (10 or less per group), the limited comparisons with controls, and side effects that occurred in about two-thirds of individuals receiving active therapy. At this time, the National Institute of Health (NIH) recommends that immunotherapy in PANDAS be reserved for patients participating in controlled double-blind protocols.

See also: Chorea; Choreiform Disorders; Obsessive-Compulsive Disorder; Sydenham's Chorea; Tics, Complex; Tics, Simple; Tourette Syndrome.

Further Reading

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Relevant Websites

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http://www.nih.gov – National Institute of Health.
www.movementdisorders.org – The Movement Disorder Society.

Paraneoplastic Movement Disorders

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Paraneoplastic Movement Disorders

The term 'paraneoplastic syndrome' refers to symptoms and signs caused by remote effects of cancer that are not caused by metastasis, coagulopathy, infection, or treatment side effects. Paraneoplastic syndromes can affect most organs and tissues, including both the peripheral and the central nervous systems.

The most common paraneoplastic neurological syndromes are sensory neuropathy, Lambert–Eaton myasthenic syndrome (LEMS), cerebellar degeneration, and limbic encephalitis.

Movement disorders have been rarely reported as a remote complication of malignancy.

In this article, we review the most commonly reported paraneoplastic movement disorders.

Chorea

Progressive paraneoplastic chorea, initially described by Albin and colleagues, represents a rare presentation of paraneoplastic central nervous system disease. Most reported cases of paraneoplastic chorea do not represent an isolated choreiform disorder, but rather have multifocal neurological symptoms, including dystonia, ataxia, sensory neuropathy, and cranial nerve palsies.

The most common malignancy associated with chorea is small-cell lung carcinoma.

Breast carcinoma, thymoma, non-Hodgkin's lymphoma, renal cell carcinoma, and primary cerebral lymphoma have also been associated with paraneoplastic chorea.

Vernino and colleagues reported the largest series of 16 patients presenting with chorea in a paraneoplastic context. All patients were smokers. In 11 patients, involuntary movements were the initial or the most prominent symptoms. Additional neurological manifestations present in 14 patients included vision loss, progressive peripheral neuropathy, limbic encephalitis, cerebellar ataxia, LEMS, and myelitis. Eleven patients had biopsy-proven small-cell lung carcinoma. Cancer diagnosis preceded the onset of chorea in only two patients.

Paraneoplastic chorea usually relates to collapsin response-mediating protein-5 (CRMP-5), a neuronal cytoplasmic protein related to the collapsing-mediator protein family. In the largest reported series of 121 patients who

were CRMP-5 seropositive, chorea was found in 11 % of the patients. The serum titers of CRMP-5-IgG do not correlate with the severity of chorea or the severity and nature of the accompanying neurological manifestations. Paraneoplastic chorea has also been linked to the anti-CV2 antibody initially assigned to an antibody with oligodendrocyte-restricted immunoreactivity. The anti-Hu antibody (ANNA-1), the most common marker of autoimmunity related to small-cell lung cancer, has been associated with chorea as well.

Neuropathological studies in patients with paraneoplastic chorea are sparse. Neuropathological findings are nonspecific and include marked neuronal loss, gliosis, mocroglial activation, perivascular lymphocytic infiltration, and microglial nodules within the basal ganglia. The most common magnetic resonance imaging (MRI) findings include nonenhancing T2 hyperintensities in the caudate and putamen, the thalamus and cortex being spared. In some cases, however, brain MRI is normal at presentation.

Treatment is directed at the underlying malignancy, and treatment outcomes vary. Although some report improvements in chorea in the majority of patients treated with symptomatic therapy, chemotherapy, or intravenous methylprednisolone, others document treatment failure.

A subacute onset of chorea in adults should raise the possibility of a paraneoplastic cause. Computerized tomography of the chest and a serological evaluation should strongly be considered in these patients.

Dystonia

Dystonia has been rarely described in paraneoplastic syndromes. In these sporadic cases, dsytonia coexists with other involuntary movements, mainly chorea and parkinsonism. Cerebellar degeneration, peripheral and cranial neuropathy, and other neurological signs may be present as well. Although dystonia may be an initial neurological manifestation of a paraneoplastic process, it usually emerges during the course of the illness. Jaw opening dystonia and laryngospasm are common in paraneoplastic syndromes associated with type 2 antineuronal nuclear antibody (ANNA-2), also known as 'anti-Ri'. In a series of 28 ANNA-2 positive patients, 7 (25 %) had laryngospasm and jaw opening dystonia leading to stridor and impairment of nutrition. The few available autopsy data of patients with dystonia in the setting of a paraneoplastic syndrome failed to reveal the neuropathological changes in the basal ganglia systems. Treatment is not effective.

Opsoclonus–Myoclonus Syndrome

Opsoclonus–myoclonus syndrome (OMS) is a rare neurological disorder characterized by an acute onset of opsoclonus and myoclonus. Opsoclonus consists of involuntary, irregular, chaotic, continuous, large-amplitude multidirectional saccades. It is present during fixation, smooth pursuit, and convergence and persists during sleep or eyelid closure.

Myoclonic movements in OMS involve the limbs and the trunk. Patients may have associated encephalopathy, ataxia, or tremors. The etiology of OMS may be idiopathic, paraneoplastic, postinfectious, or toxic-metabolic.

In cases of pediatric paraneoplastic OMS, the most common underlying neoplasm is neuroblastoma. While approximately 50 % of children with opsoclonus are found to have a neuroblastoma, opsoclonus may be the presenting sign of an occult neuroblastoma in 2–5 % of cases. In adults, the most common OMS-associated neoplasms are small-cell lung cancer, breast cancer, and ovarian cancer. Cases of paraneoplastic OMS have been reported with non-Hodgkin's lymphoma, malignant melanoma, and renal adenocarcinoma as well. Occult malignancies are found in approximately 20 % of adults presenting with OMS.

Humoral and cell-mediated immune mechanisms have been implicated in paraneoplastic OMS. Most patients with OMS test negative for antineuronal antibodies. Cases of OMS associated with anti-Ri, anti-Hu, anti-Yo, anti-Ma1/2, anti-amphyphysin, anti-CRMP-5, and anti-Zic2 antibodies have been reported.

A thorough diagnostic evaluation for the presence of tumor is necessary in all patients with OMS. In children, a search for occult neuroblastoma is essential. A complete screening protocol includes urine vanillylmandelic and homovanillic acid, MRI of the neck, chest, abdomen and pelvis, and metaiodobenzylguanidine (MIBG) whole body scintigraphy if MRI is unrevealing. Computerized tomography of the chest, abdomen, and pelvis should be done in adults. Gynecological examination and mammography are obligatory in women. If conventional imaging is negative, whole body 18F-fluoro-2-deoxyglucose-positorn emission tomography scan should be considered.

The mainstay of the treatment is the resection of the primary tumor. In children, corticosteroids, intravenous immunoglobulin (IVIG), and adrenocorticotrophic hormone (ACTH) are the most commonly used treatment options. Rituzimab has been used as an adjunctive therapy. Treatments with steroids and ACTH are associated with long-term adverse side effects. Residual motor, behavioral, speech, and sleep disorders are commonly present. The removal of neuroblastoma itself does not improve the symptoms in most patients. In adults, there is little evidence that immunotherapy is useful in treating OMS. Nystagmus and oscillopsia may respond to propranolol, baclofen, clonazepam, and thiamine. Myoclonus can be treated with antiepileptic drugs.

Paraneoplastic Cerebellar Degeneration

Cerebellar degeneration is one of the most common paraneoplastic syndromes characterized by a subacute development of a severe pancerebellar dysfunction. Initially, patients develop symptoms that mimic a viral-like illness, such as dizziness, nausea, and vomiting. This is followed by a subacute onset of gait ataxia, and subsequently, truncal and limb ataxia, dysarthria, and dysphagia. Neuroophthalmological manifestations are common and include nystagmus, ocular dysmetria, saccadic pursuit, saccadic intrusions and oscillations, and skewd deviation. Mild cognitive deficits have been described in a minority of affected patients. The clinical course is usually rapidly progressive, leading to severe functional disability within few weeks to months.

Paraneoplastic cerebellar degeneration (PCD) is most commonly associated with small-cell lung cancer, ovarian and breast carcinoma, and Hodgkin's disease. Cerebellar degeneration may precede the tumor by many years. Only about 50 % of patients with suspected PCD test positive for antineuronal antibodies in serum or cerebrospinal fluid (CSF). The most common onconeuronal antibodies associated with a pure paraneoplastic cerebellar syndrome are anti-Yo and anti-Tr antibodies. Anti-Yo is usually related to the presence of breast or ovarian cancer in postmenopausal women. Anti-Tr antibodies are markers of patients with PCD in Hodgkin's disease. Small-cell lung cancer is associated with several antibodies, including anti-Hu, voltage-gated calcium channel antibodies (VGCC), and anitibodies against CRMP-5, or ANNA-3. When VGCC antibodies are present, LEMS may coexist with PCD. Paraneoplastic OMS may coexist with the cerebellar degeneration in patients with breast or lung cancer associated with anti-Ri antibodies.

Brain MRI in PCD is initially normal, but can demonstrate cerebellar atrophy in later stages of the disease. CSF examination shows mild lymphocytic pleocytosis with elevated protein, oligoclonal bands, elevated immunoglobulin synthesis, and negative cytology in about 60% of patients. The neuropathological hallmark of the PCD is diffuse cerebellar Purkinje cell loss with a proliferation of Bergmann glia. Inflammatory infiltrates are occasionally present in the cerebellar cortex, deep cerebellar nuclei, and inferior olivary complex.

Treatment is directed at the underlying malignancy. In most cases, PCD does not improve with cancer treatment. Immune therapy is rarely effective, although there are reports of an improvement with plasmapheresis, immunosuppressive treatment (cyclophosphamide, tacrolimus), or IVIG. Symptomatic treatment involves neurorehabilitation with speech and swallowing therapies.

Prognosis in anti-Yo and anti-Hu-associated PCD is generally poor, and many patients are nonambulatory within 3 months. Patients with anti-Tr antibodies and Hodgkin's disease are more likely to improve than those with other antibodies. Patients with PCD associated with small-cell lung cancer and the absence of onconeuronal antibodies may have much better recovery after tumor treatment compared with patients with antibodies.

Patients with paraneoplastic cerebellar degeneration need thorough and continued monitoring aimed at cancer detection at an early stage, since this may increase the chance of meaningful recovery.

Parkinsonism

Parkinsonism is a very rare manifestation of a paraneoplastic nervous system disorder. Only a few cases of paraneoplastic parkinsonism have been reported in association with multiple myeloma, lymphoma, breast carcinoma, and bronchial carcinoma. Parkinsonian symptoms precede the diagnosis of cancer from 3 months to 2 years, and manifest as rapidly progressive symmetric parkinsonism. Paraneoplastic parkinsonism can mimic progressive supranuclear palsy. Other movement disorders, such as painful dystonia and myoclonus, may coexist with parkinsonism. Additional clinical features include cerebellar dysfunction, myopathy, cardiomyopathy, neuropathy, and autonomic dysfunction.

Antibodies to the Ma2 onconeuronal proteins that usually cause paraneoplastic limbic or brainstem encephalitis have been linked to several cases of paraneoplastic parkinsonism. Most of these patients had testicular germ-cell tumors or small-cell lung cancer. It is speculated that patients with anti-Ma2 encephalitis are more likely to develop parkinsonian-hypokinetic features than patients with other paraneoplastic disorders. CSF analysis is usually normal, and brain imaging unremarkable. Postmortem brain examination reveals astrocytosis in globus pallidus, loss of nigral neurons (mainly pars reticulata) without signs of inflammation, and a loss of Purkinje neurons. Parkinsonism usually does not improve with the cancer treatment. Rapidly progressive parkinsonism should raise the suspicion of a paraneoplastic disorder.

Stiff–Person Syndrome

Stiff–Person syndrome (SPS) is a rare neurological disorder characterized by muscle stiffness and painful spasms, initially described by Moersch and Woltman in 1956. The onset of SPS is usually during the third to sixth decade. Women appear to be affected more than men. Stiffness and muscle spasms are prominent in axial and proximal limb muscles, resulting in lumbar hyperlordosis. Muscle spasms are precipitated by sudden movement, noise, or emotional upset. Symptoms are absent during sleep or anesthesia.

Approximately 70 % of patients with SPS have a non-paraneoplastic form of this disorder associated with antibodies against glutamic acid decarboxylase (GAD). An autoimmune etiology of SPS is proposed based on its association with autoantibodies and other autoimmune diseases, and its response to immunomodulatory therapy. Electromyogram (EMG) reveals the existence of continuous motor unit activity in the affected muscles at rest. The cornerstone of the treatment represents symptomatic care with benzodiazepines and baclofen. Other options include IVIG, steroids, and plasma exchange.

In about 20% of patients, SPS develops as a paraneoplastic neurological disorder associated with elevated amphyphysin autoantibodies. Amphyphysin is a presynaptic nerve terminal protein critical for neuronal synaptic vesicle endocytosis. Antibodies to amphyphysin may be directly pathogenic in at least some cases of paraneoplastic SPS. Paraneoplastic SPS is rarely associated with anti-GAD antibodies. Malignancies most commonly associated with SPS are breast carcinoma, small-cell lung carcinoma, and lymphoma. SPM has also been reported in patients with thymoma and renal cell and colon carcinoma. Prominent clinical features of paraneoplastic SPS are the involvement of the upper extremities and less prominent spinal lordosis. Advanced age, subacute onset, rapid progression, and poor treatment response to benzodiazepines should raise the suspicion of a paraneoplastic SPS, and prompt a screening for neoplasm. The treatment of the neoplasm is critical. Symptomatic treatment options are similar to non-paraneoplastic SPS.

See also: Ataxia; Chorea; Dystonia; Opsoclonus-Myoclonus Syndrome; Parkinson's Disease: Definition, Diagnosis, and Management; Stiff Person Syndrome and Variants.

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Paratonia (Gegenhalten)

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Glossary

Frontal release signs – Primitive reflexes considered to reflect a disorder affecting the frontal lobes. These reflexes are physiological in the newborn. Their reappearance is due to a dysfunction of inhibitory pathways during late adult life.

Rigidity (or muscular rigidity) – An involuntary, *velocity-independent,* and sustained tonic muscular contraction, leading to a continuous resistance to passive movement throughout the range of motion; it is one of the clinical hallmarks of Parkinson's disease.

Spasticity – An involuntary, *velocity-dependent*, increased muscular resistance to stretch. Thus, the amount of resistance to stretching is at least partly determined by the speed with which a spastic muscle is stretched. In a clinical context, it is important to differentiate spasticity from rigidity.

History and Definition

In 1910, Dubré coined the French term 'rigidité paratonique'; and in 1927, Kleist the German expression 'Gegenhalten,' which literally means 'holding against.' Today, most clinicians use the term paratonia (PT). In the following decades, various definitions have been applied, making it almost obsolete to use such a poorly defined term. In 1998, Beversdorf proposed two types of PT, namely oppositional PT ('Gegenhalten,' 'paratonic rigidity') and facilitory PT ('Mitgehen'). The second type has been questioned, not only for linguistic reasons (the newly created word 'facilitory') but also because there may be overlapping of imitation behavior with echopraxia. In 2007, a consortium of experts came to a consensus that PT is a 'form of hypertonia with an involuntary variable resistance during passive movement.' In the following, we will focus on studies implicitly or explicitly applying this latter definition. Facilitory PT has only been discussed as an allied condition (see **Table 1**).

Pathophysiology

Since Denny-Brown's (1950) seminal work on motor dysfunction due to cerebral lesions, PT has been associated with frontal lobe dysfunction and considered as a cortically generated frontal disinhibition sign. As pointed out by Chatterjee, frontal lobes regulate, among others, goal-directed behaviors, a hierarchy of reflexive movements, approach and avoidance behaviors, response inhibition, and perseverations. After frontal damage, a patient may have trouble in both generating actions in the absence of stimuli and inhibiting them in the presence of stimuli. Consequently, PT may result from defective inhibition of a reflexive movement, secondary to a proprioceptive sensation or a passive movement. It is thus a motor perseveration. The hypothesis of PT as a frontal disinhibition sign is largely predominant in the scientific literature, but some authors have also emphasized that PT shows a strong dependence on the environment and can be considered as an imitation behavior. So far, there has been no proposal for the exact pathways involved in PT generation, although the requirement of bilateral frontal–subcortical lesions has been proposed. Chatterjee proposed that it should be studied if PT or the inability to inhibit simple movements in response to simple external stimuli also correlates with the inability to inhibit complex social behaviors in response to complex internal stimuli.

Table 1 The clinical spectrum of paratonia

- *Paratonia sensu strictu*
  Syn: 'Gegenhalten'
  Oppositional PT
  Paratonic rigidity
- *Facilitory Paratonia*
  Syn: 'Mitgehen'
  Overlapping with:
  Motor perseverations
  Echopraxia
  Imitation and utilization behavior
  Kral procedure

Prevalence and Risk Factors

There is no epidemiological study on the prevalence of PT, as defined above, in the elderly population. However, frequency of PT, defined as maintenance of an arm elevation after being released, has been studied by Tweedy et al. and Benassi et al. In both studies, it did not sufficiently discriminate between the elderly subjects without disease of the central nervous system and demented patients. Despite these restrictions, the impact of PT on prognosis and associated symptoms in dementia has been thoroughly studied. In a multiracial study of 80 patients with Alzheimer dementia (AD), Vahia and colleagues found an association with frontal symptoms as well as disease stage. PT was present in 48% of the patients with a moderate stage of the dementia and in 83% of patients with the most advanced stage of the disease. There was no link with age, race, sex, depression, physical health, neuroimaging, and neuropsychiatric symptoms. Risse and colleagues followed 28 patients with clinical AD diagnosis until death. PT was present in 18 out of 22 patients with pathological confirmation of the diagnosis. Conversely, PT was also present in five out of six patients with another pathological diagnosis. In the study by Franssen and colleagues, the prevalence of PT in the AD population was 86%. When compared with other release signs, PT was most consistently present. However, the survey listed by Risse and colleagues illustrates a large range of prevalence of PT in the older literature (18–88% of the patients with AD). These authors concluded that PT is not a useful indicator of any specific pathological diagnosis. Case reports have also mentioned PT as a prominent finding in Creutzfeldt disease, hereditary spastic paraplegia with frontal lobe signs, Hashimoto encephalopathy, and in subacute sclerosing panencephalitis. Finally, 'Gegenhalten' has been used in the psychiatric literature to describe a feature of negativism in catatonia.

The Clinical Spectrum of PT

Patients with PT demonstrate an involuntary resistance against any passive movement of the limbs. Occasionally they are able to suppress the resistance when fully relaxed or when focusing their attention on the moving limb. The degree of resistance varies with the speed of the passive movements. It increases when the extremity is moved

more rapidly and decreases or even disappears when it is moved more slowly. PT increases with progression of dementia, from active assistance ('Mitgehen') to active resistance ('Gegenhalten'). Sometimes both features coexist in the same patient.

Diagnostic Work-up

PT is a bedside diagnosis. Usually, it does not require any supplemental diagnostic procedures. Recently, an assessment tool based on the consensus definition of PT and consisting of five criteria have been proposed. The interobserver reliability was high (see **Table 2**), and the authors considered this instrument 'a valid and reliable assessment tool for PT in elderly people with dementia' (see **Figure 1**).

Beversdorf and coworkers (1998) proposed a five-point scale modified from the Kral procedure (also described as 'motor perseveration') to rate the severity of the allied facilitory PT. The rating score correlated with other frontal motor signs, frontal cognitive signs, and dementia severity. The authors emphasized that severity of facilitory PT was also linked with echopraxia and the inability to inhibit eye movements to peripheral stimuli.

Table 2 Criteria of the paratonia assessment instrument (PAI)

- An involuntary variable resistance during passive movement
- Absence of the clasp-knife phenomenon
- Resistance to passive movement occurs in any direction
- Resistance must be felt in either one limb in two movement directions or in two different limbs
- Degree of resistance correlates with the speed of movement (e.g., a low resistance to slow movement and a high resistance to fast movement)

Source:
Hobbelen JSM, Koopmans RTCM, Verhey FRJ, Habraken KM, and de Bie RA (2008) Diagnosing paratonia in the demented elderly; reliability and validity of the PT assessment instrument (PAI). *International Psychogeriatry* 20: 840–852.

Differential Diagnosis

PT can be easily distinguished from the spastic clasp-knife phenomenon. The differentiation from Parkinsonian (lead pipe) rigidity is more challenging. PT shows a variable degree of resistance, depending on the speed of the applied passive movements, whereas in Parkinsonian rigidity, the degree of resistance is constant, whether the limb is moved slowly or rapidly. PT does not show any exacerbation during contralateral reinforcement. Cogwheeling is not a helpful diagnostic sign because it reflects the combination of tremor or myoclonus of any cause with PT or Parkinsonian rigidity. In the most advanced cases of dementia, the paratonic resistance is so pronounced that the examiner is no more able to further accelerate the movement and thus adequately differentiate from Parkinsonian rigidity. The special subtype of eyelid PT or resistance to passive opening of the eyes has to be distinguished from blepharospasm.

Allied Features

Considered to be a frontal release sign, PT has been linked to glabellar blink, snout, sucking, rooting, grasping, and palmomental reflex. It has also been associated with dyspraxia or the inability to copy gestures and commands, despite intact muscle strength, coordination, and sensation. Within the wider spectrum of pathological motor behaviors induced by prefrontal lesions, PT has been mentioned side by side with the tendency to imitate the examiner's gestures, to compulsively manipulate objects in front of the patient (imitation and utilization behavior;

Figure 1 Evaluation of paratonia with the paratonia assessment battery (PAI). The examiner performs passive movement of the shoulders, elbows, and hips in flexion and extension. Reproduced from, Hobbelen JSM, Koopmans RTCM, Verhey FRJ, Habraken KM, and de Bie RA (2008) Diagnosing paratonia in the demented elderly; reliability and validity of the PT assessment instrument (PAI). *International Psychogeriatry* 20: 840–852, with permission from Cambridge University Press.

echopraxia), to instinctively grasp these objects, and to show motor perseverations, motor impersistence, or reduced motor activity.

Management

There is no treatment to abate PT. We even do not know if passive movement therapy, currently used in patients with late stage dementia, enhances or ameliorates PT. Currently, Hobbelen and coworkers (2008) are conducting a large randomized clinical trial to study the potential efficacy of this treatment on the severity of PT.

Prognosis

It is unknown whether the occurrence of PT in the elderly population *without* dementia has any prognostic significance. In AD, PT is usually more pronounced in the later stages of the disease and has thus been reported to predict a worse disease prognosis.

See also: DYT9, Paroxysmal Dyskinesia with Spasticity; Rigidity.

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PARK1, Alpha Synuclein

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Glossary

Gene mutation – A variant that differs from the ancestral form and can be passed on to subsequent generations. Mutations can be beneficial, neutral or detrimental, for example when associated with a specific disease phenotype.

Lewy bodies – Protein- and lipid-containing cellular inclusion bodies that are characteristic of Parkinson disease and related disorders. Related structures called Lewy neurites are swollen axons or dendrites that, like Lewy bodies, are highly positive for α-synuclein.

Protein aggregation – The tendency of some proteins to self-associate, forming species that are initially relatively soluble but eventually mature into higher molecular weight insoluble forms called fibrils.

Synucleins – A group of small proteins found in most vertebrates that were named for their localization to synapses and nuclei. Mutations in the α-synuclein gene, *SNCA*, cause Parkinson disease and related disorders in humans.

Although Parkinson disease (PD) is a relatively common disorder, the underlying cause of most cases is not known. Since the early descriptions of PD, ideas about etiology have developed and, over time, several have been proposed, discarded, and rediscovered. Although very rare, several genetic forms of PD have been found that cause disease in given families. Of these, the first to have been discovered was a point mutation in the gene *SNCA*, which codes for a small synaptic protein, α-synuclein. α-Synuclein is important for understanding the relationship between familial and sporadic, or non-inherited, forms of PD but also gives us some clues as to the otherwise apparently distinct events in PD, namely the clinical symptoms and the pathology of the disease. However, as important as α-synuclein is to our understanding of PD, there remain an important series of unknown aspects related to how, precisely, altered synuclein protein causes disease.

What is Known About α-Synuclein

Genetics

The first discovery of a mutation in the α-synuclein gene, *SNCA*, was reported in 1997 by Polymeropoulos and colleagues. Several families were found where a single amino acid change, substituting Alanine 53 for a Threonine in the protein, segregated with disease in a dominant fashion. Since then, two other point mutations have been found, A30P and E46K, where a single copy of the mutation causes disease. These mutations are important because they show that PD can be inherited in a Mendelian fashion, even if this not always true.

Another important set of mutations are those where the protein sequence is identical to the wild-type human version, but there are extra copies of the whole gene, that is, multiplications. Families with one extra copy (i.e., a duplication) or two extra copies (triplication) on one chromosome are reported. These are predicted to increase the amount of protein by 50% and 100%, respectively, which has been confirmed at least for the triplication cases. These mutations are important because they show us, very clearly, that the normal protein can be associated with PD. This implies that more subtle misregulation of the normal protein might be important in the lifetime risk of PD, even in people without mutations.

What is not true is that α-synuclein mutations always cause PD, at least not in the sense of typical sporadic PD. Several individuals in the families with point mutations show symptoms that indicate involvement of the cerebral cortex, including dementia that precedes the movement disorder typical of PD. This is perhaps best illustrated by the multiplication mutations. Duplications of α-synuclein are associated with a disease where the brainstem, specifically the substantia nigra, is predominantly affected. However, triplication cases have much more widespread pathology, including a more substantial involvement of the cerebral cortex. This is consistent with the idea that PD spreads from the brainstem out toward the cortex, a hypothesis proposed by Braak from observations of the pathology of sporadic PD cases.

As well as familial cases, α-synuclein may also be a risk factor for sporadic PD. Several studies have identified common genetic variants (polymorphisms) around the normal synuclein gene that are associated with lifetime risk of PD. If 50% increases in the amount of α-synuclein in the brain are causal for PD, then perhaps more subtle increases would change the relative risk over lifetime.

In summary, mutations in α-synuclein support the idea that rare genetic variants can be helpful in understanding the causation of common diseases.

Protein Chemistry

How, then, do mutations or increased amounts of α-synuclein act on the protein to trigger a neurological disease? Much of our current thinking about this problem relates to the physical properties of the protein, which is quite unusual.

α-Synuclein and its close relatives have evolved to have a high degree of flexibility in their structure. Most proteins have a limited repertoire of folded structures that they can adopt. In contrast, α-synuclein is capable of adopting one of several forms, depending on the context. In solution, in a context outside of the cell, α-synuclein adopts an open, flexible conformation and is therefore referred to as one of the class of natively-unfolded proteins.

Within a neuron, α-synuclein protein is predominantly found in association with presynaptic vesicles where neurotransmitters are stored. This is likely a result of the ability of the protein to associate with lipids, which it does by folding into a broken α-helix. The c-terminal region of α-synuclein, which is heavily negatively charged, projects out from the surface of lipid vesicles into the cytosol.

α-Synuclein can also form a number of aggregated forms that are stabilized by β-sheet like interactions. The process of protein aggregation is fairly well characterized in cell free systems and involves the formation of initially small oligomers that then seed the formation of larger structures. Over several days, this process results in the formation of highly stable fibrils that resemble structures isolated from Lewy bodies (see section Pathology: α-Synuclein Deposition as a Marker of the PD Process).

The aggregation process follows concentration-dependent kinetics and we can extrapolate that mutations that result in higher protein concentrations are associated with an increasing tendency to form aggregates. Two point mutations, A53T and E46K, also shift the dynamics of this process toward fibril formation. The third dominant

mutation, A30P, decreases lipid binding and promotes the formation of relatively soluble oligomers. This observation is one line of evidence suggesting that the mature, very insoluble, fibrils are not necessarily the damaging form of the protein in diseased brains but rather than the intermediates for protein aggregation may be more relevant.

Overall, these data suggest that a likely way in which mutations in α-synuclein cause disease is to promote protein aggregation although this hypothesis is tentative because the data to support or refute the idea in more intact systems is somewhat equivocal.

Pathology: α-Synuclein Deposition as a Marker of the PD Process

In addition to the genetic data, the neuropathology of PD also provides a link between α-synuclein and sporadic PD. The principal reason for this is that Lewy bodies, a characteristic pathological hallmark of PD and related diseases, are readily stained with antibodies against α-synuclein. Currently, PD is a clinical and pathological diagnosis, which requires both the clinical syndrome of a movement disorder and the presence of Lewy bodies in the *postmortem* brain. The term parkinsonism is preferred for cases with the clinical symptoms of PD where Lewy bodies are absent or unknown whereas Parkinson disease should be reserved for Lewy-body positive parkinsonism.

Therefore, and this is a definitional argument, α-synuclein deposition into Lewy bodies is a required event in sporadic PD. Although the number of cases is low, autopsied individuals carrying α-synuclein mutations have a high density of Lewy bodies and other α-synuclein positive lesions. Furthermore, the density of Lewy body staining is at least partially correlated with the major symptoms. Persons who had PD tend to have Lewy bodies in surviving neurons in the substantia nigra whereas patients with diffuse Lewy body disease (DLBD) where pathology is found in the cortex are also affected with dementia.

α-Synuclein can be biochemically isolated from the brain of patients with PD or DLBD. The forms of the protein recovered are often relatively insoluble and carry a number of posttranslational modifications. Lewy bodies contain α-synuclein positive fibrillar structures that may be related to those that can be generated *in vitro*. There is also a more limited amount of data showing that oligomers, which are of intermediate solubility, can be recovered from brains of patients with synucleinopathies.

Collectively, these observations suggest that the pathological process is shared between inherited and sporadic PD and that α-synuclein is, at least, a good marker of the process in both situations. Furthermore, the transformation of α-synuclein from soluble, monomeric α-synuclein through oligomers to deposited fibrils that occurs in laboratory settings may be relevant to the pathology of PD.

What is Unknown, or Unclear, About α-Synuclein

Normal Function

One consideration that arises from the identification of cases with multiplications of α-synuclein is that the difference between normal and abnormal concentrations of the protein is surprisingly modest. In the triplication families, twice as much α-synuclein as normal is associated with a very aggressive, early onset disease and, as discussed above, it is likely that quite small differences in overall expression is associated with risk of sporadic PD. α-Synuclein is a relatively abundant protein in many organs and is especially highly expressed in the brain. This leads to several outstanding questions in the field. Why is α-synuclein present in the brain? Can we remove it and decrease risk for PD or will this cause damage to the brain? Both of these questions can be reduced to one critical one: what is the normal function of α-synuclein?

One way to address this is to remove the gene by making a knockout mouse. Such animals are viable and apparently normal from birth through their normal lifespan. Subtle differences in synaptic function have been noted in some studies, but there are no dramatic phenotypes. This might be related to the fact that there are two homologuous genes, β- and γ-synuclein which may compensate for lack of α-synuclein, but double knockouts have only a similarly modest phenotype. This suggests that α-synuclein and its near homologues do not have an essential role in the nervous system, a contention possibly supported by the fact that invertebrates such as *Drosophila* with functional nervous systems lack recognizable synuclein genes.

α-Synuclein is only loosely attached to membranes such as synaptic vesicles and synaptic activity can cause the protein to lose lipid interaction, which then reassociates with vesicles only slowly. This does not tell us what the normal function of synuclein is, but may support the idea above that α-synuclein has a modulatory role and further suggests that understanding the relation between α-synuclein and electrical activity may be productive.

The normal function of α-synuclein is therefore somewhat mysterious outside of a potential connection to neuronal activity. This may become a critical question if we want to develop was to deal with α-synuclein in a therapeutic way for PD/DLBD patients. For example, can we remove all α-synuclein and leave brain function intact? Part of the answer to this question also depends on understanding why α-synuclein is associated with disease and, therefore, whether normal function is at all relevant to the disease process.

Dysfunction and Death

Because mutations in α-synuclein are associated with progressive neurodegenerative disease, and because the

same protein is found in cases with sporadic PD, it can be reasonably inferred that the protein is associated with neuronal damage in some way. However, this leaves a number of open questions as two exactly how and why neuronal damage occurs, how we might model that process and how to stop it.

Because of the evidence that mutations are associated with protein aggregation, it has been suggested that the aggregated α-synuclein triggers neuronal damage. Reasonable candidates for such a toxic agent are the relatively soluble oligomers that form along the way to mature fibrils. If true, this implies that a mature Lewy body, with heavily aggregated α-synuclein, might not be the actual toxic agent and might actually represent an attempt of a neuron to detoxify the partially aggregated species. However, this hypothesis is hard to test directly as few model systems reported to date reproduce both neuronal cell loss and mature Lewy body formation and it thus remains uncertain what form of α-synuclein mediates toxicity and whether Lewy bodies represent a cause or consequence of disease. It does seem reasonable that mature Lewy bodies take a long time to form, perhaps several years, based on results in grafts in the human brain.

Also uncertain are the processes by which α-synuclein in any form causes damage to neurons. Mutant α-synuclein has been reported to affect many functions of the cell, including protein turnover pathways, mitochondria and responses to other detrimental agents such as oxidative stress or ion homeostasis. Some of these may be especially important in neurons. Based on the observation that α-synuclein is involved in synaptic function, it is interesting that neurons in the substantia nigra that are relatively vulnerable in PD have a high autonomous electrical activity that is dependent on calcium influx. We might even speculate that such neurons that play important roles in the maintenance of posture may be working especially hard in obligate bipeds such as humans or other primates. However, there is currently no specific target of α-synuclein toxicity that readily explains why the brain is especially vulnerable to its effects.

Presumably, these two questions, understanding what the toxic species of α-synuclein is, and why this causes toxicity, are related to one another. They also underpin attempts to both develop models for the phenomenon and ways to interfere with the process and develop new ways to treat PD. These remain important challenges for the PD field.

Acknowledgments

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See also: Alpha-synuclein; PARK2, parkin; PARK3; PARK5, UCH-L1; *PARK6, PINK1*; PARK7, DJ1; *PARK8, LRRK2* (Dardarin); Parkinson's Disease: Definition, Diagnosis, and Management.

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PARK2, parkin

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Clinical Phenotype

Mutations in the *parkin* gene (the PARK2 locus) were originally described in Japanese kindred where parkinsonism is inherited as an autosomal recessive trait. The phenotype seen in these kindred is early-onset parkinsonism – the most common age of onset is between 20 and 40 years, but cases younger than 10 years have been reported. Therefore, this form of parkinsonism was termed autosomal recessive juvenile parkinsonism (ARJP). Affected individuals have a slow disease progression and good response to levodopa therapy. Additional symptoms include hyperreflexia, diurnal variation with sleep benefit (motor symptoms may improve after sleep), dystonia, early postural instability, freezing, festination or retropulsion, and autonomic dysfunction. Motor complications of levodopa therapy such as ON–OFF fluctuations are common and occur earlier than in idiopathic Parkinson's disease (PD). Although dementia is not usually observed, psychiatric symptoms, including anxiety, psychosis, obsessive–compulsive disorder, and behavioral abnormalities, are common. These psychiatric symptoms are not specifically associated with *parkin* mutations as they can also be observed in other early-onset forms of Parkinson's disease (EOPD). Another interesting finding is that olfactory function is preserved in *parkin*-associated PD, whereas it is decreased in typical PD and autosomal dominant forms of PD.

Imaging

Parkin-associated PD cases have been studied by functional imaging using positron emission tomography (PET) with ^{18}F-dopa and ^{11}C-raclopride. Findings in affected *parkin* homozygotes, unaffected *parkin* heterozygotes, and unaffected compound heterozygotes were compared with those of healthy control subjects and cases of sporadic, idiopathic PD. Compared with healthy controls, *parkin* homozygotes and unaffected compound heterozygotes showed a decreased ^{18}F-dopa uptake in the putamen that was more prominent posteriorly. In addition, they showed a decreased ^{11}C-raclopride binding. The pattern is similar to that observed in the sporadic PD individuals and is suggestive of presynaptic-striatal dysfunction and alterations in the level of postsynaptic-D2-receptors. In asymptomatic *parkin* heterozygotes, there was a significant difference in ^{18}F-dopa uptake in the striatum. This suggests that asymptomatic mutation carriers have an ongoing neurodegenerative process and provides support for haploinsufficiency as a potential mechanism. Another interesting insight gained from these studies is that PET abnormalities may not correlate with disease severity.

Neuropathology

The neuropathological findings in ARJP associated with homozygous *parkin* mutations consist predominantly of severe neuronal loss in the substantia nigra (SN) pars compacta, with the most severe loss seen in the medial and ventrolateral regions. There is less pronounced neuronal loss in the locus ceruleus (LC) and the SN pars reticulata is usually spared. Although Lewy bodies are absent, neurofibrillary tangles (NFT) are seen in the SN, LC, hippocampus, and cortex. However, the NFT burden is considerably less than that associated with Alzheimer's disease (AD) pathology. In some cases, diffuse tau-positive astrocytes were observed in the caudate, putamen, and subthalamic nucleus, and a few in the SN. In other cases, there were α-synuclein-positive and ubiquitin-positive inclusions in the pedunculopontine nucleus, but not in the SN, LC, or subthalamic nucleus. In contrast to *parkin* homozygotes, Lewy bodies were found in a *parkin* compound heterozygote.

Genetics

Linkage analysis of 17 Japanese families with ARJP revealed that the parkinsonian phenotype maps to the long arm of chromosome 6 at 6q25.2–27. Through positional cloning, the *parkin* gene was identified. Over 100 different types of mutations in *parkin* have been described to date, including point mutations, deletions, and copy number abnormalities. Since its original description in the Japanese population, many different *parkin* mutations have been described in different ethnic populations. Indeed, mutations in the *parkin* gene are the most common cause of familial PD that is inherited as an autosomal recessive trait worldwide. *Parkin* mutations have also been associated with ~10–20% of apparently sporadic cases with an early disease onset of <45 years. In addition, heterozygotes and compound heterozygotes have been reported. Multiple *parkin* mutations segregate

in some kindred. There are kindred in whom different members have homozygous and heterozygous copy number abnormalities, while another member is a compound heterozygote. Heterozygosity for a *parkin* mutation may be a risk factor for PD and also appears to significantly influence the age of PD onset – individuals with two *parkin* mutations had an earlier age at disease onset and longer disease duration than those with just one mutation. That heterozygotes for some *parkin* alleles develop late-onset parkinsonism suggests that haploinsufficiency of *parkin* function may underlie the development of PD.

Copy number abnormalities are common in EOPD, occurring in up to 60% in some studies, and may exist in combination with point mutations or deletions. It is therefore important to assess *parkin*-copy number in EOPD patients. It is interesting to note that an increased number of parkin mutations predisposes individuals toward earlier disease onset, increased prevalence of dystonia, and positive family history.

Gene Structure and Expression

The *parkin* gene is among the largest human genes, second in size to the *dystrophin* gene. It spans 1.3 Mb of genomic DNA and its 4.5-kb transcript, generated from 12 exons, encodes a protein product of 465 amino acids. It is present in many human tissues, and in particular, is expressed in different regions in the brain, including the SN.

A molecular genetic analysis of the chromosomal region that includes *parkin* revealed that two genes, *parkin* and *parkin coregulated gene* (*PACRG*), share a common promoter region. More specifically, *parkin* and *PACRG* are arranged head-to-head on opposite DNA strands and share a common 5′-flanking promoter region. This bidirectional transcription activation region contains a transcription factor AP4-like site, a GC-rich region, and an oncogene MYC-like site.

In certain ethnic populations, the region of the bidirectional transcriptional activation appears to be associated with susceptibility to leprosy. This effect appears to be population specific and has been identified in Vietnamese and Brazilian, but not in Indian populations. Both *parkin* and *PACRG* are expressed in a wide range of tissues, including Schwann cells and macrophages, the primary host cells of *Mycobacterium leprae*, the causative agent of leprosy.

The Parkin protein contains an N-terminal ubiquitin-like domain (UBL) followed by a linker and two C-terminal RING finger domains that are separated by an in-between ring (IBR) domain. The RING–IBR–RING (RBR) structure is found only in eukaryotes in which it appears to be highly conserved. Given the similarity of the UBL to ubiquitin, Parkin is thought to function as an E3-ligase. E3-ligases conjugate ubiquitin moieties to proteins that are targeted for degradation through the proteasome. Mutant Parkin from ARJP patients shows a loss of the ubiquitin-protein-ligase activity, supporting the postulated E3-ligase function.

The Parkin protein is found in both cell bodies and processes of neurons, but not in glia, in the midbrain, basal ganglia, cerebral cortex, and cerebellum.

Parkin–Protein Interactions

Parkin's size and domain structure facilitate its participation in multiple protein interactions. Characterization of the three-dimensional structure of an IBR domain isolated from Parkin revealed that it contains two zinc-binding sites that are required for correct folding, which in turn is necessary for proper Parkin–protein interactions.

Numerous studies have identified protein interactions in which Parkin participates. Some of the most important interactions are described as follows.

Parkin binds to the E2 ubiquitin-conjugating enzyme-8 (UBCH8); ubiquitinates itself; and promotes its own degradation. It interacts with the Parkin-associated endothelin-receptor like receptor (Pael-R). The accumulation of Pael-R can lead to cell death, and the insoluble form of Pael-R accumulates in the brains of ARJP patients. Parkin ubiquitinates Pael-R and promotes degradation of its insoluble fraction, thus suppressing cell death. Interestingly, Pael-R, Parkin, α-synuclein, and ubiquitin accumulate in Lewy Bodies and neurites. Pael-R is localized within the core of Lewy Bodies, whereas Parkin and α-synuclein accumulate in the halo and in neuronal cell bodies and processes. Parkin also interacts with carboxy terminus of Hsc70-interacting protein (CHIP), a mammalian E4-like molecule that positively regulates Parkin E3-ligase activity.

Parkin functionally interacts with a glycosylated form of α-synuclein (α-Sp22), with loss of *parkin* function leading to the pathologic accumulation of α-Sp22. Parkin also interacts with synphilin, an α-synuclein-interacting protein. Coexpression of α-synuclein, synphilin-1, and Parkin leads to the formation of Lewy body-like, ubiquitin-positive, cytosolic inclusions.

The *parkin* gene is located at a fragile site and many copy number abnormalities have been associated with ARJP. The *parkin* gene has been implicated in tumorigenesis as a likely tumor suppressor gene. It appears that *parkin* inactivation may contribute to the initiation and progression of cancers, as tumor-derived cell lines contain *parkin* deletions or duplications.

Parkin is S-nitrosylated in vitro and in vivo in a mouse model of PD and in the brains of patients with PD and diffuse Lewy body disease (DLB). The enhancement of Parkin's E3-ligase activity by S-nitrosylation may be an important mechanism by which Parkin function is

regulated. Parkin S-nitrosylation enhances its E3-ligase activity at earlier time points but inhibits its E3-ligase activity at later time points, suggesting that alterations of the ubiquitination of Parkin substrates may underlie the neurodegenerative process. Parkin may protect against dopamine toxicity by decreasing oxidative stress and interfering with the activation of apoptotic programs such as the MAPK8/caspase pathway.

The DJ-1 gene, another gene linked to early-onset PD, interacts with Parkin. Parkin binds to monomeric DJ-1 and prevents DJ-1 homodimer formation.

Synaptotagmin XI (SYT11) interacts with Parkin, suggesting a role for Parkin in the regulation of the synaptic vesicle pool and in vesicle release. Parkin binds to synaptotagmin XI's C2A and C2B domains, resulting in synaptotagmin's polyubiquitination and enhancing its turnover. Truncated and missense-mutated Parkin proteins reduce parkin-synaptotagmin XI binding affinity and ubiquitination. In sporadic PD brain sections, synaptotagmin XI is found in the core of Lewy bodies.

Parkin interacts with p38 (JTV1), a structural component of the mammalian aminoacyl-tRNA synthetase complex, as well as with Bag5, a negative regulator of heat shock protein 70 (Hsp70) and Parkin.

Endogenous dopamine can covalently modify Parkin in rodent and human dopaminergic cells. Dopamine-induced loss of Parkin may represent a potential mechanism contributing to the selective degeneration of dopaminergic neurons.

Parkin interacts with another key player in PD pathogenesis, leucine-repeat-rich kinase 2 (LRRK2). LRRK2 interacts preferentially with the C-terminal R2 RING finger domain of Parkin, and Parkin interacts with the COR domain of LRRK2.

Parkin can interfere with epidermal growth factor receptor (EGFR) internalization and degradation and promote phosphoinositol-3K (PI3K)/AKT (protein kinase B) signaling.

Parkin's interaction sites have been mapped using genome-wide high-throughput analysis of protein–protein interactions. Parkin's UBL domain interacts with UbCH7, UbCH8, and the SKP1/CUL1/F-box (SCF)-like, ubiquitin-ligase complex, the subunit of 26S proteases. The linker region interacts with Bag5, 14–3–3 and the form of DJ-1 mutated in DJ-1-linked PD, synaptotagmin XI, and the p38 subunit of amino acyl tRNA synthetase. The IBR domain interacts with the 20S protease subunit α4. Finally, the RING domain interacts with synphilin. The spatial specificity of interactions that occur within the Parkin protein and the large number of interactors results in a complex pattern of interactions that may also be temporally and spatially regulated. It is conceivable that Parkin enters into different protein interactions at different points in time and different tissues.

Animal Models

Both invertebrate and vertebrate model systems have been developed to investigate the possible functions of Parkin. As many *parkin* mutations are loss-of-function alleles, these models have been useful to analyze how a loss of *parkin* function might underlie a disease mechanism.

Several different *parkin* knockout mouse models have been generated. None of the mouse models shows any neuronal loss in the SN. However, some, but not all knockouts, exhibit more subtle phenotypes that include motor and cognitive deficits and physiologically affect neurotransmission.

The excellent genetics of the fruitfly *Drosophila melanogaster* has been useful to develop a model system to assess *parkin* function. A characterization of the interactions of *parkin* and *Pink1* mutants supports the view that *parkin* acts downstream of *Pink1* in a linear pathway. While loss of either *parkin* or *Pink1* function results in a similar phenotype involving mitochondrial dysfunction, Parkin overexpression is able to rescue the muscle defects of *Pink1* mutants, but not vice versa. The involvement of the *Pink1–parkin* pathway in regulating mitochondrial function provides support for the view that mitochondria play an important role in PD pathogenesis.

Concluding Remarks

The isolation and characterization of *parkin* have contributed significantly to our understanding of the pathogenesis of PD. Mutations in *parkin* are a common occurrence in EOPD, but they also appear to be involved in PD cases having later disease onset.

The *parkin* gene is large and its protein product is involved in an extensive array of protein–protein interactions. From the available information, two patterns are emerging about the cellular functions of Parkin: The first is its involvement in protein degradation via its ubiquitin-ligase activity. The second is its involvement in pathways regulating mitochondrial function via its interaction with Pink1 and DJ-1.

Several questions concerning *parkin* remain to be elucidated. These include how the expression of this rather complex gene is regulated, how extensively it functions in tumorigenesis or signaling pathways, whether its differential temporal and spatial regulation contributes to its involvement in cellular processes in addition to the extensive array of those already known, and whether, given its association with pathogenesis in EOPD, *parkin* is involved in developmental processes. Future research will more fully elucidate the function of *parkin* and its links to the different cellular processes that underlie the pathogenesis of PD.

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PARK3

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Glossary

Dopamine – Important neurotransmitter involved in multiple brain functions.
Gene – DNA-sequence bearing the building code for a protein.
Linkage analysis – Statistical method to identify the localization of the gene responsible for an observable trait, for example, a genetic disease.
Parkinson's disease – Common neurodegenerative disorder caused by a degeneration of dopaminergic neurons.
Sepiapterine reductase – Enzyme critical to the synthesis of tetrahydrobiopterine, a cofactor of dopamine synthesis.

Parkinson's disease (PD) is a common neurodegenerative movement disorder, characterized clinically by akinesia, rigidity, and rest tremor. Pathologically, neuronal loss, predominantly of dopaminergic neurons of the substantia nigra, but also in many other brain areas, is usually accompanied by α-synuclein positive inclusions in cell bodies and neurites (so called Lewy pathology). The disease commonly occurs as a sporadic disorder, but several loci and genes have been discovered to cause Mendelian forms of PD.

A dominant locus has been mapped to chromosome 2p13 (PARK3) in a group of families of European ancestry. In these families, the clinical and pathologic features relatively closely resemble those of sporadic PD. A common haplotype identified in two of the families, whose ancestors could be traced to a relatively small region in Northern Germany and Southern Denmark, suggested a common founder and supported the linkage results. The haplotype was refined to a region of about 2.5 Mb, but so far the causative gene in these families has not yet been identified. Several candidate genes in the region, including those for transforming growth factor-α (TGFα), sideroflexin-5, and several others have been excluded.

Further evidence for an involvement of the PARK3-locus in PD came from a large collaborative European study, using a whole genome association approach in a cohort of sib-pairs. One of the most prominent linkage peak of this study mapped close to the PARK3 region.

As already the initial linkage study provided evidence for a reduced penetrance of the putative mutation at the PARK3-locus, subsequent work focused on its potential role as a risk factor in sporadic PD. Interestingly, two

independent studies implicated the PARK3-locus as a disease modifying locus influencing age at onset in two sib pair cohorts with PD. Specifically, DeStefano et al. found evidence for association between a later PD age at onset and allele 174 of marker D2S1394, which is contained within the original linked haplotype. Pankratz et al. performed a genome screen to identify genes influencing the age at PD onset using 276 families. Significant evidence of linkage to chromosome 2p near the PARK3 locus (logarithm of odds [lod] = 4.8) was observed. Karamohamed et al. extended the work of DeStefano by genotyping additional single nucleotide polymorphisms (SNPs) in the vicinity of marker D2S1394. They reported association of one SNP and a haplotype across the gene for sepiapterine reductase (SPR) with age of onset in sibships of North American origin. This finding was confirmed in a further study thoroughly assessing the SPR gene haplotype structure, and its contribution to PD by studying a cohort of 600 sporadic PD cases ascertained from Germany as well as in familial PD samples from five different European countries. This study again demonstrated an association with age of onset at the markers D2S2110 and rs1876487 in the familial data set, as well as an association with PD susceptibility to several intercorrelated SNP markers and haplotypes in an LD block spanning the SPR gene in the sample of sporadic PD patients.

Given all converging evidence, DNA variant(s) in or around the SPR gene appears to influence PD onset. Coding regions of potential PARK3 candidate genes, including SPR have been screened for pathogenic mutations in PD families. The failure to detect such mutations could indicate that the functional variant affects expression or splicing regulation rather than the protein structure itself.

A recently published study has revealed a mutation in the 5′ UTR of the SPR gene as a cause of dopa-responsive dystonia. SPR is an interesting candidate gene, because it catalyses the conversion of 6-pyrovyl-tetrahydropterin (PTP) to tetrahydrobiopterin (BH4). Functional variants in the SPR regulatory regions may, therefore, modify the age of onset of PD.

Previous studies have shown that BH4 acts not only as a cofactor for tyrosine hydroxylase (TH) and is, therefore, important for dopamine biosynthesis, but also stimulates NOS isoforms (inducible(iNOS), neural(NOS), and endothelial (eNOS)). It has been suggested that iNOS confers protection to PD.

In summary, there is evidence from multiple studies that the PARK3 locus on chromosome 2p13 contributes to, and/or modulates sporadic and familial PD. At present, SPR is the most likely candidate gene in this region.

See also: Alpha-synuclein; PARK1, Alpha Synuclein; PARK2, parkin; PARK3; PARK5, UCH-L1; *PARK6, PINK1*; PARK7, DJ1; *PARK8, LRRK2* (Dardarin); Parkinson's Disease: Definition, Diagnosis, and Management; Parkinson's Disease: Genetics.

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PARK5, UCH-L1

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Genetics

The gene encoding ubiquitin carboxy-terminal hydrolase L1 (UCH-L1, also known as ubiquitin carboxyl-terminal esterase L1 and ubiquitin thiolesterase) was identified as the *PARK5* locus (OMIM 191342), using a candidate gene approach focusing on genes involved in ubiquitin-mediated protein degradation. The *UCH-L1* gene is located at 4p14 and contains 9 exons spanning 11.5 kbp of DNA. A heterozygous mutation in exon 4 of *UCH-L1* that resulted in a Ile93Met missense mutation was found in a German sibling pair affected with Parkinson's disease (PD). Two deceased members of the family, the paternal grandmother and a paternal uncle, were also affected. However, the father of the affected siblings was asymptomatic, although he was positive for the mutation. This suggests either that the mutation shows an autosomal dominant mode of inheritance with incomplete penetrance or that another unknown, pathogenetic factor contributes to the disease in this family. Despite extensive genetic screening in families with autosomal dominant PD, the Ile93Met mutation has not been found in other patients. However, the Ile93 residue is highly conserved: it is found in the paralogous gene UCHL3, the rat and mouse orthologs of UCHL1, and the homologous genes in yeast and the plant *Arabidopsis thaliana*. Therefore, either the Ile93Met substitution in UCH-L1 gene is a rare cause of familial PD or it is inherited with the parkinsonian phenotype as a result of a coincidental genetic mutation.

Clinical Phenotype

The parkinsonian phenotype in the German family is similar to sporadic Parkinson's disease (PD) and included resting tremor, rigidity, bradykinesia, postural instability, and good therapeutic response to levodopa. The disease onset was approximately at age 50.

Neuropathology

To date, there are no reported neuropathological findings as none of the gene-positive individuals has come to autopsy.

Genetic Association Studies in Sporadic PD

Numerous association studies have evaluated whether the *UCH-L1* gene plays a role in the sporadic form of PD. Most have focused on the potential importance of a non-synonymous polymorphism in exon 3 of *UCH-L1* that appears in about twenty percent of the Caucasian population and results in a Ser18Tyr amino acid change. An initial study in European sporadic PD patients found that this polymorphism was underrepresented in PD patients (odds ratio of 0.53; 95% CI = 0.30–0.94; $p = 0.03$). Although conflicting results were obtained in additional studies, a meta-analysis that pooled data from 11 association studies (1970 cases and 2224 controls) found an inverse association of the Ser18Tyr polymorphism with PD. There, 18Tyr carriers had an odds ratio of 0.84 (95% CI = 0.73–0.95), homozygotes had an odds ratio of 0.71 (95% CI, 0.57–0.88), and the 18Tyr allele showed a stronger association with early onset PD. However, these findings have not been reproduced in additional studies. A large case–control study (3023 sporadic PD patients) did not find that the Ser18Tyr variant was protective against PD under any mode of inheritance, screening of haplotype tags in the *UCH-L1* gene did not detect any other associated variants, and an updated meta-analysis that included 6594 individuals did not observe an association with PD. Given the meta-analyis results, it appears unlikely that the PARK5 locus is implicated in sporadic PD pathogenesis. However, polymorphisms in the UCH-L1 gene may play a role in PD pathogenesis in distinct ethnic groups.

Biochemical Functions of UCH-L1

UCH-L1 belongs to a family of deubiquitinating enzymes that recycle ubiquitin monomers from polypeptide–ubiquitin chains in the proteasome. UCH-L1 is normally expressed in neurons and testis and it is almost absent from other tissues. Indeed, it is highly abundant in the brain, constituting 1–2% of total soluble protein, and its 1.3-kb transcript is particularly abundant in the substantia nigra. It is a component of Lewy bodies. It has a molecular weight of 24.8 kDa and contains 223 amino acids.

Three distinct biochemical activities are associated with UCH-L1. UCH-L1 monomers catalyze the hydrolysis of ubiquitin–peptide polymers in vitro to free ubiquitin monomers. This activity is important in vivo for

recycling ubiquitin monomers from polypeptide–ubiquitin chains in the proteasome. It can also form dimers in vitro that have an ubiquitin–protein ligase activity that is capable of promoting α-synuclein aggregation. Thus, UCH-L1 acts as a hydrolase in its monomeric form and as a ligase in its dimeric form. The third UCH-L1 function is independent of its enzymatic activities. UCH-L1 can bind to mono-ubiquitin molecules in vivo. This leads to stable neuronal mono-ubiquitin levels by inhibiting their degradation in the brain.

Biochemical support that the Ile93Met mutation could cause PD in the German family has come from investigations assessing the impact of this mutation on the enzymatic functions of UCH-L1. Ile93Met UCH-L1 is associated with a marked decrease in ubquitin hydrolase activity, suggesting that *PARK5*-associated PD might result from insufficiency in the recycling of ubiquitin. An alternative possibility is that this mutation increases α-synuclein aggregation by altering the monomer to dimer ratio and increasing UCH-L1's ubiquitin-ligase function to promote α-synuclein aggregation. Transgenic mice expressing Ile93Met UCH-L1 show age-dependent loss of dopaminergic neurons: a pathological hallmark of PD.

In contrast to the biochemical findings for Ile93Met UCH-L1, Ser18Tyr UCH-L1 has an unchanged hydrolase activity and a reduced ubiquitin-ligase activity for α-synuclein in vitro. This may account for a protective effect of the 18Tyr variant in PD.

As might be expected, loss-of-function mutations in UCH-L1 do not recapitulate the likely gain-of-function phenotype that is associated with the apparent dominant allele leading to Ile93Met UCH-L1. Mouse UCH-L1 loss-of-function mutations (generated from an in-frame deletion of exons 7 and 8) confer a gracile axonal dystrophy (gad) phenotype, which is characterized by sensory and motor ataxia due to peripheral nerve axonal degeneration. Although degenerating neuronal axons accumulate amyloid Aβ-protein and ubiquitin–proteasome-positive deposits, brain neurons show no neurodegenerative features, and no parkinsonian phenotype develops.

There is additional evidence that UCH-L1 plays an important role in neurodegenerative processes. Absence of UCH-L1 protects cells from acute, stress-induced apoptosis, and administration of UCH-L1 alleviates the β-amyloid-induced synaptic dysfunction and memory loss in a mouse model of AD.

Conclusion

UCH-L1 is clearly an important protein for normal neuronal function. There is no clear-cut genetic association between polymorphisms at the *PARK5* locus and PD. If *UCH-L1* mutations do contribute to the pathogenesis of PD, they are rare, and their mechanisms of action are not yet fully elucidated.

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PARK6, PINK1

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Glossary

Haploinsufficiency – A disease state that results when a single functional copy of a gene in a diploid organism cannot produce enough gene product to provide for a normal phenotype.

Genetics and Clinical Features Associated with PINK1 Mutations

Homozygous mutations in the phosphatase and tensin homolog (*PTEN*) *induced putative kinase 1* (*PINK1*) gene were initially identified in three consanguineous Italian kindreds in which parkinsonism was inherited as an autosomal recessive trait. Both nonsense (W437X) and missense (G309D) mutations were identified in the *PINK1* gene, located at 1p36. The parkinsonian phenotype in *PINK1* kindreds is milder than that of idiopathic Parkinson's disease (PD) with earlier disease onset (age 20–40), slower progression, and good therapeutic response to lower doses of levodopa. The *PINK1*-associated phenotype shares similarities with that of *parkin*-associated phenotypes, including focal dystonia and sleep benefit. Since the original description of the W437X and G309D mutations, additional mutations have been described in both Caucasian and Asian populations. In addition to the originally identified homozygous mutations, heterozygous and compound heterozygous mutations have been described. Heterozygous *PINK1* mutations may predispose individuals to PD, although this finding is still controversial. Heterozygous mutations in *PINK1* have been associated with a PD phenotype, raising the possibility of haploinsufficiency as an underlying mechanism. Interestingly, in contrast to homozygotes, a compound heterozygote had a later disease onset than *PINK1* homozygotes. While most of the mutations described to date are missense or nonsense mutations, deletions have also been reported, and these are associated with dementia. This may suggest that more substantial decreases in *PINK1* function are associated with more severe PD phenotypes. The pathology underlying *PINK1*-associated parkinsonism with homozygous mutation remains unknown as no cases have yet come to autopsy.

Imaging studies have been performed in homozygous and heterozygous *PINK1* individuals. Homozygotes show an ^{18}F-dopa uptake pattern similar to that seen in idiopathic PD with 80–85% reduction of uptake in the caudate and putamen, whereas heterozygotes show 20–30% reduction in the same regions.

The Function of PINK1

The function of the PINK1 protein, which is highly conserved among metazoans and has been identified in both vertebrates and invertebrates, has not yet been fully elucidated. It is a serine–threonine kinase localized to the intramembrane region of the mitochondria and is associated with the inner mitochondrial membrane. Several reports suggest that PINK1 is also present in the cytoplasm. The presence of PINK1 in the cytoplasm may be linked to proteasomal inhibition. Given that the mutations associated with PD are recessive and loss-of-function mutations, it is conceivable that the cytoplasmic PINK1 fraction is the PINK1 that accumulates in the cytoplasm because of defective degradation due to proteasomal dysfunction.

The Regulation of *PINK1*

PINK1 expression appears to be regulated in several ways. In humans, it is differentially expressed in both the brain and body at the mRNA and protein levels. In humans, the highest levels of *PINK1* mRNA expression primarily are seen in neurons and less in glia in the hippocampus, substantia nigra, and cerebellar Purkinje cells. In the brain, PINK1 protein is detected in all cell types, primarily in a cytoplasmic pattern consistent with mitochondrial localization. It is detected in Lewy bodies in sporadic PD as well as in *PINK1* heterozygotes.

The transcriptional regulation of *PINK1* has been investigated. One report suggests that the abundance of *PINK1* mRNA is at least partly regulated by the presence of a noncoding antisense transcript that under physiological conditions positively influences the abundance of the cis-transcribed *PINK*1 mRNA. *PINK1* genomic variants are associated with altered *PINK1* transcript levels, indicating additional levels of control over *PINK1* mRNA expression. Differential mRNA splicing has also been implicated in the regulation of *PINK1* expression. In a sporadic parkinsonian patient, a splice-site mutation leads to several aberrant mRNAs. A naturally occurring

splice-site variant contains only the final four exons of the *PINK1* gene.

The PINK1 protein may be regulated at the level of the proteasome, as proteasomal inhibition leads to an increase of cytosolic PINK1.

Endogenous PINK1 is proteolytically modified at its amino terminus to produce a mature protein – the immature form is a 581 amino acid proprotein that is cleaved at position 77 to yield a 504 amino acid mature protein. In addition, the levels of functional PINK1 may be regulated by other proteins, such as heat-shock protein Hsp90 (Hsp90/Cdc 37), which appears to regulate the ratio of processed to unprocessed protein.

PINK1-kinase activity is regulated at multiple levels, apparently through intramolecular interactions. Removal of either the C- or the N-terminus impacts on PINK1-kinase activity by increasing its autophosphorylation activity. Removal of its N-terminus may interfere with its ability to be translocated into the mitochondria.

Proteins Interacting with PINK1

The interactions of PINK1 with other proteins offer additional insights into its normal biological roles and how their disruption may lead to PD. To date, PINK1 has been shown to interact with the TNF receptor associated protein 1 (TRAP1), DJ-1, and HtrA2. TRAP1 is a mitochondrial chaperone that is also identified as heat shock protein 75 (Hsp75). PINK1 binds TRAP1 and phosphorylates it both in vitro and in vivo. PINK1 phosphorylation of TRAP1 protects it against oxidative-stress-induced cell death by suppressing the release of cytochrome c from the mitochondria. The ability of PINK1 to promote TRAP1 phosphorylation is impaired by the presence of mutations that have been associated with PD (G309D, W437X, and L347P).

PINK1 and DJ-1 interact at both the biochemical and genetic levels. PINK1 has been shown to interact with DJ-1 in cotransfection experiments; coexpression of wild-type PINK1 and DJ-1 suppresses MPP^+-induced cell death, whereas coexpression of mutant PINK1 and DJ-1 enhances susceptibility of cells to MPP^+-induced cell death. Furthermore, familial PD patients have been described with heterozygous mutations in both *PINK1* and *DJ-1*.

More recently, the mitochondrial serine–protease HtrA2 (Omi) has been shown to interact with PINK1. Interestingly, heterozygous mutations in this gene identified in German PD patients result in defective activation of the protease activity of Omi/HtrA2. Cells overexpressing one of the mutations (S399) exhibited mitochondrial dysfunction, altered morphology, and were also more susceptible to stress-induced cell death. Because of its association with PD, the gene for Omi/HtrA2 has been named the *PARK13* locus. Other studies have shown that Omi/HtrA2 is phosphorylated via the activation of the p38 pathway in a PINK1-dependent manner. HtrA2 phosphorylation is decreased in the brains of PD patients carrying *PINK1* mutations. PINK1-dependent phosphorylation of HtrA2 may regulate the proteolytic activity of HtrA2 and contribute to increased resistance of cells to mitochondrial stress conditions.

Summary and Conclusion

In summary, PINK1 appears to have an important role in maintaining mitochondrial integrity under conditions such as oxidative stress and proteasomal dysfunction. Despite the considerable information provided by the studies described above, several questions regarding the function of PINK1 remain unanswered. Since PINK1 is a PTEN-induced kinase, one question is whether PINK1 has a role in the phosphatidyl-inositol-3 kinase (PI3K) signaling pathway. PTEN has been implicated in regulating the oncogenic PI3K/Akt signaling pathway, in angiogenesis, and in the formation and maintenance of neuronal circuits in the brain. Dysregulated PI3K/PTEN signaling has been implicated in neurogenesis and neuronal connectivity. While PINK1 may exert its function through the maintenance of mitochondrial integrity, in light of recent data implicating neurodevelopmental processes in PD pathogenesis, it may also be that other aspects of its function relating to its potential association with the PI3K/PTEN pathway may contribute to neurodegeneration in PD.

See also: Mitochondrial Dysfunction; PARK2, parkin; PARK7, DJ1; Parkinson's Disease: Genetics.

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PARK7, DJ1

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Glossary

Dimer – Complex formed by two simpler protein components (monomers). A dimer is termed homo-dimer or hetero-dimer when the two monomers are constituted by identical or different protein species.
Genotype – The observed characteristics or status present at a given genomic position.
Monogenic (Mendelian) – Normal or pathologic trait determined by the effects of a single gene or chromosomal locus.
Phenotype – The observed characteristics (normal or pathologic) at biochemical, cellular, or whole organism level (with the exception of the genotype).
Sporadic – Adjective used to indicate a phenotype (e.g., a disease) that is not known to have occurred in other family members (as opposed to Familial). Sporadic is not synonymous of nongenetic. A sporadic disease can be entirely genetic in origin (e.g., autosomal recessive diseases).

Definition and History

The gene termed *DJ-1* was first described in 1997 as a putative oncogene. However, the interest in the biology of *DJ-1* gained momentum in 2003, with the discovery that its mutations cause a form of early-onset human parkinsonism, leading to its current designation as *PARK7*. The link between *DJ-1* and parkinsonism was found by genetic analyses of families in which several subjects developed early-onset parkinsonism in association with inherited loss-of-function mutations in the gene.

Parkinsonism is defined by the clinical combination of slowness of movement (also termed bradykinesia), tremor at rest, and muscular rigidity. When no causes are identifiable, the disease is defined as primary or idiopathic. Parkinson's disease (PD, idiopathic parkinsonism) is the most common form of primary, degenerative parkinsonism, currently defined by the presence of this syndrome in the absence of other atypical clinical signs, and with beneficial response to dopamine-replacement therapy. This clinical entity is associated with the progressive loss of dopamine-producing neurons in the brain and (usually) with the presence of protein inclusions (termed Lewy bodies) in the surviving neurons.

PD is uncommon before the age of 40-years, and its incidence increases with age. If the symptoms start before the age of 40 years (45 for other Authors), the disease is referred to as 'early-onset PD.' In most cases PD occurs in sporadic form, but about 10–15% of patients report one or more affected relatives. The cause of PD remains still unknown in most patients. However, several Mendelian forms of the disease have been identified, which are transmitted in either an autosomal dominant (*PARK1*, *PARK8*) or an autosomal recessive (*PARK2*, *PARK6*, *PARK7*) fashion. *PARK7* is one of the genes known to cause autosomal recessive forms of degenerative parkinsonism with early-onset.

The *PARK7* gene (also termed *DJ-1* or *DJ1*) (OMIM #606324) is abundantly and ubiquitously expressed in the brain and other body tissues, and encodes a protein of 189 amino acids, which bears the same name (PARK7 or DJ-1). The protein belongs to a large superfamily named after a shared, evolutionary conserved domain (ThiJ/PfpI), and its subcellular localization includes

cytosol and mitochondria. In normal conditions, two PARK7 protein monomers associate to form homodimers. Moreover, there is evidence that posttranslational modifications (mainly oxidation) produce several PARK7 protein variants. Despite cellular abundance, evolutionary conservation, and ubiquitous presence, the exact function of the PARK7 protein remains unknown.

Pathogenesis

The pathogenesis of this form remains poorly understood, but is believed to be primed by the loss of the normal function of the PARK7 protein. On the basis of the currently available data, the PARK7 protein appears to be a multifunctional neuroprotective molecule that includes antioxidant and molecular chaperone properties. This is intriguing, as there is evidence of oxidative stress and protein misfolding occurring in the brain of patients with common forms of PD and other neurodegenerative disorders. The chaperone activity of PARK7 seems redox dependent, being activated in response to oxidative stress. One possibility to explain the seemingly multiple effects of PARK7 is offered by the known capacity of this protein to bind mRNA species, thereby being potentially able to influence disparate cellular pathways. The homologs of the *PARK7* gene have been knocked out in different model organisms, including mouse, fruit fly, zebrafish, and nematode. Overall, these models failed to recapitulate the features of human disease, but they highlighted important roles of the PARK7 protein in the physiology of the brain dopaminergic systems, as well as in the protection of neurons from oxidative stress. Understanding the function of the PARK7 protein and how its dysfunction cause disease might provide clues into the mechanisms of neurodegeneration also in more common forms of parkinsonism. However, whether the pathogenesis of the disease caused by the PARK7 defect overlaps with the other forms of autosomal recessive, early-onset parkinsonism or with that of the common, late-onset forms of PD, remains unclear at this juncture.

Epidemiology

The disease causing, homozygous or compound-heterozygous mutations in *PARK7* are rare, being detected in only 1–2% of patients with early-onset PD. Moreover, in a similar percentage of patients, only a single-heterozygous mutation is detected, the role of which in the disease causation remains doubtful. They might represent just rare disease-unrelated variants. However, some of these single-heterozygous mutations might cause disease by affecting the PARK7 dimer formation or function (a mechanism termed 'dominant negative'). More than 20 different *PARK7* mutations have been identified in patients with parkinsonism (**Table 1**), including point mutations (missense, truncating, splice site mutations), and large genomic deletions or duplication. However, only 13 mutations were found in homozygous or compound-heterozygous state, and are therefore more likely to be disease causing. The mutational spectrum of *PARK7* is therefore broad, and the screening of this gene is complex, requiring copy number assay (gene dosage) in combination with direct sequencing, in order to achieve high sensitivity. *Parkin (PARK2)* gene mutations are a much more common cause of autosomal recessive early-onset parkinsonism than are mutations in *PARK7* or *PARK6 (PINK1)*. The screening of *PARK7* and *PARK6* might be therefore appropriate especially if *parkin* mutations are not found.

Clinical Features, Differential Diagnosis, Management

The current knowledge about the clinical phenotype associated with *PARK7* mutations is limited by the small number of patients with clear disease-causing mutations, and by the wide phenotypic variability present even in patients from the same family. Overall, the patients with disease-causing homozygous or compound-heterozygous *PARK7* mutations resemble those with mutations in the other genes for early-onset parkinsonism (*parkin* or *PINK1*). Parkinsonism symptoms appear usually before 40 years of age, and they are exquisitely responsive to L-dopa or dopamine agonists, with, in some patients, development of L-dopa-related motor fluctuations and dyskinesias. The progression of the parkinsonism is slow in most cases.

In a single consanguineous family from Southern Italy, *PARK7* mutations have been detected in association with a broader phenotype, including early-onset parkinsonism, motor neuron disease, and behavioral and cognitive disturbances. The clinical spectrum of the *PARK7*-related disease might therefore be broader than the pure parkinsonism. In patients with *PARK7* mutations, structural brain imaging with computed tomography (CT) or magnetic resonance imaging (MRI) scans have been unremarkable. Functional brain imaging with positron emission tomography (PET) or single photon emission computed tomography (SPECT) showed the abnormalities of the nigrostriatal dopaminergic system that are classically seen in patients with PD. Therefore no clinical or imaging features allow distinguishing the patients with mutations in the *PARK7* gene from those with mutations in *parkin* or *PINK1*, or from those without identifiable gene mutations, indicating that genetic testing is essential for an accurate etiologic diagnosis.

The pathology associated with *PARK7* mutations remains unknown as necropsy studies in patients with this form have not been reported so far. Lewy bodies in patients with idiopathic PD contain no substantial PARK7

Table 1 *PARK7* gene mutations detected in patients with parkinsonism

Zygosity	*Mutation*	*Predicted effect*	*Patient origins*	*References*
Homozygous	Exon 1–5 del	No mRNA expression	Dutch	Bonifati et al.
Homozygous[a]	g.168_185dup	Unknown	Italian	Annesi et al.
Homozygous	p.L10P	Missense	Chinese	Guo et al.
Homozygous	p.M26I	Missense	Jewish	Abou-Sleiman et al.
Homozygous	p.E64D	Splicing abnormality	Turkish	Hering et al.
Homozygous	p.P158 del	Unknown	Dutch	Macedo et al.
Homozygous[a]	p.E163K	Missense	Italian	Annesi et al.
Homozygous	p.L166P	Missense, protein instability	Italian	Bonifati et al.
Double heterozygous[b]	c.56delC;c.57G→A	Protein truncation	Hispanic	Hague et al.
Double heterozygous[b]	IVS6–1G→C	Splicing abnormality	Hispanic	Hague et al.
Double heterozygous[c]	p.A39S	Missense	Chinese	Tang et al.
Compound heterozygous[d]	g.159C→G	Unknown	Italian	Tarantino et al.
Compound heterozygous[d]	IVS4 + 3insA	Unknown	Italian	Tarantino et al.
Single heterozygous	Exon 5 del	Protein truncation	Serbian	Djarmati et al.
Single heterozygous	Exon 5–7 del	Protein truncation	Tyrolean	Hedrich et al.
Single heterozygous	IVS5 + 2–12 del	Splicing abnormality	Russian	Hedrich et al.
Single heterozygous	Exon 1–5 dup	Unknown	Dutch	Macedo et al.
Single heterozygous	p.A104T	Missense	Hispanic	Hague et al.
Single heterozygous	p.A104T	Missense	Chinese	Clark et al.
Single heterozygous	p.D149A	Missense	Afro-Caribbean	Abou-Sleiman et al.
Single heterozygous	p.A179T	Missense	Dutch	Macedo et al.
Single heterozygous	p.T160T	Unknown[e]	Not reported	Pankratz et al.
Single heterozygous	p.A167A	Unknown[e]	Not reported	Abou-Sleiman et al.
Single heterozygous	p.A167A	Unknown[e]	Not reported	Pankratz et al.
Single heterozygous	p.V186V	Unknown[e]	Not reported	Hering et al.
Single heterozygous	3′UTR + 120insA	Unknown[f]	Not reported	Abou-Sleiman et al.
Single heterozygous	3′UTR + 203G→A	Unknown[f]	Not reported	Abou-Sleiman et al.

[a]Promoter (g.168_185dup) mutation and missense (p.E163K) mutation, detected both in homozygous state, in patients with parkinsonism–dementia–amyotrophic lateral sclerosis complex.
[b]The c.56delC;c.57G→A and the IVS6–1G→C mutation were detected in the same patient with early-onset parkinsonism.
[c]Found in combination with a single-heterozygous mutation (p.P399L) in the *PINK1* gene in two Chinese sibs with early-onset parkinsonism.
[d]The g.159C→G and IVS4 + 3insA mutations were detected in the same patient, and shown to be in compound heterozygosity. The g.159C→G mutation lies in the promoter and might affect gene expression; IVS4 + 3insA might affect mRNA splicing.
[e]Silent mutation; effects on mRNA splicing, mRNA stability, translation efficiency, cannot be excluded.
[f]Mutation in the 3′ untranslated region; effects on mRNA stability cannot be excluded.

immunoreactivity. However, PARK7 immunoreactivity is present in the neuronal inclusions that characterize other neurodegenerative diseases, collectively known as tauopathies, and in the multiple system atrophy, suggesting a possible participation of the PARK7 protein in their pathogenesis. Unless novel therapeutic or neuroprotective strategies become available on the basis of the specific disease etiology or pathogenesis, the therapeutic approach to the patients with *PARK7* mutations is not different from the approach to any patients with early-onset PD. Whether the prognosis of this form is different from the other forms of early-onset PD remains unknown due to the small number of patients reported with *PARK7* disease-causing mutations and to the wide clinical variability.

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See also: Alpha-synuclein; PARK2, parkin; PARK3; *PARK6, PINK1*; *PARK8, LRRK2* (Dardarin); Parkinson's Disease: Definition, Diagnosis, and Management; Parkinson's Disease: Animal Models; Parkinson's Disease: Genetics.

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PARK8, LRRK2 (Dardarin)

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Glossary

Paralog – Genes related by duplication within one genome. Orthologs retain the same function in the course of evolution, whereas paralogs evolve new functions, even if these are related to the original one.
Ortholog – Genes in different species that evolved from a common ancestral gene by speciation. Normally, orthologs retain the same function in the course of evolution.

PARK8 (*LRRK2* Gene)

Genetics

The *PARK8* locus was originally identified in a Japanese kindred transmitting a Parkinson's disease (PD) phenotype in an autosomal dominant manner. Linkage analysis mapped the locus to chromosome 12p11.2–q13.1, and several years later, through studies of 51 families associated with autosomal dominant PD, mutations in the gene leucine-rich repeat kinase 2 (*LRRK2*) were identified. Since then, at least 20 different mutations have been

described in *LRRK2*. Mutations in *LRRK2* have a worldwide distribution and account for ~7% of familial PD cases and have also been identified in sporadic PD cases. A large study of *LRRK2*-associated PD revealed that six of the mutations described to date can be considered pathogenic, the most common being G2019S. This mutation is found in 4% of familial PD cases and 1% of sporadic PD cases. There are different frequencies of the familial mutations in different ethnic populations. An apparent geographic latitude gradient exists: the highest frequency of mutations is seen in the Middle East, and a decreasing frequency is seen in more northern latitudes in Europe. Approximately 30–40% of familial PD cases in Arab and Ashkenazi Jewish populations are associated with *LRRK2* mutations, while this number is ~6% in the European population.

Clinical Phenotype

The PD phenotype associated with the *PARK8* locus originally described in the Japanese kindred is indistinguishable from that of sporadic PD. The phenotype seen in most *LRRK2* kindreds consists of tremor that is often asymmetrical, rigidity, bradykinesia, and a good response to levodopa therapy. In one study, the parkinsonian phenotype of both motor and nonmotor symptoms was more benign than that of idiopathic PD. The disease has usually a late onset (>50 years). Penetrance appears to be age dependent ranging from 28% at the age of 59 to 74% at the age of 79. There is no clear-cut difference between the phenotypes of heterozygotes and homozygotes.

The phenotypic similarity of *LRRK2* families to idiopathic PD also extends to findings from imaging studies. ^{18}F-dopa PET studies have revealed that individuals with *LRRK2* mutations exhibit a pattern of uptake that in most cases is indistinguishable from that of idiopathic PD, with a maximum reduction of ^{18}F-dopa uptake in the putamen. Some variability in the functional imaging findings in *LRRK2* cases is seen and is consistent with the compensatory changes. These include downregulation of the dopamine transporter (DAT) and upregulation of decarboxylase activity.

Neuropathology

The neuropathology associated with *LRRK2* mutations is pleiomoprhic, both within the same and among different kindreds. Even though individuals carry the same mutant *LRRK2* allele, different neuropathologies have been observed. In some cases, there is neuropathology consistent with Lewy body PD; in some other, diffuse Lewy body disease (DLB); in a few other, there is only nigral degeneration; and in yet other cases, findings consistent with progressive supranuclear palsy (PSP). There are synuclein-positive and tau-positive inclusions, and LRRK2 protein can be detected in the Lewy bodies (LB) and in dystrophic neurites in the brainstem. Interestingly, LRRK2 protein is not restricted to the brain regions that are associated with pathology in PD. Its subcellular localization includes the nuclear envelope and cytoplasm. Furthermore, in one study, there were LRRK2-positive-globular inclusions with punctate α-synuclein-positive staining in the lower brainstem (dorsal motor nucleus of the vagus). This finding raises the possibility of an association between early α-synuclein pathology and *LRRK2* function.

The *LRRK2* Gene

Structure, expression, and protein product

The *LRRK2* gene is large (144 kb) and has a coding region of 7.4 kb comprised of 51 exons. It is expressed in regions affected by PD such as the striatum, substantia nigra pars compacta, and cortex. The regulation of *LRRK2* mRNA expression and message stability has not yet been elucidated.

The LRRK2 protein has also been called dardarin, as some of the families in which mutations were identified were of Basque origin, and darda is the word for tremor in the Basque language. Dardarin is a large, 2527 amino-acid protein that contains seven different domains: starting near the N-terminus are armadillo repeats, then an ankyrin (ANK) repeat domain followed by a leucine-rich repeat (LRR) domain, a Ras of complex protein (ROC) GTPase domain, a C-terminal of Roc (COR) domain, a kinase domain similar to that found in members of the tyrosine kinase-like (TKL) subfamily, and finally a C-terminal WD40 domain.

The different domains suggest that dardarin is a multifunctional protein that is involved in multiple protein–protein interactions. ANK repeats are repeated amino-acid motifs that serve as a protein–protein interaction module and serve in a wide range of cellular functions. A number of human diseases are associated with defects in proteins containing ANK repeats. Armadillo repeats are tandem repeats of 42 amino acids that mediate interactions with other proteins. They have been identified in proteins involved in transcriptional activation, nuclear transport, signaling, and cytoskeletal regulation. The LRR domain contains LRRs arranged in tandems of two or more repeats, resulting in a solenoid structure that is conducive to protein interactions. The Roc and COR domains characterize proteins that belong to the ROCO protein family. In invertebrates, members of this family are involved in cell division, chemotaxis, and development. In humans, they have been implicated in epilepsy and cancer. These proteins also appear to have the ability to activate intramolecular kinase domains. Indeed, it appears that *LRRK2* mutations such as G2019S and I2020T have a kinase-activating effect. This is consistent with the genetic data that, given the dominant inheritance of the parkinsonian

phenotype, support a gain-of-function disease mechanism. Proteins containing WD40 domains are also involved in protein interactions and especially in processes such as cell cycle progression and histone binding.

The rather complex structure of the LRRK2 protein product suggests that it has a multifunctional role. Besides the obvious kinase and GTPase functions, it has the potential to bind a wide range of proteins including transcription factors and signaling molecules.

There is a paralog of *LRRK2*, *LRRK1*, which also encodes a rather large protein of 2052 amino acids. It is located on chromosome 15q26.3. The two genes are evolutionarily conserved in vertebrates and appear to share a common ancestral gene. In the two invertebrate model systems, *Drosophila melanogaster* and *Caenorhabditis elegans*, there is only one *LRRK* ortholog. To date, mutations in *LRRK1* have not been associated with PD.

LRRK2 domains and mutations associated with PD

The multiple structural motifs included in LRRK2 make it very likely that it is involved in multiple protein–protein interactions. Its motifs can be identified both in prokaryotes and eukaryotes, and their evolutionary conservation suggests that they play important roles throughout the evolution.

From the study of other protein kinases, we know that the kinase catalytic domain consists of N-terminal and C-terminal lobes that are connected by a hinge-like region. This structure forms a cleft in which the protein substrate can bind along with Mg^{2+} and ATP. Within the C-terminal lobe lies an activation sequence consisting of 20–35 residues. The C-terminus of the molecule is also required for autophosphorylation. Phosphorylation of the activation sequence alters its conformation. Phosphorylation is required for kinase activation, as the conformational change allows access of the substrate and is required for catalysis. The mutation most commonly associated with PD, G2019S and the less frequently PD-associated mutation, I2020T, lie at the N-terminal boundary of the activation segment and therefore are likely to interfere with kinase activation. While the genetic data described above support an activating role for the G2019S substitution, a decrease in kinase activity may also be consistent with a gain-of-function mechanism, given the multitude of potential protein interactions.

The seven-ANK repeats of LRRK2 form antiparallel helices followed by a β-hairpin loop. These can be stacked together to form a curved structure. These repeat domains apparently undergo a two-state folding transition. Studies of other proteins containing ANK repeats show that the number of ANK repeats is a molecule affects its energetics. The addition or removal of repeats may alter the folding process of the protein molecule. For example, the folding pathway of the ANK repeats in Notch, a protein involved in multiple cell-fate decisions throughout development, is selected based on the local energetics. Differential folding will impact the protein interactions in which the molecule participates. One of the PD-associated *LRRK2* mutations, R793M, is located within the ANK domain. It is not yet clear how this substitution affects the folding pathway or protein interactions utilizing the ANK domain.

Multiple amino acid substitutions caused by *LRRK2* mutations associated with PD are located in the LRR domain. Four mutations (R1067Q, S1096C and S1228T, I1122V) are located at the surface of the structure formed by the LRR repeats. These may interfere with the as yet unidentified protein interactions.

Other PD-associated mutations are located in the WD40 domain. Proteins containing WD40 domains are functionally diverse, making it difficult to predict the function of this domain in LRRK2. The three-dimensional structure of the WD40 repeats consists of a propeller-like structure formed by four-stranded antiparallel β-pleated sheets. At least one of the amino-acid substitutions associated with PD is located at the surface of the structure formed by the WD40 domain. It is conceivable that this amino-acid substitution interferes with interactions between the WD40 domain and an unidentified protein.

Recent studies have shown that LRRK2 exists as a dimer under native conditions. This state appears to be stabilized by the interactions between multiple structural domains.

In cell cultures, LRRK2 is localized to the Golgi apparatus, plasma membrane, and synaptic vesicles. It can resist solubilization from the membrane suggesting that it is associated with lipid rafts. This association does not appear to be influenced by the I2020T mutation. It suggests that LRRK2 is involved in signal transduction, membrane trafficking, and cytoskeletal organization. Interestingly, alpha-synuclein also localizes to the presynaptic cell membrane and is associated with lipid rafts. LRRK2 has also been localized to lysosomes, endosomes, and mitochondria. An interaction of the ROC domain of LRRK2 with parkin has been reported.

LRRK2 is also a member of the receptor-interacting protein kinase (RIPK) family. Members of this protein family can function as sensors of cellular stress and integrators of different cellular functions implicated in inflammation and cell survival. Members of this protein family are involved in the nuclear translocation of the NF-κB transcription factor and in the activation of mitogen-activated protein kinase (MAPK) pathways including the extracellular signal-regulated kinase (ERK), the c-Jun amino terminal kinase (JNK), and the p38 MAPK. The MAPK pathways are three-tiered pathways involving an MAPK kinase kinase (MAPKKK), an MAPK kinase (MAPKK), and an MAPK. This is a kinase cascade in which the kinase in each level activates the kinase in

the successive level by phosphorylation. Transcription factors, mitochondrial and cytosolic proteins are likely substrates of these kinases.

Given the LRRK2's multiple protein domains and its possible plethora of protein–protein interactions, identifying genes whose expression is affected by the absence of LRRK2 function can provide insight into LRRK2's cellular functions. Gene expression profiling using microarray analysis in neuroblastoma cell lines with suppressed endogenous LRRK2 mRNA revealed changes in 187 genes. These genes are involved in axonal guidance, nervous system development, cell cycle control, cell differentiation, cell communication, the MAPKKK cascade, and Ras-protein-signal transduction.

Summary and Conclusion

The identification and characterization of *LRRK2* have provided significant insights into the potential mechanisms underlying PD pathogenesis. Its localization in the lower brainstem with punctuate α-synuclein staining may implicate it in the temporal and spatial sequence of neuropathological stages that have been associated with sporadic PD.

LRRK2 is a rather complicated gene with complex regulation and a large potential for protein–protein interactions. Its multiple functional domains most likely impact multiple different pathways. At this point, we have only a partial understanding of its potential protein–protein interactions. Elucidating the nature of these interactions, and how they are affected by *LRRK2* mutations will provide significant insight into our understanding of PD pathogenesis.

The pleiomorphic pathology observed within one kindred, as well as between different kindreds, for a single dominant mutation suggests that multiple, distinct cellular processes can be affected by a single *LRRK2* mutation. It is unclear whether this reflects a stochastic process involved in one or more cellular processes impacted by the *LRRK2* mutation or reflects genetic or potentially subtle environmental differences. In any case, given the frequency of *LRRK2* mutations leading to PD, it will be important, and a significant challenge, to identify modifiers of LRRK2 function at both the genetic and environmental levels. This information will also add an important dimension to our understanding of the complexity of PD pathogenesis.

LRRK2's ability to form a dimer under native conditions adds further complexity to its role in the etiology of PD, as its functional ability may be related to its ability to maintain a dimeric structure. In individuals with *LRRK2* mutations, multiple types of dimers may be formed between potentially and differently structured LRRK2 proteins.

LRRK2's multiple domains may be used to facilitate its interactions with different proteins at different time points or in different cell types. Consequently, it is possible that *LRRK2* participates in different cellular processes at different times during development than it does later in adult life. Further delineation of the cellular processes and gene networks involving *LRRK2* in different cells and at different times will undoubtedly contribute to elucidating the mechanisms underlying neurodegeneration in PD.

See also: Alpha-synuclein; Dopamine Transporter: Aging and Parkinson's Disease; Neuroimaging, Parkinson's Disease; PARK2, parkin; PARK3; PARK5, UCH-L1; *PARK6, PINK1*; PARK7, DJ1; Parkinson's Disease: Definition, Diagnosis, and Management; Parkinsonism: Genetics; Parkinson's Disease: Genetics; PET Imaging in Movement Disorders; SPECT Imaging in Movement Disorders.

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Parkinson Hyperpyrexia Syndrome

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Glossary

Akinesia – The inability to initiate movement due to difficulty in selecting and/or activating motor programs in the central nervous system. Common in severe cases of Parkinson's disease akinesia is a result of severely diminished dopaminergic stimulation.
Dopamine – A neurotransmitter activating five types of dopamine receptors in the human brain. Dopamine is produced in several areas of the brain, including the substantia nigra and the ventral tegmental area and hypothalamus. It is responsible for the mediation of motor control, behavior, and emotions.
Creatine phosphokinase – An enzyme expressed by various tissue types, mostly muscles. It catalyzes the conversion of creatine and serves for intracellular energy transport. Clinically, creatine kinase is assayed in blood tests as a marker of myocardial infarction (heart attack), rhabdomyolysis (severe muscle breakdown), muscular dystrophy, and in other diseases.
Hyperpyrexia – An excessive and unusual elevation of set body temperature to greater than or equal to 41.1 °C (106 °F), or extremely high fever, that is often fatal.
Neuroleptic malignant syndrome – A life-threatening condition caused by an adverse reaction to antipsychotic drugs, that is characterized by muscle rigidity, fever, autonomic instability, and cognitive changes and is associated with an elevated creatine phosphokinase (CPK) level.
Rhabdomyolysis – The rapid breakdown of skeletal muscle tissue due to injury to muscle tissue caused by physical (e.g., crush injury), chemical, or biological factors, leading to the release of breakdown products of damaged muscle cells into the bloodstream. Some of these, such as myoglobin, are harmful to the kidney and may lead to acute kidney failure.

Definition and History

Parkinsonism-hyperpyrexia syndrome (PHS) is an acute life-threatening condition in patients with Parkinsonism exposed to dopamine replacement therapy (DRT) that is characterized by high fever, muscle rigidity, alteration of consciousness, and autonomic instability. The first case was described in 1973 under the name of 'akinetic crisis.' In 1981 clinical similarity to neuroleptic malignant syndrome (NMS) was pointed out. Since then, this condition has been reported under multiple names: Neuroleptic malignant-like syndrome, malignant syndrome of Parkinsonism, acute akinesia, levodopa-withdrawal hyperthermia, dopaminergic malignant syndrome, and finally, PHS.

Epidemiology

Although PHS is a rare complication of Parkinson's disease (PD), its true incidence is unknown and is likely underestimated. Reports suggest that 0.3–3.6% of all PD patients develop PHS each year. This number includes only severe cases that require hospitalization; many others may remain unrecognized. There are reports of PD patients who had frequent or even daily mild episodes of PHS that eventually became severe and fatal. Patients with idiopathic PD at any stage and other parkinsonian disorders, such as multiple system atrophy, progressive supranuclear palsy, dementia with Lewy bodies, etc. can develop PHS. Patients on high doses of DRT with prominent wearing-off phenomenon, young-onset idiopathic PD, and more advanced stages of the disease are at higher risks. Males develop PHS more frequently than females.

Risk Factors

In the first reports, withdrawal from DRT was considered to be the sole cause of this syndrome, as most patients

developed PHS during 'levodopa holidays.' It is now recognized that not only rapid discontinuation of DRT but also any abrupt changes in medication regimen can provoke PHS. Some examples include changes from rapid release to slow release carbidopa/levodopa, discontinuation of tolcapone or amantadine, change from carbidopa/levodopa to dopamine agonists, change from one agonist to another, or simply changes in daily schedule of medications intake. Most patients who develop PHS are on high doses of levodopa, but some are on other medications for PD, such as dopamine agonists or amantadine alone. Changes in diet, worsening of constipation, bowel obstruction, and other factors affecting medication absorption can also provoke PHS. The time from the changes in medication to the onset of the symptoms can be as short as several hours and as long as 7 days. Medication withdrawal or change is responsible for about 30% of all cases. Any other physiological stressors can precipitate PHS. Among them are infection, surgery, injury, hypo- or hypernatremia, dehydration, heat stroke, overheating, anorexia or poor food intake, perimenstrual period, and others. In about 5% of cases, wearing-off symptoms alone trigger PHS, therefore putting the patients with advanced disease and severe motor fluctuations at higher risk for PHS. Another 5% of patients develop PHS in the absence of any obvious triggers. Recent expansion of surgical treatment for PD presents new risk factors for PHS. Sudden discontinuation of medications after deep brain stimulation (DBS) surgery was reported to provoke PHS. However, in other cases, DBS was shown to be protective against PHS, either preventing it or making symptoms milder. DBS hardware failure can cause PHS, and therefore, should be considered a neurosurgical emergency. PHS can happen more than once in the same patient with a different provoking factor for each event.

Pathophysiology

Although the pathophysiology of PHS is not completely understood, it is considered to be a state of acute functional dopamine deficiency in the basal ganglia and hypothalamus, with transient refractoriness to DRT. This feature is very important as it differentiates PHS from the wearing-off phenomenon. The latter responds to the administration of DRT, specifically levodopa and apomorphine. Patients with PHS, in contrast, demonstrate transient unresponsiveness to the escalating doses of dopaminergic treatment. It was documented that PHS symptoms were present despite high serum levels of levodopa. Patients who are susceptible to PHS have baseline alteration of dopaminergic neurotransmission with narrow safety margins to any changes of their dopaminergic tone. Disturbance of dopaminergic neurotransmission in the hypothalamic thermoregulatory system is likely responsible for severe hyperthermia in PHS. In addition, abnormalities in muscle membrane permeability, surge of calcium from sarcoplasmatic reticulum, changes in central and peripheral sympathetic outflow, and central serotonin mechanisms had been implicated.

Clinical Picture

PHS is characterized by very high fever, extreme muscle rigidity, autonomic instability, and altered consciousness. Hyperpyrexia was reported to be as high as 41.7 °C. Muscle rigidity almost universally leads to rhabdomyolysis with a marked elevation in creatine phosphokinase (CPK) up to $50\,000\ \mathrm{U\,l^{-1}}$. Autonomic dysfunction can present as blood pressure instability, tachycardia, nonparalytic ileus, diaphoresis, or anhydrosis. Changes in cognition are ranging from agitation and hallucinations to confusion, stupor, and even coma. Leukocytosis is frequent. Serious complications are common and include acute renal failure, disseminated intravascular coagulation, autonomic instability, aspiration pneumonia, respiratory distress, and infections. The length of the single episode can range from several hours to several days, the longest reported being 29 days.

Treatment

PHS should be treated as a neurological emergency. The key to success is an early recognition and the initiation of treatment. DRT should be reinstituted as soon as possible with escalating doses and frequency of medication administration. Bromocriptine should be added at 2.5 mg t.i.d. initially and then titrated upwards as needed. Subcutaneous apomorphine or lisuride infusions can be considered. Due to dysphagia and high risk of aspiration pneumonia, the medications have to be given via a gastric infusion. Initiation of parenteral feeding, needed in many patients during prolonged episodes, might result in sudden changes in medication levels and potential worsening of the symptoms. Therefore, feeding should be started slowly and preferably at night time when the body's requirements for dopamine are lower. Symptomatic treatment with adequate hydration, hemodynamic support, and prevention and management of systemic complications, such as aspiration, infection, thromboembolism, should be started immediately. Dantrolene sodium $10\ \mathrm{mg\,kg^{-1}\,day^{-1}}$ in divided doses can be used for muscle relaxation. Hyperpyrexia should be treated aggressively with antipyretics, cooling blankets, etc. In addition to these well-accepted steps in the management of PHS, attempts have been made to treat it with methylprednisolone pulse therapy, electroconvulsive therapy, the NMDA-antagonist memantine, and other measures. These, however, must be studied further.

Prevention

Patients at risk should be identified and educated about PHS. Sudden medication changes should be avoided. The patients and their caregivers should be instructed to continue uninterrupted administration of DRT during any concomitant illness, surgeries, etc. All potentially precipitating events should be avoided if possible. This includes motor fluctuations with wearing off. DBS should be considered earlier in the patients at risk, as it was shown to minimize risks for PHS by decreasing wearing off phenomena.

Prognosis

Morbidity from PHS is high. Among the patients who survive PHS, about 30% have worsening of symptoms of Parkinsonism and never return to their pre-PHS baseline. Mortality from PHS is reported to be between 4% for treated and 20% for untreated episodes.

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Glossary

Parkinson's disease – A neurodegenerative disorder characterized by tremor, slowness (bradykinesia), rigidity, and balance compromise.

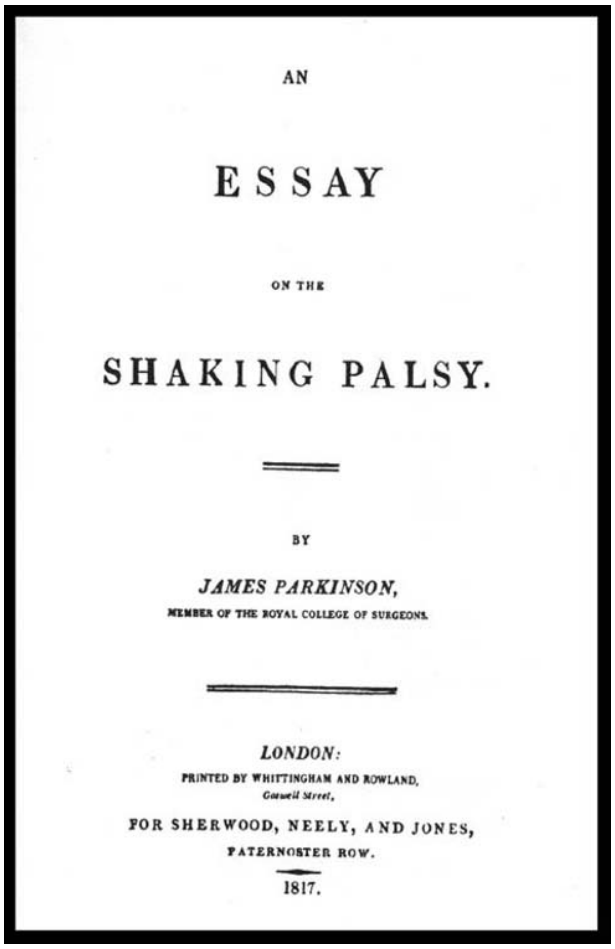
Biographical Details

James Parkinson (1755–1824) was born on 11 April 1755 at No. 1 Hoxton Square in the parish of St. Leonard's, Shoreditch, England (today part of central London) to John and Mary Parkinson. His father was an apothecary, surgeon, and anatomical warden. The young James served as an apprentice to his father and often joined him on resuscitation and recovery operations for the Royal Humane Society. James Parkinson continued the family medical tradition and practiced in an office behind the main house at No. 1 Hoxton Square.

Parkinson studied at the London Hospital Medical College for 6 months in 1776 as one of the school's earliest medical students. Other medical experiences included an apprenticeship with his father and rescue missions for the Royal Humane Society. He obtained his diploma of the Company of Surgeons in April 1784 shortly after his father's death and was elected Fellow of the Medical Society of London in 1787 after the delivery of his first paper, 'Some Account of the Effects of Lightning' describing the dermatological and neurological sequelae. Even in this early work, Parkinson demonstrated his keen observational skills, breadth of medical knowledge, and humble writing style.

An Essay on the Shaking Palsy

An Essay on the Shaking Palsy (1817) is considered to be Parkinson's greatest contribution to medicine and his only contribution to the field of movement disorders (**Figure 1**). The 66-page octavo volume described a series of six cases,



AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:

PRINTED BY WHITTINGHAM AND ROWLAND,

Goswell Street,

FOR SHERWOOD, NEELY, AND JONES,

PATERNOSTER ROW.

1817.

Figure 1 Front piece from James Parkinson's seminal work, *An Essay on the Shaking Palsy*.

three of which were never actually examined by Parkinson, but rather observed on the street. The cases differed in severity of disease and depth of observation, but Parkinson's astute clinical descriptions captured the insidious onset and long duration of disease, asymmetry of motor signs and rest tremor, sense of weakness, flexed posture, and festinating gait. He noted the progressive disease course with increasing immobility and dependence, disturbances of sleep, speech and bodily functions. In his view, there was sparing of the 'senses and intellect.' In the *Essay*, Parkinson also discussed the historical knowledge of tremor and gait disorders, possible etiologies, neuroanatomical localization, and proposed treatments. His succinct description of the salient features of tremor, slowness, propulsive gait, and balance difficulties is evoked in his short summary that is commonly cited:

> Involuntary tremulous motion with lessened muscular power in parts not in action and even when supported; with a propensity to bend the trunk forward and to pass from a walking to a running pace.

Parkinson did not provide his readers with any recommendations on treatments. He acknowledged that bleeding and vesicatory therapy had been advocated by others. While discussing 'considerations respecting the means of cure,' he wrote with a vision of the challenges that modern neurologists and researchers still face:

> . . . There appears to be sufficient reason for hoping that some remedial process may ere long be discovered, by which, at least, the progress of the disease may be stopped.

Reviews of the *Essay* in London medical journals were overall praiseworthy, although some criticized Parkinson's view on anatomy and causation. Although copies were difficult to find, the knowledge of the *Essay* and of paralysis agitans as a clinical disorder spread throughout the medical community. The celebrated French neurologist Jean-Martin Charcot obtained a copy from Dr. Windsor, Librarian at the University of Manchester, after a frustrating search and encouraged his pupils to translate the highly informative work. In the 1860s, Charcot coined Parkinson's disease as an eponym for paralysis agitans and added other key descriptions, including rigidity to the phenotype of the disease. This eponym has remained in the nosographic vocabulary into the twenty-first century.

Other Contributions

In addition to *An Essay on the Shaking Palsy*, Parkinson made numerous other contributions to medicine and science. Environmental injuries and accidents comprise a common theme in his works. Highlights of his early medical career include his first paper, 'Some Account of the Effects of Lightning' (1789). The potential dangers and injuries associated with childhood play and pranks are enumerated in the serious but artistic literary tale, *Dangerous Sports* (1808).

Parkinson's medical works included handbooks for the lay public and scientific reports of medical problems ranging from hydrophobia to trismus. He sought to improve the general medical and social welfare of laborers, with better designed trusses. His monograph on gout included personal experiences with his father's and his own afflictions with gout.

Parkinson was well known in the fields of chemistry and geology. His interest in chemistry sparked a fascination with geology and led to his acquisition and scientific analysis of specimens from the London terrain. He amassed a notable collection of fossils, shells, metals, coins, and medals at No. 1 Hoxton Square. As a renowned oryctologist, Parkinson was a founding member of the Geological Society in 1807. His first book on geology, *Organic Remains of a Former World* (1804), became a standard text on paleontology for half a century. In a style similar to that of other works, Parkinson composed *Organic Remains* in letter format rather than scientific chapters to appeal to a more general readership.

Parkinson's publications in the first decade after beginning his medical career focused on politics. In the climate of dramatic political changes, reforms, and revolutions occurring in France and England at the end of the eighteenth century, Parkinson espoused his political beliefs by distributing multiple pamphlets written under the pseudonym 'Old Hubert.' His political endeavors culminated in his role of witness before the Privy Council in a trial for High Treason regarding the Pop-Gun Plot in 1795.

In spite of Parkinson's successful career, multifaceted interests, and prominent place in his era, no portrait exists. The Parkinson heritage extended for several generations of physicians, and the name Parkinson's disease is one of the most celebrated and widely used designations in movement disorder neurology.

See also: Parkinson's Disease: Definition, Diagnosis, and Management.

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www.aneuroa.org – American Neurological Association.

Parkinson's Disease Quesionniare-39 (PDQ-39)

A Siderowf, Parkinson's Disease and Movement Disorders Center, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

Glossary

Disease-specific HRQL scales – These scales are designed to be used in a specific disease state (e.g., Parkinson's disease). Disease-specific scales are likely to be more sensitive to the impact of moderate to small differences in disease severity than *generic* instruments. By contrast, *generic* HRQL scales allow comparisons of patient groups with different diseases.

Health-related quality-of-life (HRQL) – Reflects a patient's health status and how he/she functions in his/her social roles. HRQL can be measured by instruments that focus on physical health and the overall functional ability.

Quality-of-life (QOL) – Tends to focus on psychological and sociological factors in addition to physical function. No consensus exists about what constitutes QOL or how best to measure it.

Definition and History

The Parkinson's Disease Questionniare-39 (PDQ-39) was developed by the Health Services Research Unit at the University of Oxford. It was extensively validated (see later section), and has been used as an outcome measure in epidemiological studies of health burden and in clinical trials. It is among the most widely used and cited health-related quality-of-life (HRQL) measures for Parkinson's disease.

HRQL refers to the impact that health (or disease) has on an individual's ability to complete daily routine activities satisfactorily and function in his/her social roles (i.e., family member, employee). HRQL scales capture information related to these areas from the patients' perspective. HRQL is distinguished from the concept of quality-of-life (QOL). QOL is not defined specifically by issues related to health, and is a more subjective sense of happiness or life satisfaction. There are two major categories of HRQL scales: disease-specific and generic. Disease-specific scales may be more sensitive to small differences in status within a given disorder. The advantage of generic measures is the possibility of comparisons of impact across different medical conditions.

Scale Description

The PDQ-39 derives its name from the fact that it contains 39 items. Each item is rated on a 5-point scale. An example of an item from the scale is shown in **Figure 1**. Eight domains are represented in the PDQ-39, including mobility (10 items), activities of daily living (6 items),

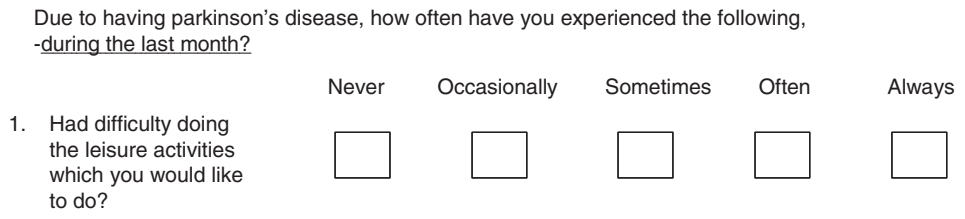

Figure 1 A representative item from the PDQ-39.

emotional well being (6 items), stigma (4 items), social support (3 items), cognition (4 items), communication (3 items), and bodily discomfort (3 items). A separate score can be derived for each domain. These scores range from 0 (no impact) to 100 (highest impact). A summary score can also be calculated by taking the simple average of the eight domain scores. A brief version of the PDQ-39, the PDQ-8, includes one item from each domain. The PDQ-8 produces a single summary index that correlates closely with the full PDQ-39 summary score.

The PDQ-39 went through a rigorous process of development and validation. It was validated in a sample of 146 patients from outpatient clinics in Anglia and Oxford. Patients were evaluated twice at a 4-month interval, the PDQ-39, the SF-36, and clinical evaluations being performed by a neurologist. The validity relative to generic HRQL and symptom burden were derived from this study. Sensitivity to change over a brief period of time as also established. A large amount of useful information may be accessed at http://www.publichealth.ox.ac.uk/units/hsru/PDQ/Intro%20pdq.

The PDQ-39 has been translated into over 50 languages. It is suitable for postal surveys as well as in person administration. Patient self-completion usually requires about 10–15 min. Recent psychometric studies of the PDQ-39 have focused on methods of imputing missing data and establishing minimally clinically significant scores.

The PDQ-39 has been used in a wide range of clinical studies. It has been used to identify which impairments contribute most substantially to HRQL in patients with Parkinson's disease. Measures of depression, cognition, and postural instability correlate most consistently with the PDQ-39 summary index score, indicating that these areas contribute to reduced HRQL. The PDQ-39 has also been an outcome measure in a number of clinical trials. In one example, patients randomized to deep brain stimulation surgery had improvements relative to best medical management in all PDQ-39 domains with the exception of communication, cognition, and social support.

Summary

The PDQ-39 is a widely used and highly feasible disease-specific HRQL measure for Parkinson's disease.

See also: Parkinson's Disease: Definition, Diagnosis, and Management; Rating Scales in Movement Disorders.

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Parkinson's Disease: Definition, Diagnosis, and Management

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Glossary

Bradykinesia – Slowness in initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions.
Dementia – Decline in intellectual functioning that is severe enough to interfere with the ability to perform routine activities of the daily living.
Freezing of gait – Paroxysmal events in which a subject is unable to initiate locomotion, to make a turn, or to walk through narrow spaces (i.e., a doorway) smoothly.
Lewy bodies – Large intraneuronal inclusions of aggregated α-synuclein.
Nigro-striatal pathway – Pathway connecting the substantia nigra pars compacta with the striatum.
Parkinsonism – Motor syndrome characterized by muscular rigidity, bradykinesia, and/or tremor.
Psychosis – Thought disorder in which objective reality testing is distorted or diminished.
Rigidity – Increase in resistance to passive movements about a joint involving both agonist and antagonist muscles supplying the joint.
Striatum – Part of the basal ganglia consisting of the caudate nucleus and the putamen.
Substantia nigra – A dark band of gray matter within the midbrain where dopamine is synthesized and released.
Tremor – Rhythmic, involuntary back-and-forth oscillation of agonist and antagonist muscles.

Definition and History

Parkinson's disease (PD) is a neurodegenerative disease characterized by the hallmarks of bradykinesia, rigidity, tremor, and postural instability. The cardinal motor features of the disease are produced by the progressive degeneration of the dopaminergic neurons of the substantia nigra pars compacta (SNc), resulting in depletion of striatal dopamine.

PD is considered an α-synucleinopathy affecting the nervous system beyond the SNc. Decreased clearance of α-synuclein within the neuronal cytoplasm is associated with widespread neuronal dysfunction and degeneration both in the central and peripheral nervous system. Involvement of areas outside the SNc likely leads to nonmotor symptoms and motor symptoms unresponsive to levodopa.

In 1817, James Parkinson published '*An Essay on the Shaking Palsy*' and described patients with resting tremor, rigidity, and postural instability. He attributed these symptoms to a lesion in the *medulla oblongata*. Fifty years later, Jean-Martin Charcot defined the cardinal features of so-called 'paralysis agitans.' He differentiated bradykinesia from rigidity, and described the association of PD with pain and dysautonomia. He was the first to suggest the term 'Parkinson's disease.'

In 1969, Hoehn and Yahr described the natural history of PD and proposed a staging scale that is still useful in the clinical setting. As early as in the nineteenth century, Bell, Meynert, and Edinger described macroscopic interconnections between the basal ganglia, but the precise function of the cortico-subcortical circuits implicated in the execution of movements was not disentangled until the second half of the twentieth century. In 1913, the deposition of intracellular Lewy bodies was firstly associated with the neuronal degeneration of SNc, but the relationship between parkinsonism and the degeneration of different nuclei in the brainstem was not clearly stated until 1953 by Greenfield. In the 1960s, Ehringer and Hornykiewicz showed that dopaminergic depletion in the striatum due to neuronal degeneration of the SNc occurred in PD. These findings led to the use of levodopa, the precursor to dopamine, to treat the motor symptoms of PD. In 1983, the discovery that an opiate derivative, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), could induce SNc degeneration helped to develop animal models of PD. This step has been essential to understand the functional anatomy of the basal ganglia and the pathophysiological bases of PD-related motor signs, fluctuations, and dyskinesias. This knowledge was also essential in the development of deep brain stimulation (DBS) as an effective therapy. Over the last 10 years, recognition of the importance of cognitive, psychiatric, and other nonmotor PD features (sleep problems, dysautonomia, visual disturbances) has broadened the phenotype of PD, so that today, PD is considered a multisystem neurodegenerative disease involving different neurotransmitters, neocortical, and subcortical encephalic regions, and the peripheral nervous system.

Pathogenesis and Pathophysiology

PD is a chronic, progressive, neurodegenerative disease with a likely multifactorial etiology, but regardless of

genetic or environmental influences, abnormal protein aggregation within neurons with synuclein accumulation appears to underlie neurodegeneration. It has been suggested that this process begins in the olfactory bulb, dorsal motor nucleus of the vagus nerve, and enteric plexus and then moves higher in the nervous system to involve the SNc and later the cortex. Recent clinico–pathological data indicate that the proposed hierarchical pattern of disease progression can be effectively reproduced in PD patients with a younger onset, but in PD patients with an older onset ($\geq$70 years), the sequence may involve neocortical regions early-on.

Dopamine regulates excitatory and inhibitory outflow of the basal ganglia. The basal ganglia consist of four main nuclei: the striatum (caudate nucleus, putamen), the globus pallidus (GP), the subthalamic nucleus (STN), and the substantia nigra. Most information to the basal ganglia arises from glutamatergic inputs originating in the cerebral cortex. The basic functional connections within the basal ganglia are based on a direct and an indirect pathway. The direct pathway enhances the execution of the motor programs originating in the supplementary motor area and the premotor cortex, while the indirect pathway – through the STN – inhibits the activity of the direct pathway.

The direct pathway is rich in D1 receptors and is composed of the GP pars interna (GPi) and the SN pars reticulata (SNr), with connections to the thalamus (VA/VL). The indirect pathway is rich in D2 receptors and is composed by the GP pars externa (GPe) and the STN, which activates the inhibitory action of GPi/SNr to the thalamus. The putamen is the main nucleus to receive the glutamatergic input from the cortex. Then, inhibitory striatopallidal connections from the putamen are directed to both the GPi (direct) and the GPe (indirect pathway). In the parkinsonian, the decrease of dopamine release to these circuits inhibits the execution of movements, and treatment with levodopa partially restores the flow of information from the cortex to the direct pathway (**Figure 1**).

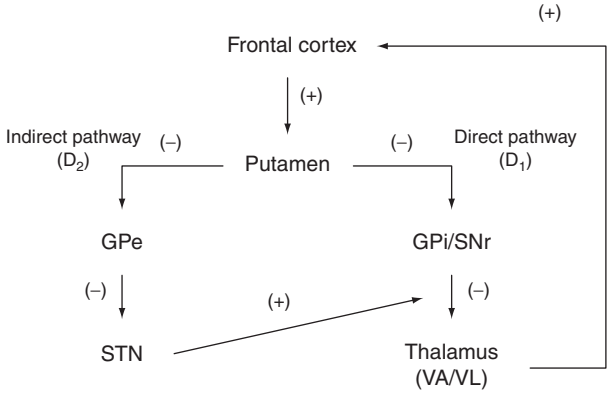

Figure 1 Schematic of basal ganglia connections.

Epidemiology and Risk Factors

PD is the second most common neurodegenerative disease after Alzheimer's disease. PD is associated with a significant increase in morbidity, disability, and mortality compared to the general population. Aging, environmental factors and genetic susceptibility appear to interact in determining individual susceptibility to PD. Higher age and male sex are associated with an increased risk of PD, age being the most determinant factor. Currently, there are between one and two million people with PD in the United States. Age of onset is usually ~65, but in up to 10%, the onset occurs before 45 years of age. Incidence rates increase after the age of 50, especially in men, and rapidly increase after age 75.

The environmental and lifestyle risk factors that have been associated with the development of PD are rural living, exposure to pesticides/herbicides, well-water drinking, and working with solvents. In opposition, epidemiological studies have shown a reduced risk of PD related to smoking habit, coffee consumption, current long-term use of calcium channel blockers, and hyperuricemia.

Genetic factors play also a role. In 1996, Polymeropoulos et al. reported linkage to chromosome 4q21–23 (*Park 1*) for a large family in whom pathologically proven PD was inherited in an autosomal dominant fashion. The *Park 1* gene codes for alpha-synuclein. Other genes have been implicated, including the *Park 2* and the *LRKK2* genes. *LRRK2* has been identified as a genetic cause of familial and sporadic PD. Several pathogenic mutations in *LRRK2*, particularly the variant G2019S, have been reported in different populations with prevalence in PD cohorts ranging from ~2% in sporadic disease in North American whites, to 40% in familial and sporadic PD in North African Arabs. The clinical features of parkinsonism and the response to levodopa treatment in patients with *LRRK2* mutations are largely indistinguishable from those of classic PD. Several other genetics links have also been identified. Monogenic forms of PD account, however, for less than 10% of PD cases.

Clinical Expression and Course

Four cardinal motor manifestations are the central features of PD: resting tremor, bradykinesia, rigidity, and postural instability with impairment of postural reflexes.

PD motor symptoms usually begin unilaterally and gradually spread to the contralateral side, yet maintaining their asymmetry over the course of the disease. Resting tremor is present in 70–80% of PD patients and mainly involves the thumb or wrist. This 'pill-rolling' tremor increases with mental stress (counting backwards) or when movements of another body part are performed.

Tremor also can involve the legs, jaw, and tongue. Tremor is more likely to be the presenting symptom in younger patients, whereas older patients may have a more prominent rigid-akinetic phenotype. Tremor may be the most visible sign of PD, but it rarely causes major disability.

Bradykinesia and postural reflex impairment are the more disabling symptoms of PD, because gait difficulties cause falls and increase the risk for fractures and injuries. Bradykinesia is usually present in the form of micrographia, impairment in the execution of fine motor tasks, reduced arm swing, hypomimia, difficulty turning over in bed, arising from a chair, gait disturbance (short-steps, festination), hypophonia, tachyphemia/stuttering, or dysarthria. Freezing, or the difficulty in initiating locomotion, making turns, or passing through narrow spaces, is also a well-known clinical feature in PD, but it is mainly present in the advanced stages of the disease.

The clinical course of PD is not limited to motor symptoms. A variety of nonmotor symptoms and disorders (**Table 1**) are common and impact on quality of life and functional disability even to a higher degree than motor symptoms themselves. Depression and dementia are the PD symptoms with a greatest impact on both quality of life and functional disability.

Most PD patients have olfactory disturbances that likely begin in the very early stages of the disease, possibly preceding the appearance of the first motor signs by a few years. As many as 70% of PD patients report hyposmia at the onset of motor deficits, while it is only found in 3% of matched healthy subjects. Olfactory dysfunction in PD has been correlated with Lewy bodies deposition and neuronal loss in the olfactory bulb.

The overall prevalence of sleep disturbances in PD varies from 60 to 95%. Nocturia (45%) and sleep fragmentation (60%) are the most commonly reported problems. Nocturnal awakenings may be prolonged, resulting in a reduction of total sleep time with consequent daytime fatigue and sleepiness. Sleep fragmentation and REM Sleep Behavior Disorder (RBD) are attributed to involvement of brainstem structures (nucleus subcoeruleus, pendunculo-pontine nucleus). RBD is often present in the early stages of PD and can precede motor symptoms by several years. Patients with 'idiopathic' RBD may also convert to PD. Excessive daytime sleepiness (EDS) is a complex phenomenon, because both disease-related disturbances and the effects of dopaminergic medications (i.e., dopamine agonists (DA)) play a role in its genesis. Restless legs syndrome (RLS) and periodic limb movement during sleep (PLMS) can also cause sleep disruption in PD and they both have been reported to be increased in PD compared to the general population.

Although early and prominent dysautonomia in a patient with parkinsonism suggests the diagnosis of multiple system atrophy (MSA), autonomic disturbances are also typical of PD and become more evident and severe in the advanced stages of the disease. Dysautonomia in PD is very similar to that in primary autonomic failure or MSA, with episodes of orthostatic hypotension, micturitional urgency, and erectile dysfunction. Several epidemiological studies have shown that constipation can precede the motor symptoms of PD by many years, an observation consistent with recent findings of α-synuclein deposition at the enteric plexus in PD patients.

Some degree of cognitive impairment is common in PD, and dementia occurs in 24–31% of patients. Between 25 and 55% of nondemented PD patients show mild cognitive defects even in the early stages of PD, characterized by frontal–subcortical impairments in attentional, executive, visuospatial, and memory functions. Cognitive impairment in PD follows a progressive evolution, and dementia appeared to be an almost inevitable outcome of PD (up to 85% of patients) in a prospective longitudinal study with a follow-up of 15–20 years. Neuroimaging studies have shown that conversion to dementia is characterized by the focal degeneration of the limbic/paralimbic and medial temporal cortices, supporting the hypothesis that dementia in PD is directly related to the propagation of the disease to neocortical structures.

Neuropsychiatric disturbances are also integral components to PD. Apathy, depression, irritability, and anxiety are present in 40–60% of patients. In fluctuating patients, mood swings and anxiety are frequent and sometimes severe, and may be as disruptive as motor symptoms. Depression can also precede the onset of motor symptoms in PD. Apathy in PD can occur independently of depression. Up to 25% of PD patients report apathy without depression, and this problem may relate to both executive dysfunction and dysfunction of the limbic circuits connecting the amygdala to the medial prefrontal cortex.

Table 1 Common nonmotors symptoms in PD

1. Olfactory dysfunction: hyposmia, cacosmia
2. Sleep problems: sleep fragmentation, REM sleep behavior disorder, excessive daytime sleepiness, restless legs syndrome, periodic limb movements
3. Dysautonomia: orthostatic hypotension, micturitional urgency, nycturia, erectile dysfunction, constipation
4. Cognitive impairment: subtle cognitive defects, dementia
5. Neuropsychiatric disturbances:
   (a) Emotional disorders: depression, apathy, anxiety, irritability
   (b) Psychosis: hallucinations (visual, auditory, tactile), delusions (delusional jealousy, paranoid), delusional misidentification syndromes (Capgras, Frégoli, reduplicative paramnesia, intermetamorphosis)
   (c) Impulse control disorders: pathological gambling, hypersexuality, punding, hedonistic homeostatic dysregulation (levodopa addiction), binge eating
6. Visual disturbances: color discrimination deficits, blurred vision, diplopia

Hallucinations are also characteristic of PD, especially patients treated for prolonged periods of time with dopaminergic medications. The frequency of hallucinations increases as the disease progresses. In the early stages of the disease minor hallucinations appear. The phenomenology of minor hallucinations is fairly stereotyped among different patients. Some PD patients report visual illusions, the feeling that someone is behind or besides them (presence hallucinations), or the fleeting vision of a person, an animal or an object coming backwards from the periphery of the visual field (passage hallucinations). These hallucinations are short-lasting (1–2 s) and the patient is absolutely aware of their unreality. Later, patients have repetitive and well-formed hallucinations that are initially recognized as hallucinations, but later can be associated with loss of insight, and delusional thinking. Hallucinations in other sensory modalities (auditory, tactile) also can occur as well as delusional misidentifications syndromes (Capgras, reduplicative paramnesia).

Impulse control disorders (ICD) have been increasingly associated with PD and dopaminergic treatment. While psychosis is more likely to be present in older and demented patients, ICD usually develop in younger and cognitively intact subjects. They seem to be also especially prevalent with the use of DA. From 5 to 10% of PD patients may develop pathological gambling, hypersexuality, binge eating, computer addiction, punding, or excessive hobbyism. Subjects with a past history of addictive behaviors or with a novelty-seeking personality are more prone to suffer these complications.

Finally, the clinical description of PD must take into account the development of motor symptoms poorly responsive to levodopa. After 10 years of disease duration, PD patients gradually develop motor symptoms that likely relate to dysfunction outside the dopaminergic nigro-striatal pathway. Some of these symptoms, especially poor postural reflexes, have a strong impact on functional disability. The progressive development of hypophonia, dysphagia, freezing, truncal flexion ('camptocormia'), and postural instability point towards a severe degeneration of the brainstem nuclei and transition to an advanced stage of PD where dopaminergic treatment cannot control these signs.

Differential Diagnosis

Because there are no biological markers for the antemortem diagnosis of PD, clinical signs, medication response, and progression guide the clinician to the diagnosis. Clinico-pathological studies have shown significant false-positive and false-negative rates for diagnosing these disorders, and misdiagnosis is especially common during the early stages of these diseases, even among movement disorder specialists.

Several sets of clinical diagnostic criteria for PD have been proposed. The UK Parkinson's Disease Society Brain Bank (UK-PDSBB) clinical criteria for PD are the most accepted and used in clinical research. The UK-PDSBB criteria require the presence of bradykinesia and $\geq$1 of the other cardinal features of the disease (rest tremor, rigidity, postural instability) (**Table 2**).

Applying these criteria, the presence of asymmetrical parkinsonism (tremor or rigidity), rest tremor, gradual

Table 2 UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria

Inclusion criteria	*Exclusion criteria*	*Supportive criteria*
Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions) And at least one of the following: • Muscular rigidity • 4–6 Hz rest tremor • Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction	History of repeated strokes with stepwise progression of parkinsonian features History of repeated head injury History of definite encephalitis Oculogyric crises Neuroleptic treatment at onset of symptoms More than one affected relative Sustained remission Strictly unilateral features after 3 year Supranuclear gaze palsy Cerebellar signs Early severe autonomic involvement Early severe dementia with disturbances of memory, language, and praxis Babinski sign Presence of cerebral tumor or communicating hydrocephalus on CT Negative response to large doses of levodopa (if malabsorption excluded) MPTP exposure	$\geq$3 required for the diagnosis of PD Unilateral onset Rest tremor present Progressive disorder Persistent asymmetry affecting side of onset most affected Excellent response (70–100%) total levodopa Severe levodopa-induced chorea Levodopa response for 5 year or more Clinical course of 10 year or more

motor progression, and levodopa response (moderate to excellent response or levodopa-induced dyskinesias) are the most predictive clinical signs for a correct diagnosis of PD.

The clinical heterogeneity of PD is relevant in the differential diagnosis of the disease. Tremor dominant parkinsonism (TDP) is characterized by initial prominent resting and action tremor, mild parkinsonism, unpredictable responses to dopaminergic medications, and a better prognosis than typical PD. It can be easily confounded with essential tremor (ET). However, ET patients have a predominant postural tremor and if they develop rest tremor, it occurs after several years of disease.

In the differential diagnosis of the akinetic-rigid and postural instability and gait disorder variants of PD, we need to include the Parkinsonism-plus syndromes, MSA, progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and secondary forms of parkinsonism related to vascular, drug-induced, metabolic, infectious, and toxic causes (**Table 3**).

MSA is a sporadic neurodegenerative disorder clinically characterized by various combinations of parkinsonian, cerebellar, autonomic, and pyramidal signs. It may be difficult to differentiate from PD because rest tremor, asymmetric akinesia, and rigidity can occur in both conditions. In the early stages, 30% of MSA patients respond to levodopa treatment. About 25% of cases with pathological evidence of MSA have a clinical diagnosis of PD during life.

PSP is characterized by the early appearance of postural instability and falls during the first year of the disease, with associated supranuclear gaze palsy. Some PSP patients may not develop gaze disturbances in the first 10 years of the disease, and one third can also respond to dopaminergic therapy at least transiently.

CBD usually has an asymmetric rigid-akinetic onset that can also improve on levodopa, which can lead to the erroneous diagnosis of PD before atypical signs arise (dystonia, apraxia, myoclonus, oculomotor disorders).

Table 3 Differential diagnosis of PD

- *Tremor dominant parkinsonism*
  - Essential tremor.
  - Dystonic tremor.
  - Psychogenic parkinsonism.
- *Rigid-akinetic parkinsonism*
  - Parkinson-plus syndromes: Multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration.
  - Vascular parkinsonism.
  - Drug-induced parkinsonism.
  - Normal-pressure hydrocephalus.
  - Metabolic, infectious, toxic parkinsonism.
  - Spinocerebellar atrophy (SCA 2, 3).
  - Psychogenic parkinsonism.

Drug-induced parkinsonism (DIP), usually from dopaminergic receptor antagonists like antipsychotics and metaclopramide, can be indistinguishable from PD. Although DIP can exhibit atypical parkinsonian features, such as bilateral and symmetric parkinsonism with postural tremor more severe than rest tremor, it can also have an asymmetric onset with predominant rest tremor and a progressive course. The association of oral-lingual dyskinesias, choreic movements, and distal athetosis suggest tardive dyskinesia, which can also occur with chronic dopamine receptor antagonists, and therefore suggest DIP. Both vascular parkinsonism and normal-pressure hydrocephalus (NPH) exhibit lower-body gait impairment. MR scans help document abnormalities to suggest these diagnoses. In NPH, gait apraxia, freezing and turn hesitation, along with micturitional urgency and cognitive impairment occur. Although these features make the differential diagnosis easier, they can be confounded with the akinetic-rigid form of PD, especially in older patients.

Some phenotypes of spinocerebellar ataxia, specifically spinocerebellar atrophy (SCA) 2 and 3, may be very similar to PD. An autosomal dominant inheritance or the appearance of clinical features more common in SCA (i.e. ataxia, supranuclear ophthalmoplegia, lid retraction, bulging eyes, diplopia, faciolingual fasciculations), help establish the correct diagnosis.

Diagnostic Work-up

Blood Tests

- *Thyroid hormones (T3, T4, TSH):* Hypothyroidism causes slowness and apathy and these signs can be confused with parkinsonism.
- *Bone and mineral metabolism:* When calcifications in the basal ganglia and dentate nucleus are observed by neuroimaging, testing for calcium, phosphate, and PTH levels in peripheral blood is mandatory.
- *Polycythemia vera:* The finding of high levels of hemoglobin has been associated with the development of leukoaraiosis and vascular parkinsonism.
- In cases of young-onset parkinsonism, ceruloplasmin levels will aid in testing for Wilson's disease.

Structural Neuroimaging

In patients with typical PD, performance of a brain CT scan or magnetic resonance image (MRI) is recommended to rule out secondary causes of parkinsonism.

- *CT scan:* This test will document brain tumors (i.e., meningioma), basal ganglia calcifications, cerebral vascular disease, and suggest NPH.

- *MRI:*
  - T1/T2/FLAIR:
  - In the diagnosis of vascular parkinsonism, these techniques are sensitive for detecting leukoaraiosis or focal lesions in the midbrain or basal ganglia.
  - In the differential diagnosis of PD versus MSA, some specific signs with low sensitivity (40–50%) but a high specificity (90%) have been described to predict the presence of MSA. T2-hypointensity in the posterior part of putamen, T2-hyperintense rim at the lateral edge of the dorsolateral putamen, T2-'hot cross bun' sign in the pontine basis, T2-hyperintensity of the middle cerebellar peduncles (MCPs), and cerebellar atrophy suggest MSA.
  - Diffusion-weighted imaging (DWI)/apparent diffusion coefficient (ADC).
  - Early neuronal degeneration may be assessed by measurement of the ADC in brain regions more sensitive to neuronal damage. In early PD, there seems to be little focal degeneration in the putamen or the MCP. Conversely, MSA and PSP patients show a significant neuronal loss in the posterior putamen in the early disease stages, and MSA patients also exhibit major degeneration in the MCP. Regional measurement of ADC (rADC) in the posterior putamen may help to differentiate PD from both MSA and PSP, and rADC in the MCP accurately differentiates MSA from PSP.

Functional Neuroimaging

- *DAT-SPECT and ^{18}Fluorodopa PET:* DAT-SPECT and ^{18}Fluorodopa PET studies document apparent neuronal loss that occurs in SNc in PD and other parkinsonian syndromes. DAT-SPECT and ^{18}Fluorodopa PET differentiate PD and atypical parkinsonism from ET, vascular, drug-induced, and psychogenic parkinsonism, but PD cannot readily be differentiated from MSA, PSP, and CBD.
- *^{123}I-MIBG cardiac scintigraphy:* As PD is associated with preganglionar dysautonomia, and MSA, PSP, and CBD are more likely to be associated with preganglionar dysautonomia without involvement of the peripheral noradrenergic system, the uptake of ^{123}I-MIBG, an analogue of noradrenaline/norepinephrine, has been used in the differential diagnosis of different types of parkinsonism. Nonetheless, further studies are needed to determine the actual value of ^{123}I-MIBG cardiac uptake in routine clinical practice.

Transcranial Ultrasound

Increased echogenicity of the SNc, as determined by transcranial sonography (TCS), is characteristic of idiopathic PD. The finding of SN hyperechogenicity helps differentiate PD from ET, vascular, and DIP. The technique may also help to differentiate PD from atypical parkinsonian syndromes (MSA, PSP, CBD). TCS is easy to implement, noninvasive, and inexpensive.

Management

Management of Motor Symptoms

- *Levodopa:* L-dopa is still the most efficacious drug in the control of PD motor symptoms. In the CALM-PD and REAL-PET studies, L-dopa showed a significantly greater improvement of the mean unified Parkinson's disease rating scale (UPDRS) score change compared to the DA, pramipexole, and ropinirole. In these studies, the main limitation of L-dopa was its higher relative risk for dyskinesias and motor fluctuations compared to DA. Several studies indicate that patients treated with levodopa do well over many years, but no study demonstrates that it has any effect on the underlying neurodegeneration.
- *Catechol-amine methyl transferase inhibitors (COMTI):* These drugs are used in association with levodopa and are not used without levodopa. In fluctuating PD patients, the use of both entacapone and tolcapone increases in daily 'on' time by a mean of 1–1.7 and 2–3 h, respectively. Changes in daily 'on' time have been related to a significant improvement in scales assessing functionality in the activities of daily living. However, the appearance of fulminant hepatitis in three patients and the frequent finding of elevated transaminases have limited the widespread use of tolcapone. Currently, with regard to safety issues, tolcapone is considered acceptable but requiring special monitoring in fluctuating patients who have failed other therapies. Since levodopa is the most efficacious dopaminergic drug both on motor symptoms and functional disability, it has been hypothesized that the use of levodopa + carbidopa + entacapone in stable and 'de novo' PD patients could prevent motor complications to the same extent that DA do. Before the publication of the results of ongoing clinical trials focused on this issue, no recommendations can be given in regard to the use of levodopa + carbidopa + entacapone in 'de novo' PD patients.
- *Monoamine oxidase inhibitors (MAOI):* Selegiline has a mild therapeutic effect on motor symptoms. It is typically used early in the disease. Initial monotherapy with selegiline does not prevent motor complications once L-dopa is initiated. It can be used to treat motor fluctuations and prolong 'on' time. Rasagiline is a new selective and irreversible MAO-B inhibitor 10-fold more potent than selegiline and is not metabolized to amphetamine derivatives. Rasagiline is effective in monotherapy in early PD, providing a modest yet clinically meaningful benefit. Data on the neuroprotective

role of this drug are waiting for the results of the clinical trial ADAGIO. In the LARGO study, rasagiline showed a comparable effect to entacapone in the improvement of daily 'on' time.

- *Dopamine agonists (DA):* DA are efficacious for the treatment of parkinsonism. The main DA are pramipexole and ropinirole, although rotigotine and apomorphine as well as other agents less widely used are available. Starting treatment with DA instead of levodopa decreases the risk of motor fluctuations and dyskinesias after 5 years of follow-up. DA have also shown to improve daily 'on' time among patients with motor fluctuations. In particular, the intermittent use of apomorphine dramatically rescues patients from 'off' periods. With regard to safety, ergot-based DA (cabergoline, bromocriptine, lisuride) have been associated with valvular heart disorders and annual echocardiograms are needed for monitoring. Daytime sleepiness can be caused by any DA, and monitoring of driving capacity is important. Disruptive neuropsychiatric symptoms, both in young-onset and older PD patients can occur with DA. ICD (gambling, hypersexuality, punding/hobbyism) are more likely in younger and cognitively intact patients, while older patients are more likely to develop hallucinations and delusions.
- *Amantadine and anticholinergics:* Amantadine is likely efficacious in improving symptomatic control of parkinsonism, both as monotherapy or in combination with other symptomatic drug. Along with clozapine, amantadine is the only drug to have demonstrated an efficacy in reducing levodopa-induced dyskinesias. Anticholinergic medications are clinically useful in the symptomatic treatment of PD, both as monotherapy and when used with other drugs. The utility of these agents, however, is limited because motor efficacy is usually only mild to moderate, and occurrence of adverse reactions such as confusional state, acute urinary retention, and blurred vision are frequent. Further, one study suggested that chronic use of anticholinergic agents is associated with a greater relative risk of developing dementia.
- *Surgical treatments:* DBS of both the globus pallidus pars interna (GPi) or the STN are efficacious in treating motor signs of PD. They induce a lower incidence of motor, behavioral, and cognitive adverse effects than ablative procedures and can be done bilaterally, so that surgical treatment in PD in most developed countries is largely confined to the use of DBS. DBS of either the STN or the GPi improves parkinsonism, motor fluctuations and dyskinesias. Although the efficacy of DBS of the STN and the GPi seems to be similar, DBS of the STN appears more likely to allow a considerable medication reduction. DBS can be associated with mechanical failures, operative complications, and infections as well as speech disturbances, eyelid apraxia, limb or facial dystonia, and apathy.
- *Intraduodenal infusion of L-dopa (Duodopa®) and apomorphine pump:* Intraduodenal infusion of levodopa (IILD), and apomorphine pumps can be used for the treatment of motor complications that cannot be controlled with optimized medical treatment. The administration of the IILD results in stabilization of levodopa levels in peripheral blood and can reduce motor fluctuations. The improvement in 'on' time achieved by the IILD is comparable to that obtained with STN-DBS, but DBS obtains better control on dyskinesias. No life-threatening adverse events have been reported with IILD, but it is expensive, requires substantial patient/caregiver education, and is not available in most countries. The apomorphine pump shows a similar profile of improvement with a similar benefit on motor fluctuations as seen with IILD and less control of dyskinesias than DBS. The development of nonmotor complications (hypersomnolence, hypersexuality, hypomania), skin nodules and the difficulties in handling the pump limit the use of this technique.

Management of Nonmotor Symptoms

Nonmotor symptoms have a great impact on quality of life and disability measures and management of these problems is paramount to overall management success in PD.

- *Depression:* is the most frequent neuropsychiatric disturbance in PD. Few randomized, controlled, double-blind studies have been performed. In controlled studies, tricyclic antidepressants (TCA – imipramine, nortriptyline, and desipramine) have been shown to be effective. However, the associated anticholinergic effects of TCA may worsen cognitive function and dysautonomia (hypotension, urological problems) in elderly PD patients. Selective serotonin reuptake inhibitors (SSRIs) are generally well tolerated in patients with PD, and do not appear to worsen motor symptoms. Although the actual efficacy of SSRIs in PD has not been well established, SSRIs are generally preferred for initial therapy because of their tolerability.
- *Apathy:* up to 35–40% of PD patients develop apathy, associated with or dissociated from depression. No pharmacological studies focused on apathy have been performed up to date. Based on studies performed in Alzheimer's disease, the use of cholinesterase inhibitors or methylphenidate may be effective.
- *Dementia:* The EXPRESS study, a multicenter double-blind placebo controlled study showed that rivastigmine (mean dose 8.6 mg day^{-1}) improves not only the cognitive function (in all cognitive domains explored), but also some of the behavioral disturbances (apathy, hallucinations) associated with PD with dementia. Clinical impression of change assessed by the caregivers

showed that the use of rivastigmine in Parkinson's disease dementia (PDD) results in an improvement of dementia in 40% of patients. Smaller studies using donepezil and galantamine show also a beneficial effect.

- *Psychosis:* Treatment of psychosis in PD with antipsychotic drugs is complicated by the risk for negative effects on PD motor symptoms. As a first step, the physician must check that there is no medical illness or other explanation for a 'toxic encephalopathy' causing hallucinations. Then, drugs used for treating motor symptoms in PD that may be exacerbating psychosis should be reduced or stopped. To avoid worsening of motor function, the proposed order to withdraw parkinsonian medications is: anticholinergic agents (including those used for treatment of urinary incontinence), selegiline, rasagiline, amantadine, catechol-O-methyltransferase inhibitors, DA, and finally levodopa. If the patient cannot tolerate lower doses of dopaminergic drugs because of the PD itself, then an antipsychotic agent should be added. Typical antipsychotic agents, such as haloperidol, will likely worsen PD symptoms. From the atypical antipsychotic agents, low-dose clozapine has been demonstrated to be effective, although low-dose quetiapine is widely used in clinical practice. The use of cholinesterase inhibitors may also be effective in the treatment of visual hallucinations in PD patients with comorbid cognitive impairment.
- *Impulse control disorders (ICD):* The best treatment of ICD is to avoid their appearance. Addictive behaviors are difficult to reverse once they have emerged. DA in younger patients seem to be the main risk factors for the development of ICD, while a past history of ICD before the onset of PD (alcoholism, gambling), and certain personality traits (novelty-seeking) add to this risk. Because there is no established treatment for ICD in PD, careful screening of these factors before exposure is advised.

See also: Basal Ganglia; Basal Ganglia, Functional Organization; Bradykinesia; Corticobasal Degeneration; Deep Brain stimulation; Dementia with Lewy Bodies; Dementia, Movement Disorders; Depression and Parkinsonism; Diffusion Tensor Imaging in Parkinson's Disease; Direct Pathway; Dopamine; Dopamine Dysregulation Syndrome; Dopamine Receptors; Dopaminergic Agonists in Parkinson's Disease; Hallucinations and Movement Disorders; Indirect Pathway; Levodopa; Multiple System Atrophy; Neuroimaging, Parkinson's Disease; Parkinson's Disease: Genetics; Progressive Supranuclear Palsy; REM-behavior Disorder; Sleep Attacks; SPECT Imaging in Movement Disorders.

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Relevant Websites

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www.pdf.org – Parkinson's Disease Foundation, Inc.

www.michaeljfox.org – The Michael J. Fox Foundation for Parkinson's Research.

www.parkinson.org – National Parkinson Foundation.

Parkinsonism: Genetics

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Glossary

α-synucleinopathies – A class of neurodegenerative disorders marked by abnormal inclusions containing α-synuclein in selected populations of neurons and glia. These disorders include Parkinson's disease, multiple system atrophy, dementia with Lewy bodies, and others.
Frontotemporal dementia with parkinsonism-17 (FTDP-17) – A neurodegenerative disorder described by researchers who had studied families in which dementia and parkinsonism occurred, all of which were linked to chromosome 17. Mutations in the genes encoding the microtubule-associated protein tau (MAPT) or progranulin were later found to be causal in separate families.
MAPT – A highly soluble protein that is abundant in neurons and plays an important role in the assembly of microtubules. In the human adult brain, there are six tau isoforms. Misfolded tau protein can form insoluble aggregates that are the major constituents of intraneuronal and glial fibrillar lesions described in Alzheimer's disease and numerous neurodegenerative disorders referred to as tauopathies.
Progranulin – A growth factor involved in multiple physiological and pathological processes including tumorigenesis. Mutations in the progranulin gene have been identified in some MAPT-negative FTDP-17 families.
Tauopathies – A class of neurodegenerative disorders marked by the presence of intracellular accumulations of abnormal filaments of insoluble MAPT. These disorders include some forms of FTDP-17, progressive supranuclear palsy, and corticobasal degeneration. Alzheimer's disease shows both tau and amyloid pathology.

Introduction

Parkinsonism refers to a category of movement disorders marked by at least two of the core clinical features of Parkinson's disease (PD), including rigidity, bradykinesia, gait difficulties, and postural instability. Parkinsonism includes PD as well as dementia with Lewy bodies (DLB), multiple system atrophy (MSA), frontotemporal dementia with parkinsonism-17 (FTDP-17, also referred to as pallidopontal degeneration), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), some spinocerebellar ataxias (SCAs), variants of Huntington's disease (HD), and several other disorders. In addition, some individuals with pathologically confirmed Alzheimer's disease exhibited clinical features of parkinsonism. Clinical clues pointing toward parkinsonism other than PD include gaze palsy (PSP), early autonomic failure (MSA), early falls (PSP and MSA), ataxia (MSA and SCAs), and early dementia (DLB and FTDP-17). In contrast to the asymmetry characteristic of PD, most of the non-PD parkinsonian disorders tend to be symmetrical; an exception is CBD, which is also dramatically asymmetric. In non-PD parkinsonism tremor may only be slight or completely absent. With the exception of DLB, all forms of non-PD parkinsonism are minimally responsive or unresponsive to dopamine replacement therapy. While PD is the most prevalent form of parkinsonism, exposure to certain medications, in particular dopamine antagonists, which are still in use for psychiatric illness and as antiemetics, is also a major cause of parkinsonism.

Dementia with Lewy Bodies (DLB) *OMIM #127750*

DLB is a form of parkinsonism that is clinically characterized by progressive dementia, fluctuating cognition, visual hallucinations, and parkinsonian motor symptoms. Following Alzheimer's disease, it is the second most common form of neurodegenerative dementia in the elderly. The defining neuropathological features of DLB are the Lewy body and the Lewy neurite, abnormal filamentous inclusions that contain α-synuclein as their major component. DLB is thus classified as an α-synucleinopathy, a class of neurodegenerative disorders that also includes PD and MSA. In addition, DLB is often accompanied by Alzheimer's disease pathology including amyloid deposits.

Although DLB is generally considered as a sporadic disorder, a small number of DLB families have been described, suggesting that genetic factors contribute to DLB pathogenesis. Indeed, mutations in genes previously implicated in autosomal dominant and sporadic PD have also been linked to familial DLB: an observation that supports the notion that PD and DLB are the same

disorder on a spectrum. For example, *α-synuclein* (*SCNA*) mutations and multiplications have been associated with both PD and DLB. Similarly, mutations in the *leucine-rich repeat kinase-2* (*LRRK2*) gene, currently recognized as the most common genetic cause of familial and sporadic PD, have been identified in some DLB patients. Furthermore, mutations in the *glucocerebrosidase (GBA)* gene, the causative gene of the autosomal recessive disorder Gaucher disease, have been linked to parkinsonism including PD and DLB. These findings demonstrate that heterozygosity for a Mendelian disorder can confer susceptibility to seemingly unrelated complex disorders; they also suggest that *GBA* loss-of-function ultimately leads to neurodegeneration. In addition, a recent multigenerational mapping study identified a novel locus for familial DLB on chromosome 2q35-q36 although a causative gene in this region has not yet been identified. Moreover, there is some evidence linking *β-synuclein* (*SCNB*) mutations with DLB although co-segregation with the disease has not been established with certainty.

Multiple System Atrophy (MSA)

MSA is a progressive neurodegenerative disorder with an estimated prevalence of 1.9–4.9 cases in 100 000. Clinical features include autonomic failure, poorly levodopa-responsive parkinsonism, and cerebellar ataxia. MSA pathology is defined by glial cytoplasmic inclusions composed of filamentous α-synuclein deposits and several other proteins, while Lewy bodies are typically not found. MSA therefore represents a mostly nonneuronal α-synucleinopathy.

MSA is a late-onset sporadic disease and its etiology is still unknown. Familial MSA is exceptionally rare, and causative or predisposing gene mutations remain elusive. The 'Online Mendelian Inheritance in Man (OMIM)' database, which is a comprehensive up-to-date catalog of all known Mendelian disorders, currently does not include MSA.

Frontotemporal Dementia with Parkinsonism-17 (FTDP-17) *OMIM #600274* and *#607485*

FTDP-17 is an adult-onset neurodegenerative disorder with clinical features including personality/behavioral changes, cognitive impairment, and parkinsonism. FTDP-17 is an autosomal dominant subtype of a broader syndrome referred to as frontotemporal lobar degeneration (FTLD), which is highly heterogeneous and the second most common cause of dementia in individuals <65 years of age. In 1998, missense and splice-site mutations in the gene encoding the microtubule-associated protein tau (*MAPT*) on chromosome 17 were identified in multiple FTDP families and since then, over 40 additional *MAPT* mutations have been linked to the disorder (see http://www.molgen.ua.ac.be/FTDmutations/). The intronic splice-site mutations modify the alternative splicing of *MAPT* exon 10, thereby disturbing the critical balance in the ratio of tau isoforms containing 3 or 4 microtubule-binding repeats. Overexpression of the 4-repeat isoform is thought to disrupt cellular microtubule dynamics, which ultimately results in neuronal death. Accumulation of the 4-repeat tau isoform is also observed in two other parkinsonian disorders, namely PSP and CBD (see below).

Pathologically, *MAPT*-linked FTDP-17 is characterized by filamentous tau inclusions in neurons and glia, and the disorder is therefore classified as a tauopathy. However, not all FTDP-17 cases have positive tau pathology, and a significant number of FTDP families with autosomal dominant inheritance show linkage to 17q21 in the absence of demonstrable *MAPT* mutations. Further analysis of the 17q21 region in these tau-negative families identified mutations in the gene coding for progranulin (*PGRN*), a growth factor involved in multiple physiological and pathological processes including tumorigenesis. Brain autopsies from *PGRN*-linked FTDP-17 patients show intra- and perinuclear inclusions that are immunoreactive to ubiquitin but devoid of tau or α-synuclein deposits. The ubiquitin-positive form of FTDP is therefore often referred to as FTDU-17. Clinically, there seem to be only subtle differences between *MAPT*- and *PGRN*-linked FTDP-17, and it is intriguing that mutations in two apparently unrelated genes, located in proximity on the same chromosome, can cause a very similar disease phenotype. In addition, some cases of ubiquitin-positive familial FTLD (FTLD-U) with varying phenotypes have been attributed to mutations in the genes encoding the charged multivesicular body protein-2B (*CHMP2B*), the valosin-containing protein (*VCP*), and another locus on chromosome 9p21–13 distinct from *VCP*. Clinically, these families present with frontotemporal dementia, and in some cases, with motor neuron disease, dystonia, and other symptoms, while parkinsonism is not typical. Intriguingly, the ubiquitin-positive pathology is characterized by the accumulation of TAR DNA-binding protein 43 (TDP-43), and hyperphosphorylated, ubiquitinated TDP-43 has recently been implicated as the common pathologic substrate of familial and sporadic FTLD-U as well as amyotrophic lateral sclerosis (ALS). These disorders are therefore referred to as TDP-43 proteinopathies. Of note, familial ALS linked to *Cu/Zn superoxide dismutase* (*SOD1*) mutations does not exhibit TDP-43 pathology, implying that this rare form of ALS is not simply a familial counterpart of sporadic ALS, which is TDP-43 positive.

Progressive Supranuclear Palsy (PSP) *OMIM #601104*

PSP is the most common cause of non-PD parkinsonism (other than medication-induced) with a prevalence of

6.0–6.4 cases per 100 000. The clinical disorder is characterized by progressive symmetric axial rigidity, vertical gaze palsy, dysarthria, and dysphasia. In addition, cognitive impairments may occur in the late stages of the disease. The disorder is only minimally responsive or completely unresponsive to dopamine replacement therapy. Pathological hallmarks include neuronal loss, gliosis, and neurofibrillary tangles containing tau aggregates in the basal ganglia, diencephalon, and brainstem; PSP is therefore classified as a tauopathy. The fibrillary tangles in PSP are predominantly composed of the 4-repeat tau isoform.

The etiology of PSP is still unknown, but there is evidence for familial clustering, which implies a genetic contribution. Indeed, the association of a specific allele of the *MAPT* gene, the A0 allele, with PSP in Caucasians was first described in 1997. The A0 allele, an intronic dinucleotide polymorphism, was soon found to be in linkage disequilibrium with other polymorphisms, leading to the definition of two distinct MAPT haplotypes, referred to as H1 and H2. These haplotypes cover a region of ~1.8 Mb at 17q21 and encompass the *MAPT* gene as well as several neighboring genes. The H1 haplotype is more common, and homozygosity for H1 has been associated with an increased risk of developing tauopathies including PSP and CBD, a closely related parkinsonian condition. The H1 haplotype can be further divided into various sub-haplotypes, and the H1c variant has been shown to be a more specific risk factor for PSP, CBD, and to a lesser extent, Alzheimer's disease. As mentioned earlier, yet another set of mutations in *MAPT* is associated with FTDP-17, thus demonstrating that different variants of a single gene can be risk factors for multiple forms of parkinsonism and even nonparkinsonian neurodegenerative diseases.

Efforts to identify genetic risk factors for PSP have also included a genome-wide association study (GWAS) that scanned over 500 000 single-nucleotide polymorphisms in a pool of 288 DNA samples from pathologically confirmed Caucasian PSP patients. This pooling-based GWAS confirmed the association of PSP with the *MAPT* H1 haplotype and also identified a second significant risk locus on chromosome 11p12-p11. This novel locus was subsequently refined to a single haplotype block containing two genes, the DNA damage-binding protein-2 (DDB2) gene and the lysosomal acid phosphatase-2 (ACP2) gene (*OMIM #610898*). In addition, a genome-wide linkage study of a large Spanish family with autosomal dominant inheritance of PSP revealed association with a candidate locus on chromosome 1q31.1 (*OMIM #609454*). No linkage to the *MAPT* gene was found in this family.

Corticobasal Degeneration (CBD) *OMIM #157140*

CBD, a relatively rare cause of parkinsonism, is clinically characterized by asymmetric rigidity, dystonia and dystonic tremor of the affected limbs, a lack of dopamine responsiveness, and prominent cortical features. The neuropathology is typically marked by focal asymmetric cortical atrophy with ballooned neurons, nigral degeneration, and glial and neuronal filamentous tau pathology, especially astrocytic plaques in the affected cerebral cortex.

CBD is a mostly sporadic tauopathy, and like PSP, it is associated with homozygosity for the *MAPT* H1 haplotype leading to accumulation of tau aggregates containing the 4-repeat tau isoform. Although CBD and PSP can usually be differentiated on the basis of their clinical and pathological features, there is a considerable degree of overlap, especially in more atypical cases. Based on this overlap of clinical and pathological features as well as the genetic similarities between these two disorders, it has therefore been suggested that CBD and PSP correspond to different phenotypes of the same disease process, which is subject to additional genetic and/or environmental modifying factors. How this shared etiology can lead to such phenotypic heterogeneity will likely be the subject of future studies.

Other Mendelian Disorders Associated with Parkinsonism

Parkinsonian features have also been noted in several other late-onset Mendelian disorders, including SCA2 (*OMIM #183090)* and SCA3 (also known as Machado–Joseph Disease, *OMIM #109150*) and HD (*OMIM #143100*).

Conclusion

Parkinsonism refers to a heterogeneous group of neurodegenerative movement disorders, each marked by specific clinical, neuropathological, and genetic characteristics. Despite this heterogeneity, genetic studies have revealed several intriguing themes that are common to subgroups of these disorders. The terms 'synucleinopathy', 'tauopathy', 'amyloidopathy,' and 'TDP-43 proteinopathy' have become common parlance in the field of neurogenetics and highlight the biological hallmarks, namely abnormal protein deposits, rather than the clinical manifestations of these disorders. Using this framework, PD, DLB, and MSA are classified as synucleinopathies; *MAPT*-linked FTDP-17, PSP, and CBD as tauopathies; and FTDP-U, along with ALS and the broader syndrome of FTD-U, as TDP-43 proteinopathies. Alzheimer's disease represents both an amyloidopathy and a tauopathy. These distinct classes of proteinopathies are all thought to be disorders of dosage, where increased quantities of normal or posttranslationally modified protein lead to disease. Therapeutic strategies are therefore being developed to block or slow down the formation of these aberrant protein aggregations. Such interventions are hoped to be effective in all classes of

proteinopathies rather than in single, clinically defined disorders within these classes. Taken together, advances in understanding the genetics of parkinsonism have begun to provide insights into the pathogeneses of these disorders, thereby revealing potential therapeutic targets that will impact on the underlying causes, and not just the symptoms, of these disorders.

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See also: Parkinson's Disease: Genetics.

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http://www.molgen.ua.ac.be/FTDmutations/ – Alzheimer Disease & Frontotemporal Dementia Mutation Database.

http://www.ncbi.nlm.nih.gov/sites/entrez?db = omim – OMIM (Online Mendelian Inheritance of Man).

Parkinsonism: Vascular

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Glossary

Cerebrovascular disease – Disease of the blood vessels and, especially, the arteries that supply the brain, usually caused by atherosclerosis. When blood flow is blocked, cell death can occur, causing sudden loss of oxygen and glucose to the brain.

Lacune – A type of stroke, generally caused by occlusion of the smaller vessels in the brain, that tends to occur in the brainstem and deep grey nuclei of the brain.

Parkinson disease – A degenerative disorder of the brain that results in tremor, stiffness, slowed movements, and trouble with gait, associated with Lewy body pathology.

Parkinsonism – Symptoms of tremor, stiffness, slowed movements, and walking difficulty, without a specific cause.

Definition and History

The term parkinsonism defines a syndrome consisting of tremor, rigidity, bradykinesia, and postural instability. Besides Parkinson's disease (PD), parkinsonism can result from several other causes. Vascular parkinsonism (VP), defined as parkinsonism due to cerebrovascular disease, is an uncommon cause of parkinsonism, occurring in 3–7% of cases (see **Figure 1**). VP was initially described by Critchley in 1929. After enjoying initial popularity, the existence of VP as a clinical entity was questioned, with dissenters arguing that the vascular changes seen were incidental findings and not a pathologic cause of parkinsonism. Their case was bolstered by the varying clinical manifestations of presumed VP and by the cooccurrence of vascular lesions in some cases of histologically-proven PD with Lewy body pathology. More recently, however, improved clinical criteria and pathology studies have reestablished VP as a clinical entity distinct from idiopathic PD and other forms of parkinsonism, with implications for disease pathology, management, and prognosis. Although the use of 'vascular' implies a specific disease with a known pathophysiology, VP is more properly considered a syndrome rather than a specific diagnosis. Cerebrovascular disease itself has several underlying etiologies, each with unique pathophysiology and therefore with individualized considerations for management.

Epidemiology

The prevalence of VP varies widely depending on the specific definition used. However, studies relying on imaging or pathologic data to support the diagnosis estimate a prevalence of 3–7% among causes of parkinsonism. In the older population, the prevalence of parkinsonism ranges from 15 to 52% depending on the age and population studied, and the prevalence of VP is expected to rise with the escalating burden of hypertension, diabetes, and cerebrovascular disease worldwide. The prevalence and incidence of VP increase with male gender and increasing age, and patients with VP tend to be older than those with idiopathic PD, with an average age of onset ranging from 65 to 82 years, compared with an average age of 55 years for PD.

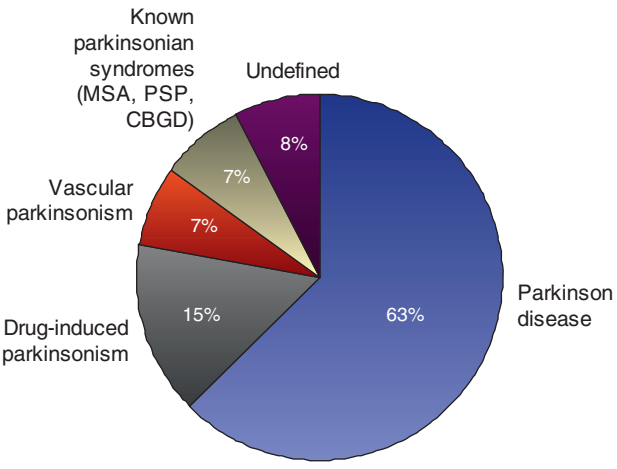

Figure 1 Most common diagnoses in parkinsonian disorders.

The proposed risk factors for VP arise from the underlying presumptive mechanism of ischemic brain disease. Of the vascular risk factors studied, hypertension and diabetes are the most consistent risk factors. Other consistent factors that have been less well-studied include heart disease, hyperlipidemia, and a positive smoking history. As compared to typical PD, Winikates et al. demonstrated that coronary artery disease was present in 30.4% of VP but only 6.9% of PD, significant carotid stenosis was present in 7.2% of VP but 0% of PD, and a positive family history of stroke was present in 37.7% of VP but 17.9% PD (all p-values <0.001). Huang et al. reported that anticardiolipin antibodies were present in 40% of their clinical VP population, as compared to a prevalence of 5% in the general population and 12% in the elderly. Although this finding is striking and has clinical implications for the management of VP, this association requires further investigation.

Despite the presence of these risk factors, a direct causal link between clinical strokes and subsequent parkinsonism remains elusive. Large striatal infarcts and territorial cerebral infarcts are an uncommon cause of parkinsonism, occurring in less than 10% of cases. When all types of ischemic stroke are examined, about one-third of patients develop parkinsonian signs and ~10% develop clinical parkinsonism. White matter lesions and small lacunar infarcts are highly associated with the development of clinical parkinsonism, with incidences of 38% for white matter lesions and 16% for lacunar infarcts in one study. Territorial strokes are often associated with parkinsonian signs but are much less commonly associated with a clinical diagnosis of parkinsonism (2.5%). Taken together, the available data implicate white matter lesions as a major risk factor for developing parkinsonism, but whether white matter lesions are causal or represent a confounding factor remains unknown.

Pathophysiology

VP is considered secondary to vascular disease, but how vascular insults cause parkinsonism remains unclear. Several ischemic pathologic changes, including lacunes, basal ganglia infarcts, and diffuse white matter lesions, occur in VP and may be associated with specific subtypes (see section Clinical Features and Differential Diagnosis). Ischemic changes are not universally associated with the clinical presentation of VP; however, these lesions occur

frequently in the elderly population without clinical evidence of parkinsonism. Due to this overlap, the clinical manifestations of parkinsonism cannot be predicted from the number, site, or size of vascular lesions. A more complete understanding of specific pathophysiology is also complicated by the coexistence of Lewy bodies and vascular lesions in PD, which occurs in up to 20% of cases examined in autopsy series. Whether and to what extent the coexisting vascular disease may modify the clinical manifestations and the course of typical PD are unknown and blurs the distinction between Lewy body PD and VP.

The variety of pathological subtypes of VP reflects the underlying heterogeneity of cerebrovascular disease. Although large (greater than 1.5 cm) focal basal ganglia lesions rarely induce parkinsonism, basal ganglia lacunes are common in VP, and the lentiform nucleus is the most common site. Chang et al. described three anatomical patterns of VP: basal ganglia infarcts; frontal lobe infarcts, and deep subcortical white matter lesions. Each type had similar clinical presentations but different prognoses, with the basal ganglia group doing the best and the subcortical white matter group doing the worst. Alternatively, Zijlmans et al. and Winikates et al. divide VP into two patterns: subcortical gray nuclei lesions of the striatum, globus pallidus, and thalamus, associated with an acute or subacute onset; and diffuse watershed lesions, associated with an insidious onset. A consecutive autopsy series by Jellinger divided VP into three pathologic patterns: subcortical vascular lesions (32%), lacunes in basal ganglia and brainstem (20%); and multiinfarct encephalopathy without nigral lesions (48%).

Table 1 Clinical differences between vascular parkinsonism (VP) and idiopathic PD

	Vascular parkinsonism	*Idiopathic PD*
Demographics		
Age	Mean 65–82	Mean 55
Sex	1:1	Male predominance
Cardinal features		
Tremor	Uncommon (30%) Postural, kinetic	Common resting
Rigidity	Present	Present
Bradykinesia	Present	Present
Postural instability	Early, common (70%)	Late, less common
Other features		
Gait disorder	Early, common (90%)	Late
Symmetry	Symmetric	Asymmetric
Limbs involved	Lower body predominant (60%)	Unilateral or upper body predominant (90%)
Corticospinal findings	Common (30–60%)	Rare
Nonmotor features		
Dementia	Early, common (45%)	Late, less common
Hyposmia	Absent	Present
Depressive symptoms	?	Common (50%)
Pseudobulbar affect	10%	Rare
Management		
Progression	Acute or step-wise	Insidious, chronic
Levodopa response	Poor, transient (<25%)	Good, sustained

Clinical Features and Differential Diagnosis

By definition, VP and other forms of parkinsonism share similar signs and symptoms, making it difficult to differentiate VP on clinical grounds alone. Still, VP and typical PD differ clinically in several ways, allowing a clear distinction in prototypic cases (**Table 1**). Differentiating VP from other forms of atypical parkinsonism is more difficult. VP is usually symmetric, similar to multisystem atrophy (MSA) and progressive supranuclear palsy (PSP). However, VP tends to predominate in the lower limbs and has a relative absence of signs in the upper body, in contrast to MSA and PSP as well as PD. Other features that define MSA and PSP, such as cerebellar signs, orthostatic hypotension, and ocular movement abnormalities, are rarely described in VP. Still, the diagnosis of VP cannot be made based on the presence or absence of a single clinical sign; rather, a clinical diagnosis of VP is made based on the convergence of appropriate clinical and imaging characteristics and a reasonable effort to exclude other forms of parkinsonism, especially drug-induced parkinsonism and other neurodegenerative parkinsonisms such as PSP, MSA, and corticobasal degeneration. Less common causes of parkinsonism should be considered in the appropriate clinical situation and include carbon monoxide, cyanide, or manganese poisoning, prion disease, chronic subdural hematoma, Wilson's disease, and normal pressure hydrocephalus.

Several clinical subtypes of VP have been described. The acute subtype occurs in ~25% of cases and is associated with the acute development of parkinsonism within 1 month of stroke onset. This subtype is more likely to have an asymmetric presentation with lesions identified in the contralateral basal ganglia on imaging. More commonly, VP presents insidiously in a stepwise progression, with symmetric bradykinesia, early gait disorder, and postural instability. Tremor is infrequent and when present is often postural or kinetic. Early dementia, corticospinal signs, early incontinence, and pseudobulbar palsy (dysarthia, dysphagia, drooling, and emotional incontinence) are all more common in VP than PD.

Diagnostic Evaluation

Diagnosing VP in the clinic remains challenging. The readily apparent group differences between PD and VP, noted above, may not be clearly present in a particular individual. To standardize the clinical diagnosis, vascular rating scales, initially developed for dementia, have been adapted for use in the parkinsonian population (**Table 2**). However, these vascular scales have not yet been validated against postmortem pathological examinations.

Imaging studies can assist in the diagnosis of VP, and magnetic resonance imaging (MRI) or computed tomography (CT) evidence of cerebrovascular disease is considered essential in most proposed diagnostic criteria. However, the presence of cerebrovascular disease does not exclude the diagnosis of PD. In studies using vascular scoring systems or clinical history of stroke without imaging criteria to define VP, MRI or CT evidence of ischemic injury was present in over 95% of patients, and no patient with VP had a normal imaging study. Evidence for vascular disease in multiple vessel territories is present in over 70% of patients. In addition to cerebrovascular disease, other abnormalities on imaging include hydrocephalus, atrophy, and nonspecific white matter changes.

Functional neuroimaging (SPECT) using ligands for the dopamine transporter (DAT) may provide additional diagnostic clues in VP. Several researchers have found that DAT imaging is abnormal in neurodegenerative parkinsonisms (PD, MSA, and PSP) but is usually normal in VP due to the preservation of presynaptic dopamine neurons. However, other studies have demonstrated that focal basal ganglia infarcts can produce DAT abnormalities indistinguishable from the pattern seen in neurodegenerative parkinsonism. The use of functional imaging in the routine assessment of VP therefore remains unclear.

Assessment of olfactory function may also help differentiate VP from PD. Although impaired olfactory function is associated with idiopathic PD, smell testing was found to be normal in patients with VP in one study of 32 subjects. Olfactory testing is simple, inexpensive, and readily available. However, this option needs to be validated in larger trials, and no data are available on whether it can successfully distinguish among other forms of atypical parkinsonism.

Table 2 Vascular rating scale for the diagnosis of VP

Clinical history	*Score*
Pathologically or angiographically proven diffuse vascular disease	2
Onset of parkinsonism within 1 month of clinical stroke	1
Personal history of two or more strokes	1
Personal history of two or more risk factors for stroke	1
Neuroimaging evidence of vascular disease in two or more territories	1
Diagnosis of VP: Patients with parkinsonism and a total score of two or more	

Source: Winikates J and Jankovic J (1999) Clinical correlates of vascular parkinsonism. *Archives of Neurology* 56: 98–102.

Management and Prognosis

Overall, parkinsonism is associated with a twofold increase in mortality, with gait dysfunction having the most significant impact on mortality and progressive disability. Compared to PD, individuals with VP are generally older and present with early falls, dementia, and poor levodopa response. All of these factors are generally associated with a poorer prognosis, and several studies suggest that VP progresses more rapidly than PD. A small subset of individuals, who present acutely with asymmetric symptoms, may remain stable or even improve spontaneously. If it occurs, spontaneous improvement is usually seen within 1–2 years.

Scant evidence is available to guide the management of individuals with VP. Principles of management have therefore been formed from clinical experience and logical extrapolation from the stroke literature. Individuals with VP generally respond poorly and transiently to dopaminergic therapy. However, Zijlmans et al. have described a subset of VP individuals, with lesions centered in the substantia nigra, who demonstrated an excellent and sustained response to dopaminergic therapy. In the absence of other symptomatic therapy, patients with VP should therefore receive a full therapeutic trial of dopaminergic therapy – generally 1 g of total daily levodopa, if tolerated, for at least 2 months.

Although no studies have examined the effects of vascular risk reduction on VP disease progression, it seems reasonable to identify and reduce the vascular risk factors in this population in the hopes of slowing further vascular lesion burden. Clinicians caring for these patients could consider an evaluation of previously undiagnosed vascular risk factors, including echocardiogram (EKG), carotid ultrasound, lipid profile, and glucose or hemoglobin A1C testing for diabetes. Individuals should be offered counseling for smoking cessation and to improve diet and exercise regimens, and known vascular risk factors should be controlled. Physical and occupational therapy can be helpful for those with early gait difficulties.

Summary

VP is an uncommon, but important cause of parkinsonism, with clinical features that can be distinguished from idiopathic Parkinson disease. MRI can help establish the presence of vascular disease but cannot exclude idiopathic

PD. Despite the association with vascular lesions, the underlying pathophysiology is poorly understood. Further research priorities include validating diagnostic criteria and diagnostic assessments, and rigorous evaluation of risk modification and potential therapeutic options for this increasingly common syndrome.

See also: Akinetic-Rigid Syndrome; Binswanger's Subcortical Arteriosclerotic Encephalopathy; Bradykinesia; Dementia, Movement Disorders; Gait Disturbances in Parkinsonism; Levodopa; Neuroimaging, Parkinson's Disease; Parkinson's Disease: Definition, Diagnosis, and Management; Progressive Supranuclear Palsy; Rigidity; SPECT Imaging in Movement Disorders.

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Parkinson's Disease: Animal Models

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Glossary

1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) – A neurotoxin that kills cathecholaminergic neurons with a greater efficacy upon dopamine neurons. It is used for producing mouse and primate models of Parkinson's disease.
Lewy bodies – Pathological intracytoplasmic hallmark of Parkinson's disease that is an α-synuclein positive inclusion.
α-synuclein – Presynaptic protein which accumulation and mutations are associated with increased risk of Parkinson's disease. It was further shown to be the main component of the Lewy bodies;
Rotenone/paraquat – Pesticides blocking the mitochondrial respiratory chain used for modeling Parkinson's disease in animals. Suspected of acting as environmental toxins.

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder, affecting 1% of the population over 55. This pathology is primarily characterized by a progressive degeneration of the nigrostriatal dopamine (DA) system associated with the presence of intracytoplasmic α-synuclein positive inclusions known as Lewy bodies. Fully developed, PD comprises motor impairments, including bradykinesia, rigidity, tremor, and postural instability.

Whereas the etiology of idiopathic PD is still unknown, its pathophysiology has rapidly advanced due to the development of relevant mammalian models. Using these models, levodopa (L-3,4-dihydroxyphenylalanine or L-dopa) was first applied to compensate striatal DA deficiency associated with the motor symptoms of PD. Unfortunately, although effective in the early stages of PD, this symptomatic therapy loses efficacy over time due to the developments of severe side effects known as

levodopa-induced dyskinesia (LID). Experimental models of PD are thus needed to gain insights into the pathological mechanisms of the disease and to develop new therapeutic strategies. Ideally, for direct relevance to human PD, a model should have the following characteristics: (1) a chronically progressive loss of DA neurons, (2) motor symptoms clearly improved by levodopa treatment, (3) nonmotor symptoms such as cognitive impairments, sleep disorders, constipation, orthostatic hypotension, etc., (4) development of LID over time, and (5) lewy body inclusions. However, it is necessary to admit that there still a long road ahead of us. Some of the available models allow reproducing at least one or two characteristics of the disease. Further, some discrepancies exist between neuropathological data obtained in PD patients and data from experimental models. Indeed, PD is a chronic degenerative disease, whereas animal models could be produced either by acute lesion or by semichronic intoxication with specific neurotoxins. It is clear that we need animal models that will come closer to the gradual progression of DA neuronal death and the subsequent evolution of parkinsonian motor and nonmotor disabilities. Current evidence suggests an involvement of both environmental and genetic factors in the progression of PD. Future pathophysiological studies should take all these factors into account. PD cannot any longer be studied as a discontinuous pathology, in which the patient passes suddenly from a normal to a full parkinsonian state. The following nonexhaustive review looks at reversible pharmacological, toxic and genetic in vivo mammalian models of PD available today and proposes a brief assessment of their relative merits.

Pharmacological Model

Those models were the first to be developed and are still in use. Depleting brain stores of monoamines with the Rauwolfia alkaloid reserpine or administering a neuroleptic, for example, haloperidol, are two reversible pharmacological models, which induce transient functional disturbances by a temporary blockade of DA neurotransmission.

The Reserpine Model

It was the first PD animal model. Reserpine, by interfering with the storage of catecholamine, results in monoamine depletion in nerve terminals and induces a transient hypolocomotion with resultant hypokinesia, akinesia, and even catalepsy.

Most of the available pharmacological studies of reserpine-induced motor symptoms, focused on rigidity or the indirect evaluation of hypokinesia. Besides this model of parkinsonism, several studies have shown that rats treated with reserpine develop orofacial dyskinesia, which is considered as a good model of tardive dyskinesia.

The precise mechanisms underlying the effects of reserpine treatment have still not been elucidated but it has been shown that the depletion reaches not only DA but also the others monoamines. Although the use of this model has suffered of a certain disaffection due to its nonselectivity and its transient nature, it provides a useful tool to investigate the symptomatic antiparkinsonian activity of new chemical entities featuring DA activity, α-adrenoreceptor blockers and glutamatergic antagonists.

The Neuroleptic Model

Parkinsonian-like symptoms including akinesia, muscular rigidity, and tremor were induced by the majority of DA antagonists both in humans and in experimental models. Catalepsy, another major early side effect of neuroleptics is characterized by the inability to change an externally imposed posture. Numerous studies have investigated the ability of antiparkinsonian compounds to counteract neuroleptic-induced catalepsy: DA agonists and levodopa, anticholinergics Glutamate agents, and GABA antagonists. Most of these studies have been performed on rodents, very few on nonhuman primates.

Although neuroleptics induce extrapyramidal symptoms resembling those observed in human PD, their relevance for animal models of PD is limited. Their action is firstly transient and reversible. They can block DA transmission but cannot induce degeneration of DA nigrostriatal neurons. The applications of this model are therefore limited.

Relevance of Reversible Models

The reserpine and neuroleptic models of PD are not the only experimental pharmacological models of PD available. Animal models of tremor have also been developed, such as the model using oxotremorine, a selective cholinergic agonist acting on muscarinic receptors. Further, like reserpine, striatal DA depletion following administration of methamphetamine has prompted to propose this psychostimulant as a good candidate to modelling PD. None of these models, however, reproduce the degenerative process of PD. They remain relevant for the study of specific symptoms but cannot provide any further contribution to the development of dynamic animal models since their transient nature excludes de facto any degenerative evolution and their characteristics do not reproduce exactly the clinical features of human PD.

Neurotoxic Models

Although it is clear that the PD does not result only from the loss of nigrostriatal DA neuron, the common feature of all neurotoxin-induced models, namely those produced broadly by the toxins 6-hydroxydopamine (6-OHDA) or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP),

is that they all induce a massive and reproducible nigrostriatal degeneration.

The 6-Hydroxydopamine Model

For approximately the last 50 years, 6-OHDA has become the most commonly used model for PD due to its specific neurotoxic effects on catecholaminergic pathways. The 6-OHDA structural analogy with catecholamines facilitates its transfer and accumulation through the high-affinity transport system located on the plasma membrane. In these monoaminergic neurons, 6-OHDA induces neurodegeneration by oxidative stress through formation of reactive oxygen species and quinones. Many other mechanisms have been involved since then. To reduce damage on noradrenergic (NA) neurons which are more sensitive to 6-OHDA than DA neurons, a pretreatment with desimipramine, a selective inhibitor of NA-reuptake injected systemically, is required. The specificity obtained is still, however, not absolute, and nonspecific lesions of the serotoninergic or other catecholaminergic systems may occur.

Whereas the rat remains the species of choice, 6-OHDA is also effective in several other species from zebrafish to primate confirming that this toxin is a powerful experimental tool. Since the toxin is unable to cross the blood–brain barrier, 6-OHDA is injected intracerebrally under stereotactic guidance to target the nigrostriatal DA pathway. Several local approaches were thus considered and toxin can be administered at the distinct parts of this ascending DA pathway, uni- or bi-laterally. Following the princeps work of Ungerstedt who injected 6-OHDA bilaterally into the rat substantia nigra (SNc), models with bilateral DA lesion have been proposed. Nevertheless, wherever the 6-OHDA was administered, rats present akinesia, aphagia and adipsia and mortality increases significantly. More recent studies have proposed partial bilateral 6-OHDA lesions, particularly at the striatal level but this model, as good as it can be, must be a compromise between lack of induced mortality and sufficient DA depletion. Accordingly, the most practical and frequent application of the 6-OHDA-lesioned model is the unilateral intracerebral injection. This allows the assessment of rotational behaviour that correlates well with the degree of lesion, in response to drugs affecting DA transmission. Several additional motor tests have also been validated in 6-OHDA rats, including akinesia or LID.

Apart from the testing of a number of antiparkinsonian compounds, the so-called 'Ungerstedt model' has greatly improved our knowledge of the physiopathology of the basal ganglia. However, the 6-OHDA model is not able to replicate many of the neuropathological features of human PD. It does not alter other brain regions and to date, the formation of cytoplasmatic inclusions (Lewy bodies) has never been observed in this model. Further, rotational behaviour, although an interesting criteria for drug discrimination, does not allow estimating all human parkinsonian symptomatology such as the nonmotor symptoms. Finally, this acute model does not induce a slow progressive neuronal death which characterizes the pathophysiology of human PD, unless when injected into the striatum.

Despite these drawbacks, the stable lesions produced by the administration of 6-OHDA allow long-term studies. For this reason, 6-OHDA model has been particularly useful to quantify motor deficit, develop pharmacological screening as well as neuroprotective studies by testing cell transplantation or neurotrophic factors.

The 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine Model

The MPTP model is probably the best characterized and most used model of PD at present. In the early 1980s, several young Californian adults developed a severe parkinsonian-like syndrome after injection of a synthetic heroin contaminated by a meperidine analogue, MPTP. The active metabolite of MPTP, MPP^+ was accumulated in DA cells via the dopamine transporter (DAT) and induced mitochondrial complex I inhibition causing oxidative stress and cell death. MPTP induces symptoms virtually identical to those of idiopathic PD and this syndrome was considerably improved by the administration of levodopa or DA agents.

As in humans, the administration of MPTP in various animals has been shown to induce a selective degeneration of the DA nigrostriatal pathway with parkinsonian-like motor impairment. The most obvious impact of MPTP-based toxin models was the development of primate models, which come the closest to human PD. Rats remain relatively insensitive to the administration of MPTP and only specific strains of mice are sensitive to its action. Further, in comparison to the level that nigral degeneration obtains in monkeys, MPTP-induced DA depletion in mice, requires higher dose and permanent behavioral PD symptoms are rarely noticeable. This led to use this model for biochemical investigation of the neurotoxic action of MPTP.

Various doses and regimes of MPTP administration (route, number and frequency of injections) are used by different laboratories and can produce varying degrees of DA loss. The most frequently protocol used for the MPTP mouse model comprises four injections of MPTP ($20\,mg\,kg^{-1}$; intraperitoneally (i.p.)) at 2-h intervals. This produces a sharp decrease in striatal DA levels and leads to a loss of DA neurons in the ventral mesencephalon.

Among the various schedules of MPTP intoxication for primates, toxin could be administered either systemically (intraperitoneal (i.p.), intravenous (i.v.), intramuscular (i.m.), or subcutaneous (s.c.)) to achieve a bilateral lesion or through the carotid on one side when a hemiparkinsonian syndrome is preferred. In the former model, a supporting therapeutic trial with levodopa is required to allow MPTP-treated animals to maintain a normal nutrition. The second model has been useful in electrophysiological studies or for studying novel antiparkinsonian therapies.

In nonhuman primates, MPTP can produce a parkinsonian syndrome that replicates almost all of the features of PD, including bradykinesia, rigidity, and postural abnormalities. The resting tremor and the lewy body inclusion, are however hardly encountered in the MPTP-treated monkey. It would seem, however, that, rather than a question of strain, it is a question of schedule of MPTP administration. Indeed, old paradigms used high doses of MPTP administration to produce acute and severe DA loss, which failed to reproduce the progressive nature of PD. At present, long-term administration of low doses of MPTP seems to be a more accurate approach to mimic the human PD pathogenesis with a slow evolution of parkinsonian syndrome. This model has also been valuable for the study of dyskinesia, since regular use of levodopa or DA agonists induces these incapacitating side effects in the MPTP-treated monkey as it does in humans.

While nonmotor symptoms of PD were more and more acknowledged as debilitating and critical unmet needs for PD patients, the MPTP monkey model(s) has been further studied for establishing if they were present as well. In fact, to our surprise, the MPTP monkey model recapitulates most if not all the motor and nonmotor symptoms. Cognitive impairments have been the first to be acknowledged and a specific model, the so-called chronic low dose model has even been specifically developed to this aim. Interestingly, levodopa impairs cognitive capabilities in these MPTP monkeys while motor symptoms are improved, exactly as in PD patients. Accordingly, the sleep disturbances, excessive daytime sleepiness and rapid eye moment (REM) sleep deregulation that are among the most frequent and disabling nonmotor manifestations in PD are fully reproduced in MPTP monkeys offering the possibility to now investigate the pathophysiology of these disorders and to test putative therapeutics.

Currently, MPTP neurotoxicity is the best available animal model to evaluate the efficacy of neuroprotective and neurorestorative strategies of PD. Like the 6-OHDA model, the MPTP model has facilitated enormously the comprehension of the pathophysiology of the basal ganglia but also opened up new areas of research including drugs, transplants, and gene therapy. Observation of nonmotor symptoms in MPTP monkeys has also opened a new field of research and offers a platform for validating therapeutics aiming at controlling these symptoms.

Environmental Toxins Models

Several epidemiological and toxicological studies have suggested that pesticides and other environmental toxins could be involved in the pathogenesis of PD. Among the environmental toxin models of PD, paraquat, maneb (manganese ethylenebisdithiocarbamate), and rotenone have received the largest attention. One potential mechanism by which all these toxins may increase the risk for PD is through disruption of mitochondrial function.

In rodents, paraquat leads to SNpc DA neuron degeneration accompanied by α-synuclein containing inclusions. Combined with maneb, the effects on the loss of DA neurons and on reduced motor activity are greater than with paraquat alone. Nevertheless these studies are marginal and failed to provide conclusive evidence to consider pesticide model as reliable experimental model of PD.

Rotenone-infused rats resulted in a progressive formation of cytoplasmic inclusions and loss of nigral DA neurons leading to motor behavioral impairment. These motor abnormalities were reversed by levodopa. Although this model produced most of key features of PD, it originally suffered from much variability since some animals had lesions and others not. Further, rotenone induced a chronically progressive degeneration of DA neurons and also of non-DA neurons in both the basal ganglia and the brainstem. This model is thus more a multisystemic model of degeneration than originally proposed on DA neurons selectively. However, recent refinement of both the administration and the procedures have allowed to solve some of these issues, making rotenone appealing again especially considering it is multisystemic and its capacity to produce cytoplasmic inclusions.

Similarly to rotenone, chronic administration of annonacin, another inhibitor of complex I of the mitochondrial respiratory chain cause nigral and striatal (non-DAergic) neurodegeneration. Finally, proteasome inhibitors have been suggested as potential PD inducers. Several expert laboratories despite huge efforts did, however, not replicate this model.

Gene-Based Models

The discovery of several genetic alterations in familial forms of PD has enabled the development of a gene-based approach to create animal models. Genes involved in familial PD include α-synuclein, parkin, UCH-L1, PINK1, DJ-1, and LRKK2. The development of models of PD based on genes implicated in familial form has been carried out using either transgenesis or viral-mediated expression.

Transgenic Models

α-synuclein being the pathological hallmark of sporadic PD, it has been the focus of most endeavours to create a genetic model of the disease. In addition, the discovery of genomic multiplication of α-synuclein in some families demonstrated the pathogenicity of increased levels of the wild-type protein. Numerous lines expressing wild-type or mutated human α-synuclein have been generated. Most lines recapitulate the propensity of some neuronal populations to host protein aggregates (olfactory bulb, midbrain, cortex, etc.) as found in the human disease. Some lines also display nigrostriatal alterations as shown by a reduction of tyrosine hydroxylase (TH) positive

fibers in the striatum or progressive DA cell loss in the SNc. In one line, overexpression of truncated α-synuclein results in a loss of DA neurons in the SNc and a concomitant reduction of DA levels in the striatum. Several reasons may account for the lack of systematic DA neurodegeneration, including expression levels within the SNc, coexistence of human and mouse α-synuclein, upregulation of cellular defense mechanisms in response to constitutive over expression of the protein.

Among parkin knock-out models, two lines (exon 3 or 7 deletion) display alteration of DA release or metabolism and one of these lines also exhibit a loss of TH neurons in the locus coeruleus.

Two lines of DJ-1 mutant mice have been generated, with either targeted deletion of DJ-1 exon 2 or a stop codon inserted in exon 1. Both strategies failed to induce DA degeneration. However, one line showed an increased vulnerability to MPTP which could be reversed by viral-mediated expression of wild-type DJ-1.

Spontaneous in-frame deletion of UCH-L1 exons 7 and 8 leads to gracile axonal dystrophy (gad) in mice. These gad mice display tremor and ataxia due to axonal degeneration of motor and sensory neurons together with the accumulation of β-amyloid and ubiquitinated proteins. Expression of human mutant UCH-L1 (I93M) on a gad background led to a moderate loss of DA neurons in the SNc and DA in the striatum.

The justified disappointment in view of the lack of robust DA neurodegeneration in most transgenic models should be tempered by the fact that these models offer the opportunity to study molecular interactions between genes and pathways involved in the pathophysiology of PD. Also, understanding how mice can cope with genetic alterations that cause PD in humans will be a unique chance to explore future neuroprotective strategies.

Viral-Based Models

Viral-mediated expression of human α-synuclein (WT or A53T) has been shown to induce the formation of cytoplasmic inclusion, neuritic pathology and neurodegeneration in both rats and primates. Interestingly, this approach has been used to demonstrate the neuroprotective role of parkin in α-synuclein-induced DA degeneration. Thus viral-based models appear suitable to study the molecular mechanisms of α-synuclein-induced DA neurodegeneration and to test neuroprotective strategies but would now require much more attention that they have so far.

Conclusion

Currently available animal models of PD have lead largely to a better understanding of PD pathophysiology and pathogenesis as well as provide clues to novel targets for to the development of new or improved neuroprotective drugs. With regard to the development of symptomatic treatments, the MPTP primate models appear as mimicking more and more closely the human condition and represent therefore the gold standard for validating any symptomatic strategy. However, none of the currently available models reproduce the progressive loss of DA neuron that is characteristic of human PD. PD is a chronic and progressive disease whereas the numerous animal models at our disposal are produced either by acute lesion or by semichronic intoxication and thus, only offer stable models of nigral lesion. Transgenic models allow addressing complementary aspects of PD and will be important in understanding the aetiology and progression of PD. Although no perfect animal model of PD exists yet, future models could include a combination of both neurotoxin and genetically induced changes considering that both environmental and genetic factors are involved in the pathogenesis of PD. The benefit of this research will not be limited to PD. A clearer understanding of the dynamic process of neurodegeneration – the impact of the death of certain neurones on the entire neuronal system – will shed light on the whole field of neurodegenerative pathologies.

See also: 6-OH Dopamine Rat Model; Complex I Deficiency; Dopamine Depletors and Movement Disorders; Dyskinesias; MPTP; Neurofibrillary Tangles; Neuroleptics and Movement Disorders; PARK1, Alpha Synuclein; Parkinson's Disease: Definition, Diagnosis, and Management; Parkinson's Disease: Genetics; Pesticides; Stereology.

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Parkinson's Disease: Genetics

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Glossary

Autosomal dominant (AD) – A pattern of inheritance in which an affected individual has one copy of a mutant gene and one normal gene on a pair of autosomal chromosomes. Individuals with autosomal dominant diseases have a 50–50 chance of passing the mutant gene and therefore the disorder on to each of their children.

Autosomal recessive (AR) – In order for an individual to be affected, an individual must have two copies of the mutated gene (or carry two alleles with different mutations in the same gene). An individual carrying a single altered gene will himself/herself not be affected, but, when two carriers of the same altered gene have offspring, there is a 25% chance of an affected child.

Haplotype – The combination of alleles at several loci on a single chromosome – a set of closely linked genes or DNA polymorphisms inherited as a unit.

Linkage analysis – Genetic loci on the same chromosome are physically connected and tend to stay together during meiosis and are thus genetically linked. Alleles for genes on different chromosomes are usually not linked, due to independent assortment of chromosomes during meiosis. Linkage analysis is a gene-discovery technique that traces patterns of heredity in large families with apparent mendelian inheritance, in an attempt to locate a disease-causing gene mutation by identifying traits that are coinherited (which cosegregate) with it.

Single nucleotide polymorphism (SNP) – SNPs are markers that are randomly, but not evenly, spaced throughout the genome, making it possible to scan the genome for differences between cases (individuals affected by a given complex disorder) and controls (unaffected individuals). Statistical analyses of differences in the occurrence of particular SNPs between cases and controls are done to determine the loci of putative risk factor genes. SNPs are not typically mutations in risk factor genes themselves, but are simply nearby, and as such, are markers for risk of disease, though they do not contribute to risk of disease themselves per se.

Genetic Overview

PD was noted to have a familial component, as early as 1880. The discovery of Mendelian mutations in *α-synuclein* and subsequently, other genes, was a major step forward that revolutionized beliefs regarding PD etiology. Epidemiological surveys suggest that although PD beginning at age < 50 years is highly genetic, the later the onset of disease, the less so. However, longitudinal evaluation of twins with late-onset PD, via 18F-dopa positron emission tomography, suggests that cross-sectional studies may overlook presymptomatic disease. These data support the idea that the contribution of genetics to parkinsonism, including PD, may be greater than appreciated. Indeed, blood relatives of affected individuals are at a 3–4-fold increased risk for PD compared to the general population.

Disorders with a heritable component can be categorized as either Mendelian (causal) or non-Mendelian (complex). Mendelian gene variants are responsible for a small fraction of all PD (perhaps 5%). However, causal genes for PD have taught us a great deal regarding the biological pathways leading to PD and other neurodegenerative disorders. For example, it is now known that Lewy bodies stain with α-synuclein and ubiquitin antibodies. Identification of α-synuclein mutations that are causal in familial PD and the presence of this protein in pathological deposits not only in brain sections from individuals with PD but also from individuals with other parkinsonian disorders emphasize the biological importance of traditional gene discovery in research to understanding the pathogenesis of PD.

While pathological studies link typical PD to α-synuclein, there are cases of PD that do not demonstrate synuclein pathology. This point emphasizes that PD is not due to a single molecular abnormality, but rather, is a final clinical manifestation of diverse processes. It is believed that most PD is caused by multiple genetic and environmental factors, most remaining unknown. This situation places PD squarely in the category of complex human disorders (which also include Alzheimer's disease (AD), stroke, and many other disorders). Advances in technology have driven the advent of high throughput genetic studies designed to address challenges of understanding complex disease, which in turn are hoped to identify pathways and targets for therapeutic intervention. Genome-wide association studies (GWAS) allow inroads into this effort, and PD is among the first disorders

with biospecimens linked to phenotypic and SNP data to support high throughput approaches designed to discover genetic risk factors.

Mendelian Parkinson's Disease (PARK 1–13)

PARK1/α-Synuclein (SNCA)

In 1996, genetic linkage to chromosome 4q was found in a large Italian family (the 'Contursi kindred') with apparent autosomal dominant (AD) Lewy body PD. The following year a causal mutation was found in the α-synuclein gene (*SNCA*), A53T. Surprisingly, the mutation in humans is the normal sequence in mouse; thus, the pathogenic mutation is 'revertant.' A fragment of α-synuclein (also known as 'nonamyloid component of plaques,' or NACP) was previously described in Alzheimer's disease. The role of NACP in this latter neurodegenerative disease, however, remains largely unknown. The normal function of α-synuclein is also unknown. The gene is a member of a gene family reported to control inhibition of phospholipase D2 selectively and has a role in regulating synaptic transport of vesicles and/or plasticity. It has been suggested that pathogenic mutations may inhibit these functions. In vitro data suggest that the mutant protein is prone to fibrillogenesis, which may be the key feature leading to Lewy body formation.

The A53T mutation is almost fully penetrant (i.e., PD is seen in almost all of those who carry it). Most affected individuals develop PD by age 45 or younger. However, there is variability in age of onset as well as in other features, suggesting modifying genes or environmental factors. For example, one mutation-bearing individual had no symptoms at age >90 years. Another has only action tremor with no parkinsonism, and a third has clinical and pathologically confirmed dementia with Lewy bodies. The A53T mutation has subsequently been identified in affected individuals in several other families of Mediterranean origin, suggesting a founder effect. In some of these, the phenotype is broader than originally described, and includes myoclonus, severe central hypoventilation, and orthostatic hypotension. A second mutation in SNCA, A30P, is believed to be the cause of PD in a family of German origin. Moreover, genetic variability in the α-synuclein haplotype has been shown to be a risk factor for apparently sporadic PD, underscoring the biological importance of SNCA in this complex disorder.

An *α-synuclein* triplication has been reported in a large North American family (the Iowa kindred, also known as the Spellman–Muenter and Waters–Miller kindreds). This family was originally linked to another region on chromosome 4 termed PARK4. The clinical and pathological features range from PD to DLB. The age of onset in this family is usually in the fourth decade, ranging from the third to the sixth decade. These data and other data suggest that genetic variability in the *SNCA* promoter contributes to PD risk. They also support the growing body of literature suggesting that the difference in mutant α-synuclein from wild-type is quantitative rather than qualitative. Finally, the data suggest the disease process in this family is conceptually similar to the occurrence of Alzheimer's disease in Down syndrome, where overexpression of a gene (APP), is the key event.

Transgenic *α-synuclein* models have been created. Mice lacking this gene have functional deficits in the nigrostriatal system. Some groups report α-synuclein pathology in *α-synuclein* transgenic mice, while others see no changes. Transgenic *Drosophila melanogaster* cannot climb properly, and have intracellular inclusions resembling Lewy bodies in some dopaminergic neurons. Because of its relationship to idiopathic PD pathogenesis via Lewy bodies, it is hoped that these and other genetic models will reveal pathogenic mechanisms that provide therapeutic trial substrates for PD.

PARK2/Parkin

Autosomal recessive (AR) juvenile parkinsonism (ARJP) was linked to 6q25–27 in 1997. Compound mutations and homozygous deletions of the parkin gene were subsequently reported. Since then, parkin mutations have been found to be responsible for a wide phenotypic range, including clinical features identical to idiopathic PD. Those with ARJP typically develop parkinsonism before age 40; dystonia, especially foot dystonia, may be prominent. Additional features include insidious progression, sustained levodopa response, early and severe levodopa-induced motor complications, diurnal symptom fluctuations, sleep benefit, and hyperreflexia. Pathological studies have demonstrated highly selective degeneration of dopaminergic neurons in the SNpc and the locus coeruleus, classically without Lewy bodies or tau positive staining tangles (see below).

Parkin is a component of a multiprotein E3 ubiquitin ligase complex involved in the targeting of substrate proteins for degradation by a proteosomal mechanism. The phenotype associated with parkin mutations appears to be due to partial, if not complete, loss of function of the parkin protein. Most affected individuals described to date have either a homozygous deletion or compound point mutation and deletion, although in several small kindreds, only heterozygous mutations (affecting one allele of the gene) have been found. A case report showed parkin mutations to be associated with typical Lewy body PD, implying a connection between parkin and synuclein. This, along with a report suggesting that α-synuclein is a substrate for parkin, is further evidence that the ubiquitin pathway is part of the pathogenic pathway for idiopathic disease. In addition, parkin mutations have been found to be associated with tau pathology (the causal gene in

frontotemporal dementia with parkinsonism linked to chromosome 17), suggesting that parkin may be involved in multiple pathogenic routes to parkinsonism.

PARK3/Chromosome 2P

A susceptibility locus for apparent AD PD on chromosome 2p13 occurs in some families of northern European descent. The identity of this gene is not yet known. Penetrance is 40% or lower. The age of onset is in the fifth decade or later, like sporadic PD, and displays typical PD progression. Postural tremor and dementia are detected in some individuals, either in isolation, or with the PD phenotype. Postmortem data revealed pathological findings similar to those of sporadic PD in an affected individual. Finally, a genome-wide linkage analysis in a population of affected relatives (mainly affected sibling pairs) participating in a large study (GenePD) revealed that the 2p locus may be in linkage disequilibrium with a mutation influencing PD susceptibility or age at onset of PD.

PARK4/Chromosme 4P (See PARK 1)

PARK5/Ubiquitin Carboxyl-Terminal Hydrolase L1

A putative mutation in exon 4 of the ubiquitin carboxy-terminal hydrolase (UCHL1) gene was noted in an affected sib-pair with probable PD and apparent AD inheritance. Further implicating UCHL1 dysfunction in PD, case–control association studies suggest that a common variant in the UCHL1 gene, S18Y, might be protective. UCHL1 is found throughout the brain, and immunoreactivity for this protein is seen in Lewy bodies. Furthermore, like parkin (see above), it is involved in the ubiquitin-dependent pathway of proteolysis. Since the pathogenesis of PD may be related to abnormal aggregation of α-synuclein protein, which is degraded via this pathway, this fits with of PD pathogenesis involving synuclein.

PARK6/PINK1

A consanguineous family from a genetically isolated community in the southwestern region of the Netherlands has four individuals with a form of early-onset PD (PARK6). The onset of symptoms is < 40 years, and, in addition to features of PD, some subjects showed psychiatric symptoms, including psychotic episodes but no other atypical features. The causal gene is a mutation in PTEN-induced putative kinase 1 (*PINK1*). *PINK1* encodes a protein associated with mitochondrial membranes and cytoplasm and contains a putative serine-threonine kinase domain. The PINK1 protein is thought to protect against cellular, particularly oxidative, stress.

PARK7/DJ-1

A unique single kindred with early-onset parkinsonism from a genetically isolated community in the Netherlands showed evidence of linkage to chromosome 1p36. Because the disease haplotype was separated by at least 25 cM from the PARK6 locus, it was designated as a discreet locus (PARK7), and mutations in DJ-1 were subsequently found to segregate with disease. Like PINK1, PARK7 (DJ-1) localizes to mitochondria, cytoplasm, and nucleus. Also like PINK1, it is a putative neuroprotectant against oxidative stress. No DJ-1 mutations were found in a screen of 118 familial and 7 sporadic PD subjects from Europe, South America, Lebanon, Asia, Turkey, and North Africa (age at onset 12–78 years), suggesting that it is not a common cause of familial PD.

PARK8/LRRK2/Dardarin

A large family from Western Nebraska, in which 18 members spanning six generations had slowly progressive apparent AD with PD, showed linkage to chromosome 12.2q, designated PARK8. Pathological examination revealed Lewy body pathology in some but not all, and in some, tau pathology occurred alone or in combination with Lewy body pathology. Linkage to the PARK8 locus was also reported in a Japanese family. In 2004 mutations in the Leucine-Rich Repeat Kinase 2 (LRRK2) gene were reported in both the Japanese and US PARK8 families. In parallel, families of English and Basque ancestry were also discovered to harbor mutations in the LRRK2 gene, and named the relevant protein dardarin, derived from the Basque *dardara*, meaning tremor. LRRK2 mutations have variable penetrance.

The G2019S mutation is the single most prevalent pathological mutation identified in LRRK2 and is the most prevalent known genetic cause of PD, accounting for ∼3–6% of familial and 1–2% of sporadic cases of PD among Europeans and North Africans. The G2019S mutation has a geographic gradient, being highest in North African and Southern European, less so in Northern European, and very low in Asian populations. However, in Asia, other LRRK2 mutations are more common (e.g., G2385R, R1628P). The prevalence of G2019S in LRRK2 in Ashkenazi Jewish subjects with PD ranges from 12–29.7%.

Haplotype data suggests at least three different founder events; one shared by Europeans and North Africans, one associated with the Jewish diaspora, and a third associated with Asian populations.

LRRK2 belongs to the Roco gene family and has a complex structure including two domains characteristic of this family: a Ras-like GTPase domain called Roc and a C-terminal domain of unknown function called COR. LRRK2 also contains a leucine-rich repeat, a kinase domain, an Andrin repeat, and a WD40 domain. The protein is present in the cytosol and the outer mitochondrial membrane. Northern blot analysis detected a ubiquitously expressed 9-kb mRNA transcript, including in the brain. How mutations in LRRK2 lead to PD is unknown.

PARK9/Kufor–Rakeb Syndrome

This AR form of parkinsonism, Kufor–Rakeb syndrome, does not cause typical PD, and therefore is beyond the scope of this chapter. For a further clinical description see Williams et al., and for a discussion of the gene discovery see Ramirez et al.

PARK10

A genomic screen for linkage to age of onset in Alzheimer's and Parkinson's disease identified evidence for linkage of age of onset of PD to chromosome 1p. A microsatellite marker-based screen of an Icelandic population including 117 subjects with typical late-onset PD and 168 of their unaffected relatives from 51 families demonstrated linkage to chromosome 1p32. Further analysis yielded a lod score of 4.9 near marker D1S2652 within a 7.6-cM segment, subsequently designated PARK10. The specific gene affected in PARK10 is not yet known.

PARK11

Using affected sib pairs, and subsequently, other families with PD with apparent AD transmission, linkage to 2q36–q37 was found and designated PARK11. In a genome-wide association study including 443 sib pairs discordant for PD and 332 case-unrelated control pairs, one of the SNPs studied tagged PARK11. PARK11 is due to mutations in the GIGYF2 gene, with 7 different heterozygous mutations discovered in 12 unrelated French and Italian families with typical PD. The GIGYF2 gene (Grb10-Interacting GYF Protein 2) is also known as TNRC15 (Trinucleotide Repeat-Containing 15). The function of this protein is unknown.

PARK12

Using a cohort of 160 multiplex PD families who had screened negative for parkin mutations, and then enriching that sample via specified additional clinical criteria, a locus on the X chromosome was identified, designated PARK12. Follow-up studies have also found linkage Xq21–25. The associated gene is unknown.

PARK13

PD 13 (PARK13) was discovered in four German subjects with typical PD, and is caused by a G399S mutation in the serine protease HTRA2. Age at disease onset ranges from 49 to 77 years. Heterozygous carriers of the A141S mutant allele also had typical PD findings. Immunohistochemistry and functional analysis in stably transfected cells revealed that G399S mutant HTRA2 and to a lesser extent the A141S risk allele polymorphism induced mitochondrial dysfunction associated with altered mitochondrial morphology. Cells overexpressing G399S mutant HTRA2 were more susceptible to stress-induced death than were wild-type cells.

Other Mendelian Disorders Associated with PD

Spinocerebellar Ataxias

PD has been described in several of the spinocerebellar ataxias (SCAs), particularly in SCA2 and SCA3, both of which are due to different trinucleotide expansions. Expansions in SCA2 are causal for ~10% of familial but otherwise typical PD cases in ethnic Chinese, and are also found in American Indian patients, but are extremely rare as a cause of PD in Caucasians. SCA3 may be more likely to cause typical PD in those of ethnic African origin than in Caucasians. Testing is commercially available. It is notable that the PD phenotype for both SCA2 and 3 may be more common in those with intermediate-range repeat numbers; this narrow range requires precise determination of repeat size, which is not done by all diagnostic laboratories. Therefore, when ruling out SCA2 and SCA3 as a cause of PD, it is important that methods which accurately assess the repeats in this intermediate, borderline range be used.

Gaucher Disease

Gaucher disease is an AR lysosomal storage disorder due to deficient activity of β-glucocerebrosidase. An association has been reported between typical PD and type I Gaucher disease.

Wilson's Disease

This AR disease results in systemic copper deposition, especially in brain and liver. Classic PD or parkinsonism with atypical features may occur. The presence of hepatic, extrapyramidal, or mood disorders in relatives of a patient with PD should lead to evaluation for Wilson's disease, since treatment is highly effective. The causal gene a copper-transporting P-type adenosine triphosphatase (ATPase). Many mutations are responsible for disease, making genetic testing impractical. However, screening with serum ceruloplasmin, 24-h urinary copper, and slit lamp examination are straightforward.

Huntington's Disease

Huntington's disease is an AD movement disorder with full penetrance, whose wide range of phenotypes can include parkinsonism, and rarely, typical PD. It is due to a CAG (polygutamine) repeat expansion in the *huntingtin* gene on chromosome 4p16.3, with abnormal being >40 repeats. Testing is commercially available.

Genome-Wide Association Studies (GWAs) in PD

In contrast to Mendelial (familial) PD, the etiology of apparently sporadic PD remains unknown. An extensive

literature exists both claiming and disputing putative risk genes for sporadic PD including both candidate gene studies and GWAS. However, meta-analyses of most of the polymorphisms genotyped in these studies provide little or no evidence for significant association of any marker with sporadic PD, and illustrate the need for larger-scale, unbiased genomic screens in the disease. GWAS are an approach that has been proposed and used to address this need.

Assessing the association between SNPs and disease phenotypes has become increasingly used towards the goal of discovering alleles predisposing to complex disorders. In contrast to family linkage-based methods and candidate gene approaches, which identify presumed causal genes, GWAS seek to detect genetic variants that only modestly contribute to disease susceptibility. It is currently believed that GWAS in most complex disorders are likely to require at least a thousand or more cases and control samples each to have adequate power. GWAS typically scan between 300 000 and 600 000 SNPs, which serve as surrogate markers for neighboring genetic variation.

The first GWAS in PD (known as the 'LEAPS' study) genotyped ~200 000 SNPs in two US cohorts of mostly European descent. Although a combination of tier 1 and 2 analyses identified 13 SNPs significantly associated with PD, none of these SNPs retained significance following Bonferroni correction. Furthermore, the findings of LEAPS failed replication by a number of other groups, suggesting that the results may have been false positives due to inadequate sample size. Meta-analyses, made possible by the posting of GWAS data to a public access database (dbGaP, see http://www.ncbi.nlm.nih.gov/gap), did not identify any SNPs significantly associated with PD after corrections for multiple testing.

This and other PD GWAS suggest that the effect size of genetic determinants for sporadic PD is relatively small (i.e., odds ratios of less than 2), since effect sizes larger than this would have probably been detected. Furthermore, it is clear from these studies that there is not likely to be any single common genetic variant in PD with an effect on disease risk comparable to APOE-4 in Alzheimer disease. However, additional GWAS in larger cohorts have begun. For example, two family-based GWAS are being combined ('PROGENI' and '*Gene*PD') resulting in a sample size of more than 1000 PD families. Unlike preceding studies, this study will be based on cases with a family history of PD, possibly enriching the sample set for gene discovery. The first study resulting from this collaborative effort is a candidate gene study of the *MAPT* (*tau*) gene, which found that the H1 haplotype of the *MAPT* region, as well as a novel H1 subhaplotype, are significantly associated with PD. Mutations in this gene are known to be causal for AD parkinsonism (Frontotemporal dementia with Parkinsonism linked to chromosome 17, FTDP-17) and *MAPT* alleles have previously been implicated as risk factors for progressive supranuclear palsy (PSP). Intriguingly, in contrast to PSP and FTDP-17, PD is not typically characterized by a neuropathology of abnormally aggregated tau protein; therefore, it will be interesting to see how tau function influences PD biologically.

Future Directions

Genetics has revolutionized neurological research. In concert with neuropathology, neurogenetics helps us understand the biology of the disease. Characterization of the protein products of genes associated with PD, including those yet to be discovered, their interactions, and the biochemical mechanisms affected, will direct future studies of therapeutic targets and gene–environment interactions.

Many known genetic loci causal for PD are incompletely penetrant. Further, the clinical manifestations of PD are not seen until over 70% of nigral neurons are destroyed, causing an ascertainment bias against detection of disease. It follows that twin studies may not show the level of concordance one would expect for a disease with a significant genetic component. This concept has therapeutic implications, since interventional strategies would ideally be used before that symptomatic threshold is reached. In the future, genetic factors may play an important role in early, even presymptomatic detection of PD. Additionally, disease due to Mendelian causal genes have phenotypic variations within and across kindreds. This suggests that genetic factors in *cis*, *trans*, and environmental factors influence phenotype (including age of onset, rate of progression, and manifestations of symptoms). Epigenetics, copy number variation, and environmental studies are important future directions in the study of PD genotype/phenotype.

Clues to the biological process underlying PD were revealed with identification of α-synuclein mutations. The subsequent identification of this protein in Lewy bodies suggests that PD due to α-synuclein mutations may share pathogenic mechanisms with idiopathic PD. Other gene discoveries suggest that the process leading to PD may include a synuclein–ubiquitin pathway to cell death, and oxidative stress pathways.

GWAS are increasingly being used for the discovery of common genetic risk factors of small influence in apparently sporadic, complex diseases. While initial studies are exciting, the true utility of this approach generally awaits to be borne out. Alternatively, other strategies based on new technology, or optimization of existing technology (e.g., resequencing) may evolve and replace GWAS as the high throughput method of choice.

PD in general is likely to depend on molecular features for accurate diagnosis in the future, because clinical features alone are not likely to accomplish biologically meaningful categorization needed for truly interventional treatments.

We must identify additional genetic factors, learn how the biological products interact, and also identify modifying environmental factors. A systematic approach will be the key to our developing preventative strategies for PD and related neurodegenerative syndromes. While current therapies are palliative, the aim of studying the genetics of neurodegenerative disease is to supplant palliative therapies with therapies aimed at pathogenesis, which are germane to impacting the course of the disease.

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See also: Parkinsonism: Genetics.

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http://www.ncbi.nlm.nih.gov/gap – The Database of Genotype and Phenotype (DbGaP).

Paroxysmal Exertion-induced Dyskinesia

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Glossary

Dyskinesia – Excessive abnormal involuntary movements including chorea and dystonia.

Definition and History

The definition, classification, and names of the paroxysmal dyskinesias have changed over the years. This has been primarily due to the evolution of genetics and molecular

biology, which has allowed for the clarification of phenotypes and the identification of the underlying genes.

In the past, the paroxysmal dyskinesias have been categorized into four groups based upon triggers or precipitating factors. Paroxysmal kinesigenic dyskinesia (PKD) is induced by sudden movements, startle, or changes in velocity. Paroxysmal nonkinesigenic dyskinesia (PKND) is not triggered by movement or exercise, but can be triggered by alcohol and caffeine. Paroxysmal hypnogenic dyskinesia (PHD) arises out of sleep, and is now referred to as autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE). Paroxysmal exertion induced dyskinesia (PED) is precipitated by 5–15 min of physical exertion. Although the term 'paroxysmal exercise induced dyskinesia' is most commonly used in the literature, the term 'paroxysmal exertion induced dyskinesia' is also used to describe the same condition.

Pathogenesis and Pathophysiology

While PED is characterized by dyskinesias triggered by prolonged exercise, PED can be associated with a broader phenotype of epilepsy, developmental delay, migraine, and hemolytic anemia with echinocytosis. In the majority of cases (although not all), this complex phenotype is associated with mutations in the *SLC2A1* gene, which encodes for the glucose transporter GLUT1. Many different mutations within the *SLC2A1* gene have been associated with the complex PED phenotype.

Functional studies in oocytes of the GLUT1 protein, the main transporter for D-glucose across the blood–brain barrier, have demonstrated marked reduction of glucose uptake. The mutations affected the intrinsic ability of GLUT1 to transport glucose across the cell membrane by reducing the maximum transport velocity. It is hypothesized that PED can be caused when the energy demand of the brain overcomes its supply after prolonged periods of exercise. The basal ganglia, an important area in the generation of dyskinesias, are particularly sensitive to hypoxia and energy deficits.

Epidemiology/Risk Factors

This condition is rare. There have been nine autosomal dominant PED families described, and penetrance is incomplete in this familial condition. Approximately 20 sporadic cases have been reported in the literature. Secondary causes of PED have been described and include, a case of posttraumatic PED involving a lower limb, a case of PED associated with hypoglycemia induced by an insulinoma, and moyamoya disease presenting with PED.

Clinical Features and Diagnostic Criteria

Onset is typically in child hood or adolescents (9–15 years) in the familial forms, and older onset has been reported in sporadic cases. Attacks are precipitated by prolonged walking (5–15 min), or other strenuous exercise such as lifting or chewing. The attacks range in duration from 5 to 30 min, and typically involve the region of the body active during the prolonged exercise, for example the hand after handwriting or the jaw after chewing. Most commonly, however, the attack is seen in the legs, and the attacks are typically dystonic and symmetric but asymmetrical unilateral attacks involving an arm and leg are described. The symptoms dissipate after rest, and patients may describe a prodrome of sensory symptoms in the limb prior to attack.

Differential Diagnosis

Any cause of dyskinesia should be considered as part of the differential diagnosis. Sporadic causes of paroxysmal dyskinesias include lesions of the basal ganglia caused by multiple sclerosis, tumors, and vascular lesions. Paroxysmal dyskinesias can be seen in association with rheumatic fever (Sydenham's chorea), systemic lupus erythematosus, diabetes mellitus, hypoparathyriodism, pseudohypoparathyroidism, and thyrotoxicosis. Chorea gravidarum can present with paroxysms of chorea in the first trimester of pregnancy, and usually resolves after delivery. Focal seizures can present with paroxysms of dystonia.

There are a number of hereditary conditions that can present with paroxysmal dyskinesias these include:

1. Paroxysmal nonkinesigenic dykinesia: characterized by unilateral or bilateral dyskinesias lasting minutes to hours in duration which can occur spontaneously or can be precipitated by alcohol, coffee or tea, excitement, stress, fatigue, or chocolate. Attacks do not commonly occur more than once per day, and age of onset is usually in childhood or early teens.
2. Familial PKD: characterized by unilateral or bilateral involuntary dyskinesias precipitated by sudden movements such as standing up from a sitting position, being startled, or changes in velocity. Attacks can be as frequent as 100 per day to as few as one per month. Attacks are usually a few seconds to 5 min in duration but can last several hours, and age of onset is typically in childhood and adolescence.
3. PHD: this condition now goes by the name 'autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE).' Attacks associated with PHD/ADNFLE range markedly, but include dystonia, chorea, and ballism. The episodes generally occur during Non Rapid Eye Movement (NREM) sleep. Individuals are able to recall the episodes in the morning. Precipitating factors include increased activity, stress, and menses.

There are a number of other hereditary conditions, which although associated with dykinesias are not typically

paroxysmal in their presentation, these include, Huntington's disease, Wilson's disease, and benign hereditary chorea.

Diagnostic Work Up/Tests

MRI of the brain is required to rule out lesions of the basal ganglia. Fasting serum glucose, TSH, anti-streptolysin O (ASO) titer, ANA, total and ionized serum calcium, magnesium, and phosphate are required to rule out metabolic and reversible causes. Interictal and ictal EEG can be useful in identifying seizures. Serum copper, ceruloplasmin, 24 h urine copper test should be performed for the investigation of Wilson's disease. Although mutations in the *SLC2A1* gene are responsible for the majority of cases of PED, testing is not readily available, and a diagnosis is based on the clinical history and exclusion of other causes.

Management

Typically, individuals with this condition avoid prolonged activity, which triggers the attacks. In three patients who have a demonstrated mutation in the *SLC2A1* gene, a ketogenic diet was effective in reducing their symptoms. One individual who had severe PED (4–5 episodes per day unable to walk >50–100 min without pausing or dystonia) had complete resolution of the PED, and was able to run long distances once ketosis was achieved. The other two patients with mutation suffered from seizures, and were seizure free on the ketogenic diet.

Although the *SLC2A1* mutation affects the ability of the GLUT1 to transport glucose across the cell membrane, an increase in a carbohydrate rich diet and frequent carbohydrate snacks failed to improve symptoms in patients with a *SLC2A1* mutation.

There have been sporadic reports in the literature on the benefits of anticonvulsants, although this does not appear to be a consistent finding. There is a report of improvement of PED with gabapentin. There has been no reported benefit of PED symptoms with levodopa. There is a single report of a patient improving with trihexyphenydil. Most patients tried on acetazolamide had no improvement, but there was a report of one patient improving on this medication.

Prognosis

Although PED can be debilitating in its extreme form, it generally can be prevented by avoiding prolonged activity. In some cases, the PED improves as the individual gets older.

See also: DYT8, Paroxysmal Non-kinesiogenic Dyskinesia-PNKD; DYT10, Paroxysmal Kinesiogenic Dyskinesia-PKD.

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Paroxysmal Movement Disorders

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Glossary

Allelic disease – Sometimes, more than one clinical syndrome arises from abnormalities of one gene. These multiple diseases are described as "allelic disease."

Ataxia – An inability to coordinate voluntary muscular movements.

Autosomal dominant – A pattern of inheritance, in which having only one copy of a particular gene mutation (heterozygotes), results in a phenotype. Sex chromosomes are excluded. Individuals with

autosomal dominant diseases have a 50–50 chance of passing the mutant gene and, therefore, the disorder onto each of their children.
Channelopathy – A group of disorders resulting from abnormalities in the flow of certain electrically charged particles (ions, such as calcium, potassium, sodium) across cell membranes.
Dyskinesia – A general term to describe any kind of hyperkinetic involuntary muscle movement. Dyskinesias may resemble other movement disorders, and be dystonic, choreic, ballistic, or occur in combination.
Episodic – Occurring or appearing at irregular intervals.
Idiopathic – Arising spontaneously or from an unknown cause.
Kinesigenic – Triggered by sudden body movements.
Kindred – A genealogical group.
Paroxysmal – Symptoms that occur only in episodes or "attacks," out of blue, suddenly and unpredictably, followed by a relatively rapid return to normal motor function and behavior.
Psychogenic – A term used to describe physical symptoms that are thought to originate in the mind, or from emotional conflict.
Secondary – Disease or state resulting as a consequence of another disease.
Sporadic – When a genetic disease occurs without any family history, it is described as "sporadic."

Definition and History

The majority of movement disorders are either continuous or progressive. In contrast, in paroxysmal movement disorders, sudden short-lived attacks of hyperkinetic involuntary movement attack arise against a background of relatively continuous normal motor behavior/neurological examination. Consciousness is preserved during these attacks. Paroxysmal movement disorders are a heterogeneous group of disorders but can be broadly divided into paroxysmal dyskinesias and episodic ataxias (**Table 1**).

Some movement disorders do have variability and fluctuation. For example, restless leg syndrome and dopa-responsive dystonia fluctuate depending on the time of the day. Task-specific dystonia and action myoclonus can be triggered by certain postures or tasks. Myoclonus and tics can occur intermittently. However, these phenomena/disorders are traditionally not included in the rubric of paroxysmal movement disorders (**Table 2**).

Table 1 Classification of paroxysmal movement disorders

Classification	*Alternative name*
1. *Paroxysmal Dyskinesias*	
Paroxysmal Kinesigenic Dyskinesia/ Choreoathetosis (PKD)	Episodic Kinesigenic dyskinesia 1 Paroxysmal kinesigenic choreoathetosis (PKC) Dystonia 10 (DYT10)
Paroxysmal non-Kinesigenic dyskinesia (PNKD)	Paroxysmal Dystonic Choreoathetosis (PDC) Familial Paroxysmal Choreoathetosis 1 (FPD1) Mount–Reback Syndrome Paroxysmal Dystonic Choreoathetosis of Mount and Reback Dystonia 8 (DYT8)
Paroxysmal Exertion-induced dyskinesia (PED)	Paroxysmal Exercise-induced Dystonia Intermediate form of paroxysmal dystonic choreoathetosis
Paroxysmal hypnogenic dyskinesia (PHD)	Paroxysmal nocturnal dystonia Nocturnal frontal lobe epilepsy Autosomal dominant nocturnal frontal epilepsy (ADNFLE)
2. *Episodic ataxias*	
Episodic Ataxia 1 (EA1)	Episodic Ataxia with myokymia Paroxysmal ataxia with neuromyotonia
Episodic Ataxia 2 (EA2)	Episodic ataxia with nystagmus Acetazolamide-responsive hereditary paroxysmal cerebellar ataxia (APCA)
Episodic Ataxia 3 (EA3)	Episodic ataxia with vertigo and tinnitus
Episodic Ataxia 4 (EA4)	Periodic vestibulo-cerebellar ataxia (PATX)
Episodic Ataxia 5 (EA5)	
Episodic Ataxia 6 (EA6)	
Episodic Ataxia 7 (EA7)	
3. *Miscellaneous*	
Paroxysmal torticollis of infancy	
Paroxysmal tonic upgaze of childhood	
Sandifer's disease (also in **Table 2**)	

Paroxysmal Dyskinesia

Paroxysmal dyskinesias are a heterogeneous group of disorders characterized by intermittent attacks of hyperkinetic involuntary movements. The abnormal involuntary movement can be choreic, ballistic, dystonic, or a combination thereof. Hence, the more general term "dyskinesia" is preferred. The most widely used classification divides paroxysmal dyskinesia into four categories based on triggers and characteristics of the attacks; paroxysmal kinesigenic dyskinesia (PKD), paroxysmal non-kinesigenic dyskinesia (PNKD), paroxysmal exertion-induced dyskinesia (PED), and paroxysmal hypnogenic dyskinesia (PHD). However,

Table 2 Conditions that can manifest to intermittent involuntary movements, but not considered to be ''paroxysmal movement disorders''

Action dystonia
Action myoclonus
Action/intention tremor
Cataplexy
Complicated migraine
Dopa-responsive dystonia
Drug-induced dyskinesias
Epilepsy
Hyperekplexia
Myotonia
Periodic movements in sleep
Periodic paralysis
Restless legs syndrome
Sandifer's disease
Streotypies
Task-specific Dystonia
Tetany
Tics
Transient ischemic attack (limb-shaking TIA)

this classification may need to be refined when genetic discovery is made. PKD and PNKD constitute the majority of cases. Pure PED is rare, and possibly a subset of PNKD. PHD is now thought to be a form of frontal epilepsy. Paroxysmal dyskinesia can be either idiopathic or secondary. Idiopathic cases can be familial or sporadic, and some of the sporadic cases can be psychogenic.

History

Gowers is credited for reporting the first case of paroxysmal dyskinesia in 1885; he reported two patients who had "movement-induced" seizures. However, both patients had atypical features, so it is unclear whether these cases represented true movement disorders. Subsequent to Gowers, in early to mid-1900s, various case reports described extrapyramidal epilepsy, striatal epilepsy, subcortical epilepsy, reflex tonic epilepsy, and movement-induced seizures, where patients had attacks of tonic contraction, sustained twisting, athetosis and chorea, without impairment in consciousness. As the name implies, these earlier reports considered the attacks to be related to epilepsy.

In 1940, Mount and Reback wrote a seminal paper reporting a family with involuntary movement attacks (chorea and athetosis), lasting from 10 min to a few hours. The condition was inherited in an autosomal fashion, with onset in infancy or early childhood. The attacks were precipitated by caffeine, alcohol, stress, and exertion. Mount and Reback called this condition "familial paroxysmal choreoathetosis", implying extrapyramidal origin.

In 1967, Keresetz first used the word "kinesigenic" (caused by movement) to describe 10 cases of paroxysmal kinesigenic choreoathetosis (current PKD). The term "kinesigenic" became a very useful label, as kinesigenic trigger is so characteristic in this condition.

In 1977, Lance wrote an important review paper. He tried to unify various intermittent involuntary movement attacks under the term "paroxysmal dystonic choreoathetosis." He classified this condition into three categories:

1. prolonged attacks,
2. intermediate form,
3. brief attacks.

Following this tradition, in 1995, Demirkiran and Jankovic reclassified paroxysmal dyskinesias into PKD, PNKD, PED and PHD. They proposed to use the term "dyskinesia" because the involuntary movements during an attack is often not witnessed by a physician to determine the exact movement type, and even in the witnessed case, tend not to fit into the strict definition of chorea, athetosis, dystonia or ballism. Demirkiran and Jankovic's nomenclature is currently the most widely used.

In 1991, the first channelopathy was discovered; hyperkalemic periodic paralysis was found to be caused by an abnormality in the sodium channel gene. Channelopathy became an attractive mechanism to explain various episodic neurological diseases, including epilepsy, migraine and paroxysmal movement disorder. With the advancement of linkage analysis technique, various researchers have been attempting to identify the genetic abnormalities of paroxysmal dyskinesia. This will be further discussed in the pathophysiology section.

Episodic Ataxia

Episodic ataxias are characterized by recurrent spells of incoordination and imbalance. The episodic ataxia can also be primary (idiopathic) or secondary. Currently, at least seven episodic ataxia syndromes have been described in Online Mendelian Inheritance of Man (OMIM) based on the genetic characteristics, but the majority of cases are either EA-1 or EA-2.

History

Parker described 6 patients in 4 families with idiopathic familial ataxia in 1946. The attack consisted of gait ataxia and dysarthria, and ranged from 30 s to 30 min. Subsequently, multiple families have been reported, with varying manifestations of episodic ataxia. Unlike PKD, subtle abnormality in the baseline neurological examination was noted; in one group, myokymia and in another, nystagmus. In 1986, Gancher and Nutt classified the hereditary episodic ataxias into three groups;

1. episodic ataxia associated with persistent myokymia and neuromyotonia;
2. episodic ataxia associated with interictal nystagmus (and clinically very responsive to acetazolamide);
3. episodic kinesigenic ataxia.

The discovery that abnormality in potassium channel gene accounted for EA1 (1994), and calcium channel gene for EA2 (1995), altered the classification scheme, and now classification is based on genetics. Episodic ataxia with myokymia and episodic kinesigenic ataxia are now both classified under EA1, and episodic ataxia with interictal nystagmus is now classified as EA2.

Miscellaneous

There are few pediatric conditions, which are sometimes classified under paroxysmal dyskinesias: Paroxysmal torticollis of infancy, paroxysmal tonic upgaze of childhood and Sandifer's syndrome. Sandifer's syndrome is characterized by head tilt after a large meal, caused by large hiatal hernia. Historically, Sandifer's syndrome has been listed both under paroxysmal movement disorders and under conditions that should not be included in paroxysmal movement disorders (**Table 2**). All of these conditions are self-limiting, and disappear after childhood; they will not be further discussed in the text.

Pathogenesis and Pathophysiology

Paroxysmal Dyskinesia

The pathogenesis of paroxysmal dyskinesia remains a controversy as to whether it is epileptic or extrapyramidal phenomena. These two views may not be mutually exclusive, however. From the time of Gowers, paroxysmal dyskinesia has been suspected to be "epilepsy of the basal ganglia".

Physiological studies and functional neuroimaging

Electroencephalogram readings are normal in the majority of cases (except for PHD, which is now thought to be a frontal epilepsy), even when recorded during attacks. There are some reports of abnormal EEG, but the abnormalities are generally nonspecific. One study attempted invasive EEG monitoring in a patient with PKD and demonstrated discharge from the caudate nucleus and supplementary motor cortex; the authors speculated abnormality in the basal ganglia circuit could be responsible for PKD.

Ideally, functional neuroimaging study would aid in elucidating the pathophysiology; the reported results generally suggest abnormality in the basal ganglia region (**Table 3**). However, only 1 or 2 patients are studied in each study and some studies report hypoperfusion, whereas other studies report increased perfusion, thus results are inconclusive and do not give a uniform explanation of pathophysiology.

Other neurophysiological studies reported include measurement of Bereitschaftspotential, continent negative variation, startle reflex and trans-magnetic stimulation studies, but the results are not replicated and are difficult to interpret or generalize.

Molecular genetics (Table 4)

The molecular genetics of paroxysmal movement disorder is a rapidly growing field, leading to advances but simultaneously some confusion of the classification and nomenclature. As in other area of movement disorders, the question is; should classification be done based on molecular genetics, or based on clinical phenomenology? At the chemical basis of pathogenesis, channelopathy is

Table 3 Summary of PET and SPECT studies in patients with paroxysmal dyskinesia

	Interictal SPECT and PET	*Ictal SPECT*
PKD	Hypoperfusion in the posterior caudate (16) Normal FDG PET (2)	Increased perfusion in posterolateral thalamus (1) Hypoperfusion in supplementary motor cortex. Sensorimotor cortex and pallidum was hyperperfused in one, but hypoperfused in the other (2) Increased perfusion of the contralateral basal ganglia (1) Hypoperfusion of contralateral basal ganglia (1) Hypoperfusion of contralateral caudate nucleus (1)
PNKD	Normal C-raclopride PET (1) Nomral FDG PET, but decreased presynaptic dopa decarboxylase activity in the striatum and increased density of postsynaptic dopamine D2 receptor based on 18FDOPA PET and C-raclopride PET (1)	
PED		Decreased perfusion in the frontal cortex and basal ganglia, and increased perfusion in the cerebellum, resembling pattern of dystonia (2)
Secondary	low metabolism of basal ganglia (1 patient with post-trauma)	increased activity in bilateral caudate (1 patient with subacute sclerosing panencephalitis) hyperperfusion in contralateral frontal cortex and hypoperfusion in contralateral basal ganglia (1 patient with hyperglycemia)

Numbers in parentheses indicate number of patients studied in each report.

Table 4 Summary of genetic abnormality in paroxysmal movement disorders

	OMIM	*Mode of inheritance*	*Chromosome locus*	*Mutated gene*	*Mutant protein*
PKD/ICCA syndrome	128200/602066	AD	16p11.2-q12.1 (EKD1)	Unknown	Unknown
PKD2	611031	AD	Possible second locus on 16q13-q22.1	Unknown	Unknown
PNKD	118800	AD	2q35	MR-1	Has not been determined yet
PNKD2	611147	AD	Possible second locus 2q31	Unknown	Unknown
ADNFLE 1 (PHD)	600513	AD	20q13.2–13.3	CHRNA4	Nicotinic acetylcholine receptor α-4 subunit
ADNFLE 2	603204	AD	15q24	Unknown	Unknown
ADNFLE 3	605375	AD	1q21	CHRNB2	Nicotinic acetylcholine receptor β-2 subunit
ADNFLE 4	610353	AD	8p21	CHRNA2	Nicotinic acetylcholine receptor α-2 subunit
Other individual families reported					
Episodic choreoathetosis/spasticity syndrome (CSE)	601042	AD	1p	Unknown	Unknown
PED + RE + WC	608105	AR	16p12–11.2	Unknown	Unknown
PED + epilepsy + hemolytic anemia	612126	AD	1p35-p31.3	SLC2A1	Glucose transporter
Episodic ataxias					
EA1	160120	AD	12q13	KCNA1	K(v)1.1 Voltage-gated potassium channel subunit
EA2	108500	AD	19p13	CACNA1A	Ca(v) 2.1 Voltage-gated calcium channel subunit
EA3	606554	AD	1q42	Unknown	Unknown
EA4	606552	AD	Unknown	Unknown	Unknown
EA5	601949	AD	2q22-q23	CACNB4	Ca(v)2.1 Voltage-gated calcium channel subunit
EA6	600111	Sporadic	5p	SLC1A3	EAAT1 glucose transporter
EA7	611907	AD	19q13	Unknown	Unknown

See text for abbreviation

suspected to be responsible for the pathophysiology of paroxysmal dyskinesias.

In PKD families, linkage analysis mapped abnormality to chromosome 16p11.2–q12.1. This overlaps with a locus of another syndrome; infantile convulsion and choreoathetosis (ICCA) syndrome. In ICCA syndrome, epilepsy researchers were studying a familial benign infantile seizure syndrome, where seizure remitted after infancy. While taking their history, it was noted that some of the patients, as well as nonaffected family members experienced involuntary movement attacks, which resembled PKD attacks. During the investigation of PKD families, some of the patients, as well as nonaffected family members reported history of self-limited seizures during their infancy. Therefore, PKD and ICCA are now thought to be either the same disease or an allelic disease. The responsible gene has not been identified yet.

The gene responsible for paroxysmal non-kinesigenic dyskinesia (OMIM 118800) was identified on chromosome 2q35, myofibrillogenesis regulator 1 (*MR-1*) gene.

MR-1 itself is not a channel protein and the exact function of *MR-1* is unknown, but it is thought to be related to stress pathways.

Paroxysmal hypnogenic dyskinesia is now thought to be autosomal dominant nocturnal frontal epilepsy (ADNFLE), and at least 3 different genes, with possibility of additional loci are identified. All of the discovered gene abnormalities affect subunits of neuronal nicotinic acetylcholine receptors. In vitro and in vivo studies have shown that neuronal nicotinic acetylcholine receptors are abundantly expressed in the thalamus, and the mutation may cause gain of function; thus over-activating the ascending cholinergic pathway, and in turn enhancing the GABAergic function.

Other single families, with paroxysmal dyskinesia in their constellation of clinical syndrome, have been reported, with associated genetic abnormality (see **Table 4**).

Episodic Ataxia

Molecular genetics (Table 4)

Genetics of episodic ataxias are better elucidated, and shown to indeed be channelopathies. Episodic ataxia type 1 (OMIM 160120) is caused by mutation in the voltage-gated potassium channel (KCNA1) located on chromosome 12p13. In in vitro expression studies, all reported mutations impair voltage-gated potassium channel function, resulting in increased neuronal excitability.

Episodic ataxia type 2 (OMIM 108500) is caused by mutation in the subunit of P/Q type voltage gated calcium channel (CACNL1A4), located on chromosome 19p13. Over 50 mutations have been reported, with the majority of the mutations causing premature stop of the protein. Abnormality in the same CACNL1A gene can also cause familial hemiplegic migraine (FHM) and spinocerebellar 6 (CAG repeat expansion of the gene). These three disorders are allelic diseases, and there is considerable clinical overlap. P/Q type voltage gated channel is abundantly expressed in the Purkinje cells and neuromuscular junction. In EA2, intracellular pH of Purkinje cell is reported to be low. However, exactly how the abnormality in voltage gated calcium channel causes this three condition is still largely unknown. Mouse model with CACNA1A mutation has been developed and it is a subject of intense interest and research.

Other single or rare families are classified as EA3 to EA7 based on their genetic abnormality.

Epidemiology/Risk Factors

The exact incidence/prevalence of paroxysmal dyskinesias and episodic ataxias, is unknown. It is generally thought to be a rare disorder. The Consortium for Clinical Investigation of Neurological Channelopathies has estimated the prevalence of EA 2 to be lower than 1:100,000 population, based on the cases seen by experts in regional centers. However, paroxysmal movement disorders may be underreported in the medical community. If the symptoms are mild, or if patients speculate their diagnosis based on other family history, they may not seek medical attention.

Clinical Features and Diagnostic Criteria

PKD

Attacks of PKD are very brief; a few seconds to a few minutes, usually less than 1 min. The attacks are triggered by sudden movements after a period of rest, such as standing up from a seated position, initiating a stride, or starting a stroke in the pool. There may be a refractory period immediately after an attack. Some patients have multiple attacks a day, up to 100 a day. Many patients report "aura" or premonitory sensation before an attack. The attack can be unilateral, or bilateral, involving face, arm, leg, or combination of them. There is no pain. Onset is usually in early childhood, between 5 and 15 years old. Familial cases are transmitted in autosomal dominant fashion, but some patients with very classic PKD, indistinguishable from those with familial PKD, do not have a family history, and this raises the possibility of de novo mutations, or low penetrance. Some patients and/or non-affected family member may have "benign infantile convulsion."

Based on analysis of over 100 patients, a new diagnostic criterion for idiopathic PKD was proposed in 2004.

1. Identified kinesigenic trigger for the attacks
2. Short duration of attacks (<1 min)
3. No loss of consciousness or pain during attacks
4. Exclusion of other organic disease and normal neurological examination
5. Control of attacks with phenytoin of carbamazepine, if tried
6. Age at onset between 1 and 20 years, if no family history of PKD (this means that PKD diagnosis was unlikely if onset was >20 years old, unless family history exists).

PNKD

Attacks of PNKD are longer compared to PKD, and last a few minutes to a couple of hours. However, the duration of the attack alone does not separate PNKD from PKD, as shorter PNKD attacks are reported. As the name implies, PNKD attacks are not triggered by sudden movements. The precipitating factors include most commonly caffeine and alcohol, but also stress, fatigue, exercise and emotional overexcitement. Aura is reported in about half of the patients. The involuntary movements can be choreic, athetotic, dystonic, ballistic, in any limbs, and speech is

frequently affected. Some patients with PNKD report sleep-benefit; attacks would abort when falling asleep. Familial PNKD is inherited in an autosomal dominant fashion. The responsible gene was identified on chromosome 2 *MR-1* gene (see molecular genetics section above). However, not all familial PNKD kindreds harbor this mutation. In a phenotype–genotype analysis of families with *MR-1* mutation, the clinical presentation were homogeneous; some of the salient features include (1) onset of attacks in infancy and early childhood and (2) good clinical response to benzodiazepines.

Older ages of onset are reported in other atypical families, without the *MR-1* gene abnormality. Unlike PKD, a pure form of sporadic PNKD is rare and most cases of sporadic PNKD are eventually felt to be psychogenic. To date, there has been no report of positive *MR-1* gene mutation in a sporadic case of PNKD (personal communication), although *MR-1* gene testing is currently not available commercially.

PED

As opposed to PKD, attacks of PED are triggered by prolonged exercise, not by sudden movements. In some cases, exercise of one particular limb can cause attack on the same limb. Attack duration is usually between 5 and 30 min, and an attack gradually subsides when the exercise is stopped. Legs are more affected than arms, but this may be because legs are more exerted during prolonged exercise. There are familial cases, as well as sporadic cases. Some PNKD patients have their attacks triggered by exercise, and some family members of PNKD kindred report exertion cramps; thus some PED may be a subtype of PNKD.

PHD/ADNFLE

The attacks of PHD happens during sleep, and majority of PHD, especially cases with short-lasting attacks (a few seconds to a few minutes) are now thought to be frontal seizures. The attacks can vary from simple arousal to dramatic hyperkinetic involuntary movements with tonic, dystonic, or choreoathetotic features. The attack may sometimes appear bizarre or stereotypical, with ballism, pedaling movements, or pelvic thrusting. Patients may experience aura. Patients are usually awakened by an attack, and conscious to remember it, but fall back to sleep after the attack. The frequency may vary from a few times a night to a few times a year. Sleep studies show that attacks cluster in non-REM sleep, or during stage II sleep. Urinary incontinence, as well as secondary generalization may occur, in which case the seizure diagnosis is more obvious. A minority of patients may also have daytime seizures. Onsets of these attacks are usually from infancy to young adulthood.

Secondary Paroxysmal Dyskinesia

Various neurological, as well as metabolic diseases are reported to cause paroxysmal dyskinesias. The most commonly reported etiology is multiple sclerosis, which can cause both PKD and PNKD. The involuntary movement attack in multiple sclerosis is sometimes referred as "tonic spasm" or "tonic seizure." The attacks are most commonly precipitated by hyperventilation and can be extremely painful. It is thought to be a result of ephaptic transmission.

Another important cause, especially in the elderly is cerebrovascular disease. Other etiologies include metabolic disease, such as hypocalcemia, hypoglycemia and hyperglycemia. See **Table 5** for reported etiology of secondary paroxysmal dyskinesias. Many cases of PNKD, without family history are psychogenic in origin.

EA 1

The attacks of EA1 are brief, lasting seconds to minutes. However, atypical cases with longer attacks lasting up to 12 h are reported. The attacks consist of coarse tremor, dysarthria gait ataxia and limb ataxia, usually without vertigo or nystagmus. Attacks are typically triggered by fatigue, excitement, emotional and physical stress, but also sudden movements and startle, resembling PKD. In fact, some patients with EA1 are reported to have PKD attacks as well. Typically, attacks happen less than once a day, but can recur up to 30 times a day. The onset is early childhood, between 2 and 15 years old. One of the characteristics of EA 1 is interictal myokymia (also called neuromyotonia). This can be detected clinically as a constant fine skin rippling twitching, or by surface electromyography (EMG). Myokymia can happen in any limb or the face, but most notably in the periorbital, or perioral muscles, or in the fingers. Non-affected family members can have myokymia without ataxia. Other associated findings include co-existence of epilepsy, and shortened Achilles tendon on examination.

EA 2

EA2 is the most common form of episodic ataxia. The attacks are longer than that of EA1, lasting 15 min to a few days. Some patients have brainstem symptoms during their attack, including vertigo, tinnitus, dysarthria, nausea/vomiting, and oscillopsia. Some patients have hemiplegia and headache, resembling FHM, its allelic disease. During an attack, patients have spontaneous nystagmus. Patients also have interictal nystagmus, most commonly gaze-evoked nystagmus and downbeat nystagmus. Attacks can be precipitated by alcohol, caffeine, fatigue, stress and exercise. Frequency of attacks varies; it can range from a couple of times a week to a few times a year. Onset is usually between 5 and 20 years

Table 5 Causes of secondary paroxysmal dyskinesia

Paroxysmal dyskinesia	
Multiple Sclerosis	
Cerebrovascular disease	Putaminal infarct
	Thalamic infarct
	Medullary hemorrhage
	Limb-shaking TIA
	Moyamoya disease
Post-traumatic	Central
	Peripheral
Metabolic Disorders	Hypocalcemia (hypoparathyroidism and pseudohypoparathyroidism)
	Fahr's disease (basal ganglia calcification)
	Hypoglycemia
	Nonketotic hyperglycemia
	Thyrotoxicosis
Immune Disorders	SLE
	Rheumatic fever
	Antiphospholipid antibody syndrome
Infectious	HIV
	CMV encephalitis
	Meningovascular syphilis
Cerebral Palsy	
Cervical Cord Lesion	
Other	Kernicterus
	Lymphoma
	progressive supranuclear palsy
	Methylphenidate therapy
Episodic ataxia	
Multiple sclerosis	
Arnold–Chiari malformation	
Other intracranial lesion	Midbrain infarct
Mitochondrial	Pyruvate carboxylase deficiency
	Pyruvate dehydrogenase deficiency
Urea cycle	Ornithine transcarbamylase (OTC) deficiency (usually heterozygous females)
	Carbamoylphosphate synthetase deficiency
	Argininosuccinate synthetase deficiency (citrullinemia type 1)
	Arginosuccinase deficiency
	Arginase deficiency
Organic aciduria	Hartnup disease,
	Intermittent branched-chain ketoaciduria
	Isovaleric acidemia

old. About half of the patients with EA2 have migraine, and some patients develop progressive interictal ataxia, as well as interictal weakness. To complicate the matter, SCA6 patients can have intermittent "attack-like" episode of ataxia, causing clinical overlap between EA2 and SCA6.

EA3–7

Other single or rare families with episodic ataxia syndrome, without EA1 or EA2 mutation have been reported. EA3 was reported as a single Canadian family, with episodic vertigo, tinnitus and ataxia, lasting minutes. EA4 was reported in 2 families from North Carolina. Patients with EA4 have prominent vertigo, and this disease is also referred to as vestibulocerebellar ataxia. Of note, there was initial confusion regarding nomenclature of EA3 and EA4. Originally, the authors reporting the Canadian family referred to their disorder (current EA3) as EA4, and family from North Carolina (current EA4) as EA3. They later corrected themselves and OMIM adopted the current nomenclature; the Canadian family to be EA3, and the North Carolina family with vestibulocerebellar ataxia to be EA4.

EA5 clinically resembles EA2; genetic abnormality was found on calcium channel gene, but different subunit. EA6 was a single child with episodic and progressive ataxia, who also had seizures and hemiplegia. EA7 also resembled EA2 clinically, but had no interictal findings on neurological examination.

Secondary Causes of Episodic Ataxia

As in paroxysmal dyskinesia, neurological illness, such as multiple sclerosis, midbrain infarct and various metabolic diseases have been reported to cause secondary episodic ataxia (**Table 5**).

Differential Diagnosis

Paroxysmal Dyskinesia

Differential Diagnosis includes other intermittent neurological diseases such as seizures, migraines and pseudoseizures. It also includes conditions listed in **Table 2**, such as dopa-responsive dystonia, drug-induced dyskinesia, and tic disorders. Wilson's disease, benign hereditary chorea, and Huntington's disease may sometimes resemble PNKD. PED has been reported to be the presenting symptom of Parkinson's disease. In PHD/nocturnal epilepsy, differential diagnosis includes nightmares, night terrors, restless-leg syndromes, REM behavior disorders and other parasomnias. Disease that can cause secondary paroxysmal dyskinesia, listed in **Table 5** may need to be ruled out. Some of the cases may be psychogenic in origin.

Episodic Ataxia

Differential diagnosis of episodic ataxia includes other episodic disease, such as paroxysmal dyskinesia, seizures, or migraines. Patients with spinocerebellar ataxia syndrome (SCA) can have some fluctuation of their progressive ataxia, best known in the case of SCA6. Secondary causes of episodic ataxia may need to be ruled out.

Diagnostic Work-up and Tests

Paroxysmal Dyskinesia

Careful history taking and videotape documentation of the attack, if possible, are the most important first steps. Special attention needs to be paid in obtaining extensive family history; in some cases, relatives may have forgotten about their attacks in youth. If the attacks are frequent and epilepsy is suspected, electroencephalogram and video-EEG monitoring may be necessary to differentiate seizures. If the attacks happen during sleep, polysomnogram is recommended.

To investigate for secondary causes, neuroimaging and blood tests may be necessary. MRI and vascular investigation are done to rule out structural lesion, multiple sclerosis, and cardiovascular disease. Other metabolic assessments include blood glucose level, serum calcium and thyroid function tests.

Episodic Ataxias

As in paroxysmal dyskinesia, careful history taking, including family history is important. In addition, episodic ataxias have interictal abnormality in their examination; myokymia in EA1 and baseline nystagmus and mild progressive ataxia in EA2, which can aid the diagnosis. If myokymia is subtle and not observed clinically, surface EMG may help detect this. Commercial genetic testing is available for EA1 and 2. However, deletions, duplications and cryptic mutations in untranslated or intronic regions could be missed. Patients with later age of onset and progressive baseline ataxia should be screened for SCA6. Neuroimaging, such as MRI may be necessary to rule out structural causes, such as multiple sclerosis and Arnold–Chiari malformation. In addition, cerebellar vermis atrophy may be seen in EA2. Other possible metabolic assessments include serum ammonia, serum/urine amino acid level and serum pyruvate and lactate level after a glucose load.

Management

PKD

PKD responds extremely well to low dosage of antiepileptic medication, with near complete resolution of attacks. Phenytoin (dilantin) was the first reported agent that proved to be helpful, but currently, carbamazepine (tegretol) is the most widely used. Phenobarbital and valproate are also reported to be effective, as well as newer AED such as lamotrigine, oxcarbazepine, topiramate and levetriacetam. The dosage required is much lower than that used to treat epilepsy. For example, carbamazepine at the dosage of 200–400 mg day^{-1} may completely abort the attack. Thus, it is not necessary to either monitor blood level or try to push for therapeutic levels, except to monitor for compliance.

PNKD

The attacks of PNKD can respond to benzodiazepines, such as clonazepam or diazepam, although the clinical response is not as dramatic as the AED in PKD. Other medications that have been tried with mixed results include levodopa, haloperidol, anticholinergics and AEDs. Avoidance of precipitating factors such as alcohol and caffeine may help.

PED

Treatment of PED is unsatisfactory. There are isolated case reports of levodopa, acetazolamide, trihexyphenidel and benzodiazepine alleviating the attack to some degree. Avoidance of prolonged exercise may help. There is one report of posteroventral pallidotomy ameliorating the attacks of PED.

PHD/ADNFLE

The drug of choice for ADNFLE is carbamazepine. Roughly 70% of patients have remission of seizures with carbamazepine with relatively low doses.

Secondary Paroxysmal Dyskinesia

In paroxysmal dyskinesia secondary to multiple sclerosis, AED as well as acetazolamide can be helpful. AED and benzodiazepines may be helpful in other cause as well. If there is a metabolic abnormality, this needs to be corrected. Deep brain stimulation has been attempted in refractory case. One patient with PNKD secondary to a rotator cuff tear had complete resolution of attacks after globus pallidus internus stimulation. Another patient with painful PNKD secondary to brachial plexopathy had dramatic improvement after contralateral thalamic ventrointermediate (Vim) stimulation.

EA1

The attacks of EA1 can respond to both acetazolamide and AED. The kinesigenic attacks appear to respond well to the AEDs, especially carbamazepine and valproate, again resembling PKD.

EA2

The attacks of EA2 respond dramatically to acetazolamide. Acetazolamide is thought to alter the intracellular pH and as a result, change the transmembraneous potential in the Purkinje cells. It is started at a low dose, 125 mg a day, but some patients may need a higher dose, up to 500 mg twice a day. The effect may be transient in some patients. 4-Aminopyridine (4-AP), a nonselective potassium channel blocker, shows promise. In animal model of abnormal

CACNA1A mouse *tottering*, 4-AP and 3,4-diaminopyridine were helpful in preventing attacks. In one study, 4-AP prevented attacks in patients with EA 2, most likely by increasing the resting activity and excitability of the Purkinje cells.

Prognosis

In PKD, prognosis is good; it responds well to AED, and attacks tend to diminish over adulthood. In PNKD and PED, prognosis is more variable, with some remission reported. ADNFLE is usually lifelong but not progressive. As patient reaches middle age, attacks may become milder and less frequent.

For secondary dyskinesia, the prognosis depends on the underlying disease. Tonic spasms of multiple sclerosis tend to subside over time, even when the disease remains active.

EA1 usually remit in the second decade. EA2 also have a relatively good prognosis. It generally responds well to acetazolamide, and attacks can remit within few years after onset. Some patients, however, develop progressive underlying ataxia.

See also: Creutzfeldt–Jacob Disease; DYT9, Paroxysmal Dyskinesia with Spasticity; DYT11, DYT15, Myoclonus-dystonia; Eye-of-the-Tiger Sign; Oral Dyskinesia; RNA Interference.

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http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim – Online Mendelian Inheritance in Man (OMIM).

http://rarediseasesnetwork.epi.usf.edu/cinch/index.htm – The Consortium for Clinical Investigation of Neurological Channelopathies.

http://www.wemove.org/pdys/ – WE MOVE (Worldwide Education and Awareness for Movement Disorders).

Pelizaeus–Merzbacher Disease

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Glossary

GJA12 (Gap junction protein α-12) – Recessive mutations in this gene cause one form of PMLD.

MLPA (Multiplex ligation-dependent probe amplification) – Gene dosis can be precisely quantified, usually independently for each exon.

PLP1 (Proteolipid protein 1) – Main protein of myelin. Its gene is located on the X chromosome.

PMD (Pelizaeus–Merzbacher disease) – Hallmarks are nystagmus and spastic paraplegia in male patients.
PMLD (Pelizaeus–Merzbacher-like disease) – Resembles PMD, but its inheritance is autosomal recessive. Only one gene has been identified so far.

Definition and History

Pelizaeus–Merzbacher disease (PMD, OMIM 312080) is a rare, X-chromosomal disorder. It was first described by Friedrich Pelizaeus in 1885 in a large family. Neuropathological studies published by Ludwig Merzbacher in 1910 demonstrated near-complete absence of central nervous system (CNS) myelin, while myelin in the peripheral nervous system was intact.

The disease is caused by alterations (point mutations, duplications, and rarely deletions) of the proteolipid 1 (*PLP1*) gene, which was first described 1989 (point mutations) and 1994 (duplications). It is allelic with one form of the hereditary spastic paraplegias, SPG2.

There are also autosomal-recessive forms, which are called Pelizaeus–Merzbacher-like disease (PMLD). This is a heterogeneous group of disorders; only a minority of the cases are caused by mutations in the gene coding for a gap junction protein, *GJA12*.

Pathogenesis/Pathophysiology

The exact pathogenesis of PMD is not clear. PLP1 consists of 276 amino acids and is the most abundant protein of CNS myelin. It is produced by oligodendrocytes. The gene coding for PLP1 has seven exons and is extremely well conserved between species. Alternative splicing leads to the formation of a smaller protein lacking 20 amino acids, DM20; this is the predominant gene product during embryogenesis. PLP1 consists of four transmembrane parts and one intracellular and two extracellular and loops with both C- and N-terminal parts protruding into the cytoplasm and is extremely hydrophobic. After synthesis in the endoplasmatic reticulum, it is transported through the Golgi complex where it associates in membrane rafts with other myelin constituents as sulfatides, cholesterol, and galactocerebrosides. PLP1 is then transported to the plasma membrane.

Point mutations, which cause 10–20% of PMD cases, can give rise to a whole spectrum of symptoms ranging from the most severe form, connatal PMD, to X-linked spastic paraplegia (SPG2). If DM20 is not affected by a mutation, symptoms are relatively mild. However, there is no good genotype–phenotype relationship besides the observation that mutations in the N-terminal part of the gene usually lead to the more severe forms. Recently it has been shown that mutations in the extracellular loop can affect disulfide bridges, making correct folding impossible. If folding and intracellular transport of PLP1 are affected, the unfolded protein response (UPR) is activated and leads to severe intracellular disturbance and finally induce oligodendrocyte apoptosis.

Duplications of *PLP1* are the most common molecular abnormality in patients with PMD and cause up to 70% of cases. In animal models, severity of symptoms corresponds to the amount of *PLP1* overexpression. In humans, this has also been shown for the rare cases with *PLP1* triplications (about 1–2% of patients with PMD). Why PLP1 overexpression leads to disease remains unclear. It has been proposed that excessive amounts of PLP1 in the myelin rafts lead to an imbalance of other myelin constituents in the cell and adversely affects myelin assembly.

Heterozygote female carriers are usually asymptomatic. Mutations leading to mild disease in males can cause symptoms in female carriers, whereas mutations associated with severe disease do not cause symptoms in carriers. This seemingly paradox phenomenon is explained with the fact that in the case of severe mutations, oligodendrocytes where the X chromosome with the mutant allele is activated, die during myelination, and oligodendrocytes with the normal allele take over. This explains also the transient symptoms sometimes present in carriers of duplications. When mutations are not deleterious, carrier females have both normal and abnormal oligodendrocytes, which may lead to degenerative symptoms later in life.

Clinical Features and Diagnostic Criteria

Diagnosis of PMD is clinical: nystagmus and spastic paraplegia in a male patient evoke this diagnosis, MRI and genetic results can confirm it. Depending on severity and the age of onset, PMD is divided into a connatal (first described by Seitelberger in 1954) and a classical form; in between is the so-called transitional form. Isolated X-linked spastic paraplegia (SPG2, OMIM 312920) is not called PMD. There is a continuum of severity in between all these forms.

An important symptom in both forms, classical and connatal, is pendular nystagmus starting several weeks after birth. Retina and optic nerve are normal. In the connatal form, first symptoms are present shortly after birth and include stridor and severe muscular hypotonia. Sitting without support is not possible. In the classical form, infants

show muscular hypotonia that evolves later to spastic paraplegia with dystonic and ataxic components. Walking without support is usually not possible; if children learn to walk, they lose it after a few years. Cognitive abilities are much better preserved than motor features, but there is usually cognitive impairment also in the classical form of PMD. The most severe form of PMD is caused by triplications of PLP1. These children often have severe epilepsy, which is unusual in the other forms of PMD.

Children with PMLD show a similar clinical presentation although ataxia may be more prominent in some of these cases. They may also display mild neuropathy, which is usually not relevant. Mild epilepsy is common in children with *GJA12* mutations. They may experience deterioration, including the development of bulbar symptoms later in the course.

Differential Diagnosis

Children with PMD are sometimes misdiagnosed as having cerebral palsy (CP). The movement disorder resembles that of CP, but children with CP usually do not show nystagmus. MRI in CP is different and does not show hypomyelination. Vice versa, cases with hypomyelination in neuroimaging are often labeled as PMD, although clinical presentation is completely different. One example is 4H syndrome (hypomyelination, hypodontia, hypogonadotropic hypogonadism), also called ADDH (ataxia, delayed dentition, and hypomyelination).

Diagnostic Work-up/Tests

MRI will be the first and most important investigation. In almost all cases, it shows severe hypomyelination (**Figure 1**). If the patient is male, genetic testing for *PLP1* gene alterations comes next. Duplications should be looked for first; multiplex ligation-dependent probe amplification (MLPA) is an easy and reliable method to test for this. MLPA is also able to pick up triplications of *PLP1*. Interphase fluorescent in situ hybridization (FISH) can also detect duplications and would detect aberrant *PLP1* localization albeit this has been described in only one patient so far. If duplication studies are negative, sequencing *PLP1* is the next step. In affected females and if there is strong evidence for autosomal-recessive disease (or in a male patient with negative *PLP1* studies), *GJA12* should be sequenced. CSF studies, including measuring *N*-acetylaspartylglutamate (NAAG) levels, which have been shown to be elevated in children with PMD, are not part of the routine workup of a patient suspected of PMD. NAAG elevation is nonspecific and has also been demonstrated in other cases with hypomyelination.

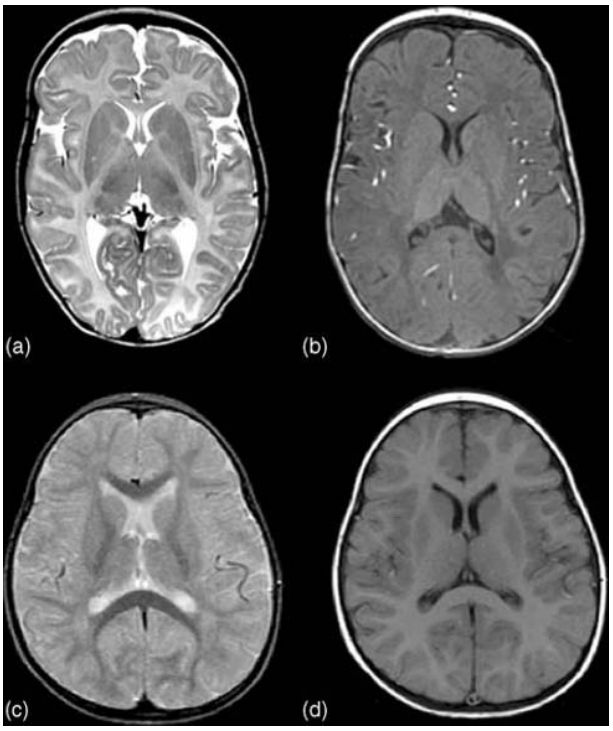

Figure 1 (A) T2w and (B) T1w axial MRI images of a 12-month-old boy with the connatal form of Pelizaeus–Merzbacher disease and a missense mutation in *PLP1*. Myelination is lacking completely in the T2w image and almost completely in the T1w image. For comparison, respective T2w and T1w MRI images of a healthy 12-month-old child (C + D).

Management

Management is supportive including physiotherapy, occupational, and speech therapy. Physiotherapy is important to avoid contractures and scoliosis and to provide adequate orthopedic support. Spasticity can be improved by baclofen. If epilepsy is present, it should be treated according to seizure type and EEG changes. Genetic counseling should be provided.

Prognosis

Prognosis depends on disease severity. In the classical form, life expectancy is not much reduced. There is evidence for a slow deterioration starting around adolescence and affecting mainly motor capacities. In the connatal form, life expectancy depends mainly on secondary complications and medical support and is very variable; death may occur already in early childhood, but also much later.

See also: Ataxia; Dystonia, Secondary; Eye Movement Abnormalities in Movement Disorders; Spastic Paraparesis.

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Periodic Limb Movements

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Glossary

A11 region – A cluster of dopamine-containing cells located in the diencephalon with projections to the spinal cord.
BTBD9 – The symbol for (Broad-Complex-Tram-Track-Bric-A-Brac Domain 9) and is a gene encoding a BTB (Poz) domain on Chromosome 6p.
Cyclic alternating pattern (CAP) – A normal phenomenon of NREM sleep characterized by a repetitive biphasic pattern of K-complex, K-alpha, microarousals, or delta bursts that periodically interrupts the theta/delta background EEG of NREM sleep.
Periodic limb movements (PLMs) – Involuntary repetitive nonepileptiform movements that frequently occur as stereotypic triphasic events involving the great toe, ankle, and hip. PLMs involve the lower limbs, but can also involve the arms. The duration of a PLM is at least 0.5–10 s; it recurs in sequences of four or more events, at 5–90 s intervals; and is associated with an elevation of the electromyogram of at least 8 uV above the baseline. PLMs can occur either in sleep designated as periodic limb movements in sleep (PLMS) or during wakefulness denoted as periodic limb movements in wakefulness (PLMW).
Periodic limb movement disorder (PLMD) – Refers to PLMS and the clinical consequences of sleep disturbance that cannot be explained by the presence of another sleep disorder.
Restless legs syndrome (RLS) – A sensorimotor disorder with four essential diagnostic criteria: (1) an urge to move the legs usually accompanied or caused by uncomfortable and unpleasant sensations in the legs, (2) the urge to move or the unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting, (3) the urge to move or unpleasant sensations are partially or totally relieved by movement such as walking or stretching, at least as long as the activity continues, and (4) the urge to move or unpleasant sensations is worse in the evening or night than during the day or only occurs in the evening or night.

Definition and Historical Review

Periodic limb movements (PLMs) are involuntary repetitive nonepileptiform movements that frequently occur as stereotypic triphasic events involving the great toe, ankle, and hip. PLMs involve the lower limbs, but can also involve the arms. PLMs occur primarily during sleep and are termed periodic limb movements in sleep (PLMS) but can occur also during wakefulness and are termed PLMs while wake (PLMW). PLMW are most strongly associated with restless legs syndrome (RLS). PLMS are also most strongly associated with RLS but may be seen in healthy individuals, and a variety of sleep disorders, including narcolepsy, REM behavior disorder (RBD), and sleep apnea as well as in neurodegenerative diseases.

The duration of a PLM is at least 0.5 s and not longer than 10 s; it recurs in sequences of four or more events,

at intervals of 5–90 s; and is associated with an elevation of the electromyogram of at least 8 μV above the baseline. The term 'periodic limb movement disorder' (PLMD) appears in the *International Classification of Sleep Disorders Diagnostic Manual*, 2nd edn., 2005, and refers to the patient with PLMS and clinical sleep disturbance that cannot be explained by the presence of another sleep disorder.

In 1953, Sir Charles Symonds coined the term nocturnal myoclonus to describe involuntary nonepileptic clonic movements of the lower extremities during sleep. In 1959, Oswald differentiated PLMS from hypnic myoclonus and concluded that PLMS are normal and unlikely to be epileptic. In 1965, Lugaresi et al. documented the association of PLMS and RLS. In 1966, Lugaresi documented the presence of periodic leg movements during sleep in the absence of RLS.

'Nocturnal myoclonus' describes a variety of phenomena; tends to occur during sleep at intervals of 20–40 s; and is rarely myoclonic (<250 ms). Accordingly, Coleman suggested an alternative term 'periodic movements in sleep.' In 1975, Guilleminault et al., described PLMS as 'a rapid partial flexion of the foot at the ankle, extension of the big toe, and partial flexion of the knee and hip.' In 1979, the Association of Sleep Disorders Centers and the Association for the Psychophysiological Study of Sleep published the *Diagnostic Classification of Sleep and Arousal Disorders (DCSAD)*, which defined PLMS and RLS as two distinct phenomena. In 1980, Coleman et al. published evidence that PLMS are not limited to RLS but occur in a variety of sleep disorders as well as neurological disorders.

In 2004, de Weerd, Rijsman, and Brinkley studied 12 patients and evaluated 469 PLMS to define the sequence of muscle activation during PLMS. The researchers monitored six muscles on the right leg: extensor digitorum brevis (EDB), tibialis anterior (TA), biceps femoris (BF), tensor fasciae latae (TFL), quadriceps (Q), soleus (S), and the TA on the left leg. Of the 469 movements analyzed, 12% occurred as the classic description of EDB-TA-BF-TFL or a variant of this sequence. The most common sequences, 32%, involved the TA followed by EDB only or EDB plus another muscle. In addition, the researchers reported that some patients consistently contracted the same muscle or muscle groups and some patients always had the same sequence of muscle involvement. The researchers also documented a positive association between the number of muscles contracted and the occurrence of an arousal from sleep.

Using advances in technology, Ferri et al. evaluated the characteristics of leg movements (LM) in 65 RLS patients with PLMS and 22 normal controls. The duration, amplitude, interval between the onset of two consecutive LM, and the interval between LM were analyzed. Based on their findings, in 2006, Ferri et al. published a new index for PLMS, 'the periodicity index.' To confirm the validity of the periodic index, Ferri et al. analyzed the structure of the LM sequence by examining Markov chains, a sequence of values that have probabilities at a time interval dependent upon the value at the preceding time. The periodicity index allows prediction of candidate leg events for PLMS. When used with the diagnostic criteria for PLMS, the periodicity index allows differentiation between true periodic limb movements and movements that mimic PLMS. The periodicity index could possibly aid in identifying the specific characteristics of LM and PLMS and in understanding how the PLM motor pattern is influenced by precipitating factors.

The significance of PLMS remains unclear. PLMS may be a predecessor to RLS, represent a subtype of RLS, or may be a marker for RLS severity. Patients with RLS are at greater risk for hypertension and cardiovascular disease. PLMS are accompanied by marked increases in blood pressure and pulse rate. Whether there is a causal correlation between these changes and the increased cardiovascular risk in RLS is under investigation. Patients with end-stage-renal-disease (ESRD) and PLMS have a higher mortality rate compared with patients with ESRD without PLMS. Accordingly, PLMS may provide a unique prognostic indicator of mortality in renal failure.

Insomnia and hypersomnia are commonly associated with PLMS. However, this association is in most cases coincidental. It is now thought that PLMS in the absence of RLS is an uncommon cause of daytime dysfunction in adults. In other words, PLMS are common but PLMD is thought to be rare. However, PLMW are prominent in approximately 15% of people with RLS and in these cases are a definite cause of insomnia. In addition, although sleep disturbance is uncommon in patients with pure PLMS in the absence of RLS, it is not at all uncommon for the sleep of the spouse to be disturbed by the PLMS. In these cases, the diagnosis of environmental insomnia is made in the bed partner and treatment of PLMS may be considered in order to treat the bed partner's insomnia.

There is some evidence that PLMD may be more of a problem in children. PLMS are commonly seen in children with attention–deficit/hyperactivity disorder (ADHD). The significance of this association is uncertain.

Pathogenesis/Pathophysiology

Neither the pathogenesis nor the pathophysiology of PLMS is known. There are at least four hypotheses.

Hypothesis 1: PLMS are caused by disinhibition of spinal cord reflexes by the pyramidal tract or a subcortical area of the brain.

The cerebral cortex does not appear to be actively involved in the generation of the PLMs, because PLMS are not associated with EEG changes on back averaging. In addition, after complete transection of the spinal cord, PLMS occur distal to the transection. This data suggest that the cortex or subcortical areas could be involved in

the inhibition of PLMS that are generated at the spinal cord level. Additional evidence against a cerebral cortex generator for PLMS is the fact that PLMS rarely involve the face.

The motor pattern of PLMS is similar to the motor pattern of the Babinski sign. Both are characterized by dorsiflexion of the great toe, fanning of the smaller toes, and flexion at the ankle. The Babinski sign occurs after injury to the pyramidal tracts and is thought to be secondary to failure of the pyramidal tracts to inhibit a spinal polysynaptic reflex. The Babinski sign is a normal finding in newborns and gradually disappears with complete myelination of the pyramidal tracts. During the recovery phase from spinal anesthesia, a time when supraspinal control of the reflex mechanism is thought to be inhibited, the Babinski sign occurs as a temporary phenomenon.

There are case reports of the onset of RLS/PLMS after injury to subcortical structures. Three separate case reports of the onset of RLS/PLMS after strokes involved subcortical structures as follows: case 1 – the left corona radiate, case 2 – left pallidum and internal capsule, and case 3 – right basal ganglia.

Hypothesis 2: PLMS result from a hyperexcited sympathetic nervous system.

The oscillator for PLMS is thought to be subcortical. PLMS occur in association with phase A of the cyclic alternating pattern of sleep (CAP). CAP is a rhythm possibly generated by a thalamocortical pathway. In addition, the periodicity of PLMS of 20–40 s is similar to that of other autonomic rhythmic functions thought to be controlled by the brainstem such as respiration and blood pressure fluctuations. Therefore, PLMS may be due to a subcortical or brainstem oscillator or failure of a brainstem generator to inhibit motor function allowing activation of a secondary motor center in the lumbosacral spinal cord.

An interrelationship among subcortical areas of the brain, sympathetic nervous system, and dopaminergic systems may be responsible for PLMS.

Ware observed cold feet and poor pulse waves in the lower extremities among patients with PLMS. Ware hypothesized that PLMS are secondary to vasoconstriction caused by over activation of the sympathetic nervous system.

Norepinephrine (NE) is a mediator for the sympathetic nervous system. Ware described three situations possibly associated with increased PLMS due to an increased availability of NE. Specifically, PLMS increased (1) after administration of tricyclic antidepressants, (2) with aging, and (3) in patients with obstructive sleep apnea syndrome (OSAS). Aging is associated with increased NE levels. Ware suggested that OSAS elevated NE levels due to secondary hypoxemia.

Ware treated patients with phenoxybenzamine, an alpha 1 adrenergic postsynaptic blocking agent that causes vasodilatation. The PLM index decreased in patients treated with phenoxybenzamine.

Researchers do not agree on how opioids reduce PLMS. Ware hypothesized that opioids decrease the available NE, leading to vasodilatation and subsequent reduction in PLMS.

Hypothesis 3: Decreased CNS levels of dopamine and/or iron cause PLMS.

Dopaminergic agents and iron both suppress PLMS. Iron is deficient in RLS patients as determined by magnetic resonance imaging (MRI), cerebral spinal fluid (CSF), and autopsy data. Iron is intricately related to dopamine. The D2 dopamine receptor is a protein that contains iron and iron is a cofactor to tyrosine hydroxylase, an enzyme that controls the rate-limiting step in the conversion of tyrosine to levodopa, a precursor to dopamine. Iron deficit leads to alteration in dopamine receptor binding. Dopamine might be relatively deficient due to defective acquisition or utilization of iron by the brain. Dopamine deficiency in the descending A11 diencephalospinal pathway may also lead to sympathetic over activity leading to PLMS (see autonomic Hypothesis 2).

Walters observed that all opioids that effectively reduce RLS/PLMS are primarily mu opiate receptor agonists, and based upon receptor-blocking studies, they hypothesized that opiates act centrally to increase dopamine levels leading to a decrease in PLMS.

Hypothesis 4: PLMS are generated centrally but a stimulus to the central nervous system generator could originate from the peripheral nervous system.

Conceivably, an abnormal sensory input from damaged nerves could trigger a generator in the brain or spinal cord to initiate PLMS. The medical literature includes several case reports of patients with both RLS and PLMS preceded by peripheral neuropathy. Peripheral neuropathy is more common in RLS than the general population as determined by clinical examination and EMG nerve conduction studies. In addition, subclinical peripheral neuropathy may be present in some patients with RLS as determined by nerve biopsy. Support for this hypothesis is limited by observations that abnormal leg sensations are not always most intense prior to PLMS.

Epidemiology/Risk Factors

PLMs occur in all ages and in both genders. Thirty percent of people over 50 years of age have PLMS, suggesting that advancing age is a risk factor for PLMS. PLMS in children occur in RLS and ADHD. Other risk factors include the following.

Medications

Mood stabilizing medications such as lithium, clomipramine, fluoxetine, or venlafaxine increase PLMS. Also dopamine receptor-blocking agents such as haloperidol increase PLMS.

Family History of PLMS/RLS

A genetic risk factor for RLS with PLMS was identified in 2007. Stefansson et al. identified three PLM candidate genes: BTBDP9 (this gene was also identified by Winkelmann), and DNAH8. Stefansson et al. found that the frequency of PLMS correlated with the presence of allele A of marker rs3923809 in an intron of the BTB (POZ) domain-containing 9 gene on chromosome 6p21.2.

Restless Legs Syndrome

Although PLMS occur in a variety of medical conditions and sleep disorders, PLMS are most closely associated with RLS. Eighty percent of patients with RLS have PLMS.

Presence of Other Medical Disorders/Diseases Associated with a High Prevalence of PLMS

PLMS occur commonly in sleep disorders such as narcolepsy, RBD and sleep apnea. PLMS occur commonly in spinal cord damage. As with RLS, PLMS may be related to iron deficiency anemia.

Less commonly, PLMS have been reported in disorders such as dopa-responsive dystonia, Parkinson's disease, Huntington's disease, Stiff-person syndrome, Isaacs' syndrome, motor neuron disease, and hyperekplexia. PLMS are also observed less commonly in childhood leukemia, renal dysfunction, fibrositis, chronic obstructive pulmonary disease (COPD), alcohol dependency, and male erectile dysfunction. Unfortunately, many studies have only a few subjects and coincidental occurrence cannot be ruled out.

Clinical Features

PLMS are nonepileptiform repetitive movements frequently involving flexion of the toe, ankle, knee, and hip. Most patients with PLMS experience repeated flexion of the lower extremities, but some complain of arm movements too. PLMS are characterized by inter- and intraindividual night-to-night variability in the frequency and motor pattern. If a group of ten patients or more is tested, the average number of PLMS is the same for the group and this allows testing of the efficacy of therapy. Although some patients complain of difficulty in falling asleep or maintaining sleep, many become aware of their movements only because of a bed-partner or parent's observations.

PLMS may be associated with increased awakenings from sleep, fatigue, or mild daytime somnolence. However, most research indicates that insomnia or hypersomnia is coincidental. Neither the severity of PLMS nor the frequency of PLMS associated with arousals correlates with the severity of daytime sleepiness or insomnia complaints. PLMS can occur before, during, or after an arousal. Although PLMS is common, PLMD is thought to be rare.

In RBD, PLMS occur during REM sleep. In other disorders, PLMS occur predominantly during N1 and N2 sleep stages in close association with phase A (the arousal phase) of the cyclic alternating pattern (CAP) of sleep. PLMS may or may not be associated with an arousal, K-complex, awakening, or changes in the EEG. The frequency of PLMS is influenced by the time of night and the patient's sleep position. Although the prevalence of PLMS increases with age, the periodic limb movement index (number of periodic limb movements per hour of sleep) does not.

PLMS occur as one of two patterns. Type one involves early night peak frequency of limb movements, which decreases over time and occurs in people with idiopathic PLMS or RLS. In type two, PLMS are more evenly distributed over the night. The type two pattern occurs in sleep disorders such as sleep apnea and narcolepsy.

Differential Diagnosis

PLMS must be differentiated from respiratory-related leg movements in sleep (RRLMS). Other conditions that can mimic PLMS include sleep starts, epilepsy, spinal myoclonus, flexor spasms from spasticity, and myoclonus associated with neurodegenerative disorders such as Alzheimer's and Jakob–Creutzfeldt's disease. PLMS must be differentiated from painful legs and moving toes syndrome, akathisia and nocturnal leg cramps.

Diagnostic Workup/Tests

A history of kicking during sleep or wearing away of bed linen in a pattern consistent with repetitive foot movements is suggestive of PLMS. The presence of PLMS cannot be determined by history but must be documented by polysomnography.

Surface electrodes are placed on each anterior tibialis muscle 2–3 cm apart or 1/3 the longitudinal length of the muscle. A candidate leg movement is defined as an increase in EMG amplitude $\geq 8\,\mu V$ above the resting baseline and ends when the EMG amplitude decreases to $<2\,\mu V$ above the baseline and remains below that value for 0.5 s. The duration of a candidate leg movement event is at least 0.5 s and no longer than 10 s. A PLM is defined as a minimum of four candidate leg movement events recurring in sequence and separated by a minimum of 5 s and no more than 90 s. PLMW must meet the same criteria as PLMS occurring during sleep but allowances are made for shifts in the baseline associated with muscle tension. PLMS at a rate of 5 or more per hour are considered possibly abnormal in childhood and adolescence.

PLMS of 15 or more per hour are possibly abnormal in adults. However, a history of related daytime fatigue needs to be present before treatment is instituted. For research purposes, during polysomnography, an esophageal monitor or respiratory inductance plethysmography is useful to distinguish respiratory related limb movements (RRLMS) from true periodic limb movements.

Actigraphy provides another means to measure limb movements during sleep. Because actigraphy is recorded on multiple nights, actigraphy addresses inter- and intraindividual night-to-night variability in the frequency and motor pattern. Actigraphy does not allow differentiation of true PLMS from RRLMS nor does it allow the identification of associated EEG arousals. The actigraph should have a maximum recording time of 10 consecutive hours per night and should be able to record approximately the same EMG signal as the polysomnograph. A minimum of three nights' recording is recommended.

A ferritin level may help to identify PLMS secondary to iron deficiency.

Management

Pharmacologic Treatment

The decision to treat PLMS is based on complaints of insomnia or daytime fatigue that can be definitely attributed to the PLMS. In such a case, the diagnosis of PLMD is made. However, PLMD is thought to be rare. PLMS on the other hand commonly disrupt the bed partner's sleep. In such a case, the bed partner is diagnosed as having environmental insomnia. The decision to treat the patient in order to treat the bed partner's insomnia is made jointly between the physician and the couple. All medications used to treat PLMD should be started at the lowest dose and increased slowly to an effective dose.

L-Dopa and dopaminergic agonists

Analogous to therapy of RLS, we consider dopaminergic drugs (levodopa/carbidopa (Sinemet), bromocriptine (Parlodel), cabergoline (Dostinex), pramipexole (Mirapex), and ropinirole (Requip)) as first line pharmacologic therapy for PLMD. There are two types of dopaminergic drugs: ergot preparations and nonergot preparations. Bromocriptine, pergolide, and cabergoline are all ergot dopamine preparations. Ergot is a common name for fungus in the genus Claviceps used in the manufacturing of ergot dopaminergic drugs. Prolonged use of ergot preparations is linked to the scaring of the heart valves (cardiac valvular fibrosis) and the scaring of the lungs (pulmonary fibrosis). Therefore, ergot preparations are used with caution.

Analogous to RLS, we recommend Ropinirole as first line therapy for PLMS. Ropinirole is available in two forms: immediate release and extended release. As with the therapy for RLS, PLMS therapy is started with the immediate release form of Ropinirole at 0.25 mg 30 min before the onset of symptoms or 1–3 h before bedtime. On the third day of therapy, Ropinirole is increased to 0.5 mg day^{-1}. After 7 days Ropinirole is increased to 1 mg day^{-1}. If symptoms persist, increasing Ropinirole by 0.5 mg every week for 6 weeks to a maximum dose of 3 mg day^{-1} is continued. On week 7, if symptoms remain uncontrolled, Ropinirole is increased to a maximum dose of 4 mg.

To convert from immediate release Ropinirole to extended release Ropinirole, a once daily extended release dose that is approximately the same as the maximum daily dose of the immediate release Ropinirole is selected. Ropinirole is metabolized in the liver and should be used cautiously in patients with liver disease.

Similar to RLS therapy, we also recommend Pramipexole as first line therapy for PLMS. Pramipexole is available in multiple dosage strengths. Pramipexole is started at 0.125 mg once daily 2–3 h before bedtime. If symptoms persist, the dose is doubled every 4–7 days up to 0.5 mg day^{-1}. The manufacturer's recommended maximum dose is 0.5 mg day^{-1} but higher doses have been used (2 mg day^{-1}). Pramipexole is excreted through the kidneys and should be used with caution in patients with renal impairment.

Carbidopa/levodopa is an older dopaminergic with a short half-life that is sometimes used off label to treat RLS and PLMS. Carbidopa/levodopa is used when symptoms occur intermittently. PLMS may respond to Carbidopa 25 mg per 100 mg levodopa given 30–60 min before bedtime. The dose may be repeated once. Because of a tendency to cause augmentation of RLS and the high association between PLMS and RLS, daily use of levodopa/carbidopa in higher doses is not recommended.

Cabergoline is a long-acting dopaminergic agent that can be used to treat PLMS but seldom used in the United States due to cost and associated side effects.

Side effects of the dopaminergic drugs include nausea, light-headedness, daytime drowsiness, orthostatic hypotension, and sleep attacks. Chorea and hallucinations are common side effects of dopamine agonists in Parkinson's disease but rare in PLMS. Compulsive gambling and compulsive shopping have been reported.

Rebound and augmentation are complications seen in RLS when patients are treated with dopaminergic agents. Patients with isolated PLMS may develop RLS symptoms and this may be comparable to the rebound or augmentation seen in RLS. Rebound and augmentation have not been described in PLMS.

Opioids: codeine, propoxyphene, hydrocodone, methadone, oxycodone, or tramadol

In a double-blind study using oxycodone and another double-blind study using propoxyphene, both medications improved sleep efficiency and decreased PLMS-associated arousals. Only oxycodone decreased the number of PLMS. There is little risk of addiction or tolerance to opioids when

used to treat PLMD. Constipation, dizziness, nausea, and vomiting are side effects associated with opioids. Patients treated with opioids should be monitored for the development or exacerbation of sleep apnea.

Anticonvulsants: gabapentin (Neurotin)

There is insufficient evidence about the efficacy of anticonvulsants for PLMD therapy. However, research documents that gabapentin ($800–1800\,mg\,day^{-1}$) improves sleep efficiency and reduces PLMS.

Benzodiazepines: clonazepam (Klonopin), temazepam (Restoril), and triazolam (Halcion)

Benzodiazepines may help patients to sleep but only higher dosages of the longer acting benzodiazepines, like clonazepam, consistently reduce the frequency of PLMS. High doses of benzodiazepines cause carry-over effects such as morning drowsiness and decreased cognition. Benzodiazepines are not recommended in patients with untreated or inadequately treated sleep apnea, because benzodiazepines may increase apnea. Addiction and tolerance to benzodiazepines rarely occurs.

Non-benzodiazepine hypnotics: eszopiclone (Lunesta), zolpidem (Ambien)

Eszopiclone and zolpidem are sometimes prescribed to help patients to sleep. To the best of our knowledge, these medications do not reduce PLMS.

Muscle relaxants: Baclofen (Lioresal)

In a double-blind study, Baclofen reduced the amplitude of PLMS and consolidated sleep. Baclofen did not decrease the number of limb movements.

Other

Other medications reported to reduce PLMS include magnesium, bupropion, phenoxybenzamine, and iron.

Nonpharmacologic Treatment

In one study, the number of PLMS decreased 30 min after electrical stimulation to the dorsiflexors of the feet and toes. There are reports that thermal biofeedback and Yoga improve periodic limb movements.

Prognosis

PLMS may be a precursor to RLS as well as a unique prognostic indicator of mortality in renal failure. PLMS in childhood occur more frequently in children diagnosed with ADHD. Patients with PLMS and RLS have a higher incidence of cardiac disease and hypertension. There is a related increase in blood pressure and pulse rate associated with PLMS. The prevalence of PLMS increases with advancing age. Although PLMS occur in healthy individuals and other medical conditions, PLMS and PLMW are strongly associated with RLS. The prognostic implications of these associations are currently unknown but are the subject of further investigation.

See also: Restless Legs Syndrome.

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Relevant Websites

www.neurotalk.org – An online support group for the discussion of brain, neurological, health and mental health conditions.

www.rls.org –This is an organization of lay people interested in RLS.

www.sleepfoundation.org – Provides comprehensive sleep medicine education and awareness programs for professionals and the general public.

www.wemove.org – A comprehensive internet source for information on movement disorders.

www.irlssg.org – The International Restless Legs Syndrome Study Group (IRLSSG) is an organization of professionals committed to advancing basic and clinical research on Restless Legs Syndrome (RLS).

Pesticides

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Glossary

Biomarker – In movement disorder neurology, a biomarker is a molecule, neuroimaging pattern or other indicator of a disorder, even when the classical signs of that disorder are not present.
Dopamine – A neurotransmitter occurring in a wide variety of animals, including both vertebrates and invertebrates. In the brain, this catecholamine activates five types of dopamine receptors — D1, D2, D3, D4, and D5, and their variants. Dopamine is produced in several areas of the brain, including the substantia nigra and the ventral tegmental area.
Lipophilicity – The ability of a chemical compound to dissolve in fats, oils, lipids, and nonpolar solvents such as hexane or toluene.
Neurotoxin – A toxin that acts on the peripheral or central nervous system.
Nitric oxide synthase (NOS) – An enzyme in the body that contributes to transmission from one neuron to another, to the immune system and to dilating blood vessels.

A pesticide is an agent used to kill undesired organisms such as insects (insecticide), snails and slugs (molluscicide), rodents (rodenticide), plants (herbicide), or fungi (fungicide). Pesticides can be categorized in a number of ways, including their acute toxicity to humans, their chemical group, or their mode of action. Pesticides may be absorbed by inhalation, ingestion or, in some cases, such as the organophosphates, through the skin. Exposure and subsequent toxicity are influenced by the pesticide chemical itself, as well as its formulation (e.g., powder, granules, candles, liquid concentrate, premixed solution, and gas), method of application (e.g., spraying, fogging, dipping, dusting), use of protective equipment (gloves, goggles, impermeable clothing, respiratory masks), and prevailing weather. Pesticide exposures may arise not only through work but also in the home, for example, insecticides for human parasites, flea treatments on family pets, exposure to timber treatment agents, use of garden pesticides, and the ingestion of pesticide-contaminated water or food. Most developed nations regularly test foodstuffs for pesticide contamination, whereas less developed countries may not.

Poisoning by acute, high-level exposure to certain pesticides has well-known neurotoxical effects, which can range from a mild skin irritation to coma or even death. Whether chronic exposure to moderate levels of pesticides is also neurotoxic and associated with a risk of movement disorders is more controversial. Most studies have found increased prevalence of symptoms and changes in neurobehavioral performance following moderate pesticide exposure, reflecting cognitive and psychomotor dysfunction. Studies conducted in the early 1980s suggested that early age exposure to rural environments and consumption of well water, lifestyles in which exposures to pesticides are thought to be more prevalent than in urban environments were associated with later development of Parkinson's disease (PD). Epidemiologic studies have also shown that a history of farming or living on a farm is associated with increased risk of PD. A meta-analysis of 19 case-control studies of pesticide exposure and PD found an almost doubling of risk in pesticide-exposed groups. The association between pesticides and PD was of similar size when comparing North American (OR 2.15, 95% CI 1.14–4.05) and all studies (OR 1.94, 95% CI 1.49–2.53). One of the largest cohort studies carried out studied the relationship between pesticide exposure and PD in over 140 000 people drawn from the American Cancer Society's Cancer Prevention Study II Nutrition Cohort. That study, which was based on self-reported current or frequent past exposure to pesticides and self-reported PD diagnosis (validated in the majority of cases by a neurologist's diagnosis of 'definite' or 'probable' PD), found that the relative risk for PD among individuals exposed to pesticides was 1.7 (95% CI 1.2–2.3). As a result, researchers have examined paraquat, as well as other pesticides and herbicides, in both epidemiologic and animal model studies. The relationship between PD and pesticides appears strongest for exposure to herbicides and insecticides and weaker for fungicides. The association of PD with exposure is best document after long duration of exposure. Toxicological data suggest that paraquat, organochlorines, alkylated phosphate, and rotenone have neurotoxical actions that potentially play a role in the development of PD. Data are more limited for other pesticides. Two of the three widely used animal models of PD employ pesticides: rotenone and 1-methy1-4-pheny1-1,2,3,6-tetrahydropyridine (MPTP). One criticism of such laboratory animal models as a model of pesticide exposure and PD is that neither the dose nor the route of administration of pesticides is representative of likely human exposures. Likewise, in the absence of long-term biomarkers of exposure to most pesticides, organochlorines being a notable exception, associations

with specific agents may be confounded by exposure to other pesticides, making it difficult to identify a single causative agent.

Laboratory studies have identified a number of mechanisms by which pesticides might lead to PD including mitochondrial dysfunction (e.g., complex I inhibition), oxidative stress, protein aggregation, and altered dopamine levels. Several pesticides act by inhibition of mitochondrial enzymes, thus disrupting cellular respiration. MPTP is a mitochondrial complex I inhibitor as is rotenone. The risk from pesticides is increased in those who are poor CYP2D6 metabolizers. A review of analytic epidemiologic studies of PD cases examined both in which exposure to pesticides was queried directly and whole-animal studies for PD-like effects after systemic pesticide exposure. However, both the epidemiology and toxicology studies were limited by methodologic weaknesses. Particular issues of current and future interest include multiple exposures (both pesticides and other exogenous toxicants), developmental exposures, and gene–environment interactions. Animal studies have found evidence that male mice exposed to maneb in-utero are at increased risk of developing neurodegeneration if subsequently exposed, as adults, to paraquat. These laboratory findings have led to the speculation that pesticide-exposed children may be at increased risk of PD in later life, although evidence for this association is lacking. Equally, it can be hypothesized that in old age, a pesticide exposure might 'tip the balance' in an individual with preexisting dopaminergic cell depletion, thus leading to PD. At present, too little is known about the timing of pesticide exposures and the role this may play in the development of PD. A large prospective cohort study of children and their exposure to environmental pesticides is required to study the role of early life pesticide exposures.

Specific Agents

The pesticide, paraquat, has a close structural resemblance to the active metabolite of MPTP, 1-methy1-4-phenylpyridinium MPP^+. It had been thought, on the basis of the similarity in their chemical structure, that paraquat acted on the brain in a way similar to MPTP. However, in vitro research suggests that paraquat exerts its toxicity on dopaminergic neurons in a different way to MPP^+. Intranigral injection of paraquat can selectively destroy dopaminergic neurons and induce behavioral changes in animal models. Treatment with dopaminergic agents prevents paraquat toxicity, suggesting that the drug or a toxic metabolite is transported into the brain by the neutral amino acid transporter. Importantly, in vitro paraquat, as well as rotenone and dieldrin, increases α-synuclein fibril formation and aggregation. Decreased toxicity is associated with increased levels of HSP70, which is known to be associated with protection against paraquat toxicity. The potential toxicity of paraquat to dopaminergic neurons might be enhanced by other agrochemicals, and combined treatment with the dithiocarbamate fungicide, maneb, appears to have synergistic toxic effects.

Humans may be occupationally exposed to organochlorine pesticides, and chronic exposure may result in a 6–8-Hz action tremor which may be of such severity that it interferes with ordinary daily activities. Tremor onset is not necessarily immediate, and may be delayed by as long as 8 months after initial exposure. Postmortem studies have found that the brains of those who died of PD were more likely to have detectable levels of dieldrin than those who died of other illnesses. Elevated levels of lindane and dieldrin have been found in the substantia nigra in PD brains. Dieldrin can deplete brain dopamine content, induce abnormal motor behavior and α-synuclein aggregation, inhibit mitochondrial and proteasome function, and induce apoptotic mechanisms to dopaminergic cells in culture. The effects of dieldrin may be suppressed by antioxidants, suggesting the involvement of oxidative stress.

The pesticide, rotenone, is also toxic to dopaminergic neurons. Rotenone is highly lipophilic and a known inhibitor of complex I of the mitochondrial respiratory chain. It has been shown that focal injection of rotenone into the nigrostriatal pathway or chronic administration to animal models results in a destruction of the nigrostriatal pathway associated with the presence of α-synuclein and ubiquitin-positive inclusions. Damage extends beyond the dopaminergic system and affects 5HT, noradrenergic and cholinergic neurons. Since rotenone induces the enzyme, nitric oxide synthase (NOS) activity in both striatum and substantia nigra, the effects of rotenone are prevented by a neuronal NOS inhibitor 7-NI.

Maneb (active ingredient: manganese ethylene-bis-dithiocarbamate) is a fungicidal dithiocarbamate molecule that contains a manganese atom. Manganese toxicity is known to induce parkinsonism, but the neuronal degeneration is found primarily in the globus pallidus and not the substantia nigra. There have been case reports suggesting parkinsonism in agricultural workers exposed to maneb. However, the geographic overlap between paraquat and maneb utilization could indicate a 'multiple-hit' environmental model that ascribes combinations of exposures as responsible, rather than only one. In animal models, both paraquat and maneb are more toxic in combination compared to each chemical alone. In combination, they have similar neurotoxical effects as paraquat alone, with very young and very old animals being most susceptible to combined paraquat/maneb. It has been hypothesized that the increased susceptibility of the older and younger animals is the result of the lack of a compensatory mechanisms (e.g., increased striatal tyrosine hydroxylase (TH) enzyme activity) within neurons to increase dopaminergic levels.

The pyrethroid insecticide, permethrin, has been examined recently in association with Gulf War syndrome and

locomotor effects. Pyrethroid insecticides may also act as an inhibitor of complex I in mitochondria, and studies from the Bloomquist laboratory measured an increase in dopamine uptake in isolated striatal synaptosomal preparations. It seems also to increase expression of the dopamine transporter (DAT) protein and a transient increase in α-synuclein expression. However, permethrin seems to increase cortical acetylcholinesterase activity and causes variable neuronal degeneration in different brain regions, indicating that permethrin toxicity is not specific for dopaminergic neurons. Further clinical and laboratory studies are needed to define the importance of this pesticide to movement disorders.

See also: Aluminum; Carbon Monoxide Poisoning; Cyanides; Dopamine; Mercury; Parkinson's Disease: Definition, Diagnosis, and Management; Pesticides.

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www.movementdisorders.org – Movement Disorder Society.

PET Imaging in Movement Disorders

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Glossary

Huntington's disease-related pattern (HDRP) – A metabolic spatial covariance pattern identified in the brains of patients with Huntington's disease.
Parkinson's disease-related cognition pattern (PDCP) – A metabolic spatial covariance pattern identified in brain regions associated with the cognitive symptoms of Parkinson's disease.
Parkinson's disease-related pattern (PDRP) – A metabolic spatial covariance pattern identified in brain regions associated with the motor symptoms of Parkinson's disease.
Positron emission tomography (PET) – An imaging technique that produces a three-dimensional image or map of functional processes in the body/brain through the use of radionuclides which emit γ-rays.

Scans without evidence of dopaminergic deficit (SWEDD) – A term used to describe patients who have clinical signs of parkinsonism, but who have normal radiotracer uptake on imaging with fluorodopa PET.
Torsion dystonia-related pattern (TDRP) – A metabolic spatial covariance pattern identified in the brains of dystonia gene mutation carriers.

Definition and History

In recent years, a number of exciting developments have taken place in the application of positron emission tomography (PET) imaging for the study of movement disorders and their response to treatment. Various radiotracers are currently available for the in vivo assessment of abnormal neuronal function in the diseased brain. In particular, a hierarchical approach integrating quantitative parameter estimation at the voxel level with spatial covariance tools for pattern analysis has greatly enhanced the role of functional imaging in the study of these and other neurodegenerative disorders.

In this article, we summarize the recent advances in the clinical investigation of movement disorders utilizing PET techniques. Parkinson's disease (PD) is the best studied of these disorders and is discussed in detail. Moreover, rather than focus on the extensive literature that has appeared on abnormalities in motor activation in movement disorders, we will review the growing body of information that has appeared on abnormal resting brain function in these disorders. This article also discusses the role of these imaging measures as biomarkers for the objective evaluation of novel therapies for movement disorders.

Diagnosis of PD

Dopaminergic Imaging

Fluorodopa: Neurotransmitter uptake, metabolism, and storage

The original application of PET in PD was to detect presynaptic nigrostriatal dopamine (DA) dysfunction as a means of patient diagnosis. It is understood that injury to the substantia nigra causes defects in the storage and release of DA in the striatum. PET studies utilizing 6-[^{18}F]fluoro-L-dopa (FDOPA) measure the uptake of this tracer and its conversion to [^{18}F] fluorodopamine by the enzyme dopa decarboxylase (DDC) in the striatal dopaminergic nerve terminals.

Many studies have demonstrated that FDOPA PET yields quantitative parameters that can discriminate PD patients from healthy control subjects and correlate with independent disease severity measures. More importantly, it has been shown that putamen FDOPA uptake correlates with nigral DA cell counts measured in postmortem specimens. In patients with early stage of PD, FDOPA uptake is relatively preserved in the caudate and anterior putamen. This is in line with the pathological finding which showed that neuronal loss in early PD takes place in the ventrolateral tier of the substantia nigra, which projects to the posterior putamen. FDOPA PET has clinical utility in differentiating classical PD from alternate diagnoses such as psychogenic parkinsonism, essential tremor (ET), and secondary forms of parkinsonism. However, striatal FDOPA uptake in atypical neurodegenerative forms of parkinsonism is indistinguishable from that of PD, especially in the early stages of the disease.

6-[^{18}F]Fluorodopamine and PET are also used for the assessment of cardiac postganglionic sympathetic nerve terminal function in movement disorders, which could effectively differentiate movement disorders. Decrement of cardiac fluorodopamine has been shown in patients with PD and pure autonomic failure, but remains intact in multiple system atrophy (MSA) patients.

Other dopaminergic radiotracers

The development of radiotracers which bind to the striatal dopamine transporter (DAT) has led to another means for imaging the nigrostriatal dopaminergic system with PET or single photon emission computed tomography (SPECT). The most extensively studied agents in this category are the cocaine analogues, such as 2-β-carbomethyl-3β-(4-iodophenyl) tropane (βCIT) and its fluoroalkyl esters (**Figure 1**). The use of DAT tracers has several potential advantages over FDOPA: (1) although dopaminergic neurons decline in normal aging, striatal FDOPA uptake appears to be maintained by the upregulation of DDC activity, which is supported by postmortem study. Therefore, FDOPA PET may be relatively insensitive to age-related decrements in presynaptic dopaminergic function. By contrast, the DAT binding agents are more sensitive to age-related dopaminergic attrition. (2) The transport of 3OMFD across the blood brain barrier can affect the quantification of DDC activity with FDOPA PET. (3) Signal-to-noise is potentially higher for DAT imaging than for FDOPA PET. Despite these advantages, recent studies have raised the possibility that DAT binding may be altered by concurrent levodopa therapy. Additionally, presynaptic DAT density is shown to be downregulated in PD. More research is warranted to determine how these findings will influence the use of this tracer in future neuroprotection trials.

The presynaptic vesicular monoamine transporter (VMAT) is involved in the packaging and transfer of monoamines to storage vesicles located in nerve terminals. Radioactive ligands that bind to VMAT sites such as [^{11}C]-dihydrotetrabenazine (DTBZ) can be used as a reliable

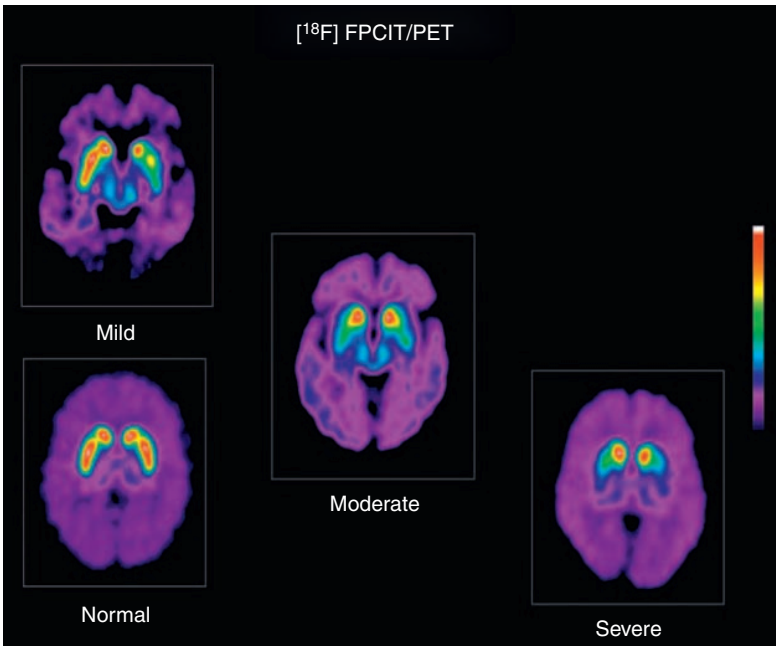

Figure 1 Images of striatal dopamine transporter binding obtained using ^{18}F-fluoropropyl-βCIT (FPCIT) and PET. Scans from patients with mild, moderate, and severe Parkinson's disease (PD) exhibit progressive declines in radiotracer uptake in the posterior putamen. Early disease is associated with marked asymmetry, which becomes bilateral with advancing motor symptoms. Caudate uptake is relatively preserved, until later stages of the disease. A scan from a normal volunteer (lower left) is included for comparison. Reprinted from Gilman S (2006) PET imaging is Parkinson's disease and other neurodegenerative disorders. *The Neurobiology of Disease*, 1st edn., pp. 821–828. Copyright 2006, with permission from Elsevier.

measure of monoaminergic and nerve terminal density. VMAT binding does not appear to be affected by concurrent antiparkinsonian dopaminergic therapy, giving it a potential advantage over other dopaminergic tracers. However, this method has comparably low signal-to-noise, and it may not be specific for dopaminergic terminals.

PET studies using ligands that bind selectively to D_1 and D_2 receptors in the striatum can be used to measure changes in postsynaptic dopaminergic function occurring during disease progression and pharmacotherapy. The radioligand [^{11}C] raclopride (RAC) can provide sensitive measures of local D_2 receptor density. It has been suggested that loss of dopaminergic nerve terminals in association with changes in the postsynaptic DA receptors underlies the motor complications that occur in the course of treatment. A relative increase of striatal D_2 receptor binding has been reported in early, untreated parkinsonian patients, particularly in the putamen contralateral to the more affected body side.

RAC is easily displaced by endogenous DA; indeed, an increase or decrease in RAC binding may not reflect D_2 receptor density. Rather, these changes may reflect alterations in the endogenous DA levels following amphetamine challenge, levodopa administration, placebo administration, motor tasks, or transcranial magnetic stimulation. In PD patients, levodopa-induced improvements in UPDRS motor ratings correlated significantly with reductions in putaminal RAC binding potential.

Metabolic Imaging

Utilization of ^{18}F-fluorodeoxyglucose (FDG) and PET have made it possible to map cerebral glucose metabolism. This imaging technique provides a measure of integrated regional synaptic activity of an afferent input neuron rather than the perikarya. Although the primary pathological motor dysfunction responsible in PD is confined to the substantia nigra, the degeneration of dopaminergic nigral projections to the striatum and other regions results in widespread alterations in the functional activity of cortico-striatopallido-thalamocortical (CSPTC) pathways.

Functional models of the basal ganglia generally predict that the loss of inhibitory dopaminergic input to the striatum causes increased inhibitory output from the putamen to the external globus pallidus (GPe), diminished inhibitory output from the GPe to the subthalamic nucleus (STN), and functional overactivity of the STN and internal globus pallidus (GPi). These changes result in decreased output from the ventrolateral thalamus to the motor cortex, which are accompanied by alterations in regional cerebral glucose metabolism. We have modeled such systems using spatial covariance methods in which principle components analysis is applied to combined samples of patient and control scans. Patterns with significantly different expression in the patient group are considered to be 'disease-related.' The PD-related spatial

covariance pattern (PDRP) is characterized (**Figure 2**) by pallidothalamic and pontine metabolic activity associated with reduced metabolism in the prefrontal cortices and parieto-occipital association cortex. The degree of PDRP expression is abnormally elevated in PD patients and correlates with disease severity and duration. In contrast to the neurochemical dopaminergic markers such as FDOPA or βCIT, PDRP expression has the attribute of increasing with disease progression. This may provide greater sensitivity in the detection of longitudinal changes in brain function, a critically important factor in the assessment of potential disease modifying agents.

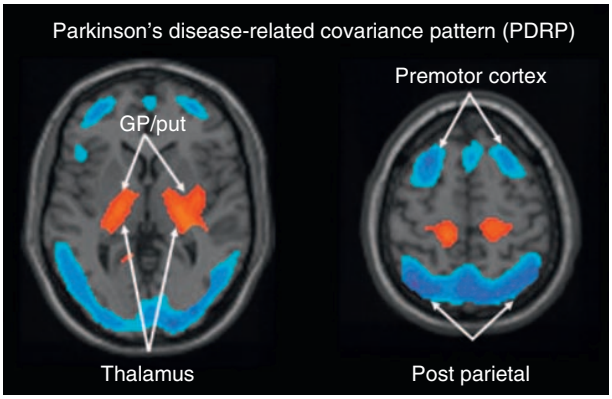

Figure 2 Parkinson's disease-related spatial covariance pattern (PDRP) characterized by pallidothalamic, pontine, and motor cortical hypermetabolism, associated with relative metabolic reductions in the lateral premotor and posterior parietal areas. (The covariance pattern was overlaid on T1-weighted MR-template images. The displays represent voxels that contributed significantly to the covariance pattern ($p < 0.001$) and that were found to be reliable on bootstrap resampling ($p < 0.05$). Relative metabolic increases are displayed in red; relative metabolic decreases are displayed in blue. The left hemisphere was cut in the transverse plane at $z = -5$ mm. The right hemisphere was displayed as a surface projection on the same brain template.)

Pattern analysis of FDG PET data can provide an accurate means of diagnosing atypical forms of parkinsonism (**Table 1**). Atypical neurodegenerative parkinsonian syndromes such as MSA, progressive supranuclear palsy (PSP), and corticobasal ganglionic degeneration (CBGD) are often difficult to distinguish from PD on clinical grounds. These diseases, however, have distinctive topographic features that can be used for differential diagnosis by metabolic imaging techniques. Single-case statistical parametric mapping (SPM) techniques can be used to categorize individual PET scans based upon characteristic disease templates (**Figure 3**). This pattern recognition approach correctly diagnosed 92.4% of the subjects in accord with clinical assessments made 2 years after PET imaging by blinded movement disorders specialists. Thus, FDG PET scans performed at the time of initial referral for parkinsonism accurately predicted the ultimate clinical diagnosis in the patients made at subsequent follow-up. Accurate differential diagnosis is also of particular importance in the context of clinical trials for parkinsonism. Inadvertent inclusion of atypical patients into pharmacological trials for PD is likely to reduce statistical power by increasing the heterogeneity of the treatment cohorts.

In the course of recent clinical trials of potential neuroprotective agents in PD, it was found retrospectively that 10–15% of enrolled subjects with clinical signs of parkinsonism had normal radiotracer uptake. Similarly, it was found that 14.6% of patients with parkinsonism

Table 1

Disease	*FDG*	*Striatal F-DOPA/DAT Binding*	*Striatal Raclopride*
Parkinson's disease	*Increased* in putamen, thalamus, brainstem, cerebellum, primary motor cortex *Decreased* in prefrontal, parietotemporal association cortices	Rostro-caudal gradient reduction. May show asymmetry in early stage	Up-regulated in early stage
Multiple system atrophy	*Decreased* in striatum, cerebellum, brainstem	Reduced ubiquously in striatum	Reduced
Progressive supranuclear palsy	*Decreased* in frontal cortex, midbrain	Mildly reduced	Reduced
Corticobasal degeneration	*Decreased* in striatum and parietal cortex on affected side	Mildly reduced	Possibly reduced
Huntington's disease	*Decreased* in striatum and temporal cortex	Normal (apart from atrophy)	Reduced
Primary dystonia	*Increased* in putamen, globus pallidus, cerebellum, supplementary motor area	Normal	Reduced
Dopa responsive dystonia	*Increased* in supplementary motor area and cerebellum *Decreased* in primary motor and premotor cortex	Normal	Up-regulated
Tourette syndrome	*Decreased* in thalamus, lenticular nucleus, hippocampus, midbrain	Normal	Normal
Essential tremor	*Increased* in cerebellum	Normal	?

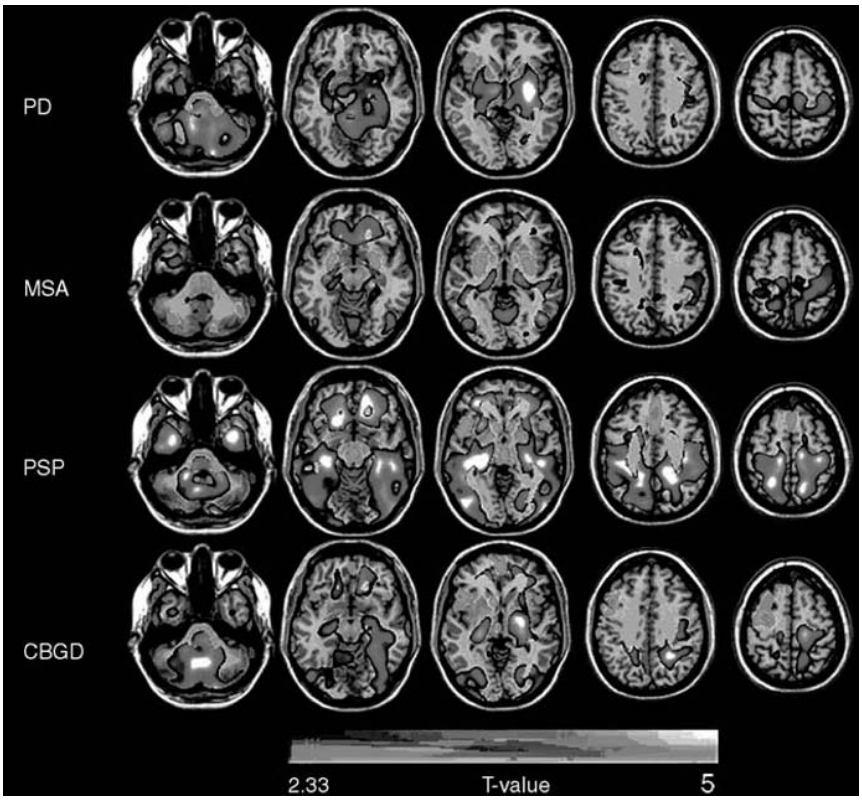

Figure 3 Templates of abnormal glucose metabolism in patients with PD, MSA, PSP, and CBGD identified by group analysis using SPM ($p < 0.01$). For image analysis, the hemispheres opposite the clinically more affected body sides appeared on the right. Reprinted from Eckert et al. (2005) FDG PET in the differential diagnosis of parkinsonian disorders. *NeuroImage* 26: 912–921. Copyright 2005, with permission from Elsevier.

referred to FDOPA PET because of diagnostic uncertainty had normal putamen radiotracer uptake. FDG PET was also conducted in a number of the same subjects at or near the time of dopaminergic imaging. PDRP expression was also normal in these subjects who had no evidence of dopaminergic deficit, that is, scans without evidence of dopaminergic deficit (SWEDD) on FDOPA PET. This suggested that the SWEDD patients were not likely to have classical PD. Indeed, these subjects did not progress at 1-year follow-up. They were found to have secondary nonprogressive forms of parkinsonism including drug-induced parkinsonism, vascular parkinsonism, dopa-responsive dystonia (DRD), and dystonic tremor. This illustrates that measurements of PDRP expression can be useful in differentiating PD from atypical parkinsonian variants, including secondary forms in which nigrostriatal dopaminergic terminals are relatively preserved.

Cerebral Perfusion Imaging

In most neurodegenerative disorders, regional cerebral blood flow and metabolism are coupled processes associated mainly with synaptic activity. We have found that PDRP expression measured off medication in cerebral perfusion images (e.g., ^{15}O-water PET, ^{99m}Tc-ethylene cysteinate dimes SPECT, arterial spin labeled [ASL] MRI, etc.) is highly correlated with network assessments in 'gold standard' FDG PET metabolic images. In a recent study, we found that the flow-metabolism couple was preserved during STN deep brain stimulation (DBS) treatment but was dissociated during levodopa administration. At the regional level, this 'uncoupling' related to treatment-mediated reductions in the putamen/GP and dorsal pons/midbrain and concurrent elevations in blood flow in these areas. Interestingly, patients with levodopa-induced dyskinesia and longer disease duration exhibited greater uncoupling at both the regional and network (PDRP) levels. The data suggest that levodopa gives rise to vasodilation in AADC-rich regions, resulting in a local oversupply of DA. For this reason, the results of cerebral perfusion studies in PD should be interpreted with caution, particularly in levodopa-treated patients.

The Role of Imaging in the Assessment of Therapy for PD

Reliable *in vivo* markers of neuronal activity are needed for the objective assessment of treatment outcome. Currently available clinical scales are relatively insensitive,

inherently variable, and potentially subjective if performed under unblinded conditions. By contrast, quantitative functional brain imaging markers may be suitable as outcome measures in trials of new symptomatic treatments for PD. Metabolic imaging biomarkers may also have a role in the objective assessment of disease modifying agents. In a recent study, rates of disease progression were assessed using FDG PET to measure longitudinal changes in PDRP expression, with ^{18}F-fluoropropyl-β-CIT to quantify DAT binding in the caudate and putamen as an index of presynaptic nigrostriatal dopaminergic dysfunction, and the motor UPDRS. We found that PDRP activity increased linearly over time, and was significantly elevated relative to healthy controls at baseline, 24 months, and 48 months. These longitudinal changes correlated with progressive declines in clinical ratings and in putamen DAT binding (**Figure 4**(**a**)). Though significant, these correlations were of modest size. This indicates that the clinical, dopaminergic, and metabolic biomarkers are not interchangeable and that each measure contributes unique information regarding disease progression.

Dopaminergic Medication

Metabolic imaging studies conducted on an off levodopa therapy have revealed localized reductions in the cerebellar vermis, putamen, globus pallidus, thalamus, and precentral gyrus. The changes observed in the activity of the PDRP network as a whole correlated significantly with clinical improvement in UPDRS motor ratings. Although not reaching statistical significance, the results of an FDG PET study with apomorphine showed similar metabolic reductions in the lenticular nucleus and thalamus, and in the occipital region. In animal models of PD, levodopa administration normalized preexisting elevations in pallidothalamic glucose utilization and reduced GPi firing rates. These findings, along with the PET results, support the notion that levodopa treatment reduces pathologically increased activity of excitatory projections to the GPi from STN.

Surgical Interventions

Surgical changes in regional glucose metabolism following GPi pallidotomy have been described in the ipsilateral motor cortex, lateral premotor, and dorsolateral prefrontal cortex – regions associated with volitional action and motor learning. Clinical improvement following this procedure correlated with reductions in the thalamic hypermetabolism and increases in lateral PMC metabolic activity. Similar regional findings were observed with GPi DBS. PDRP suppression was evident following both

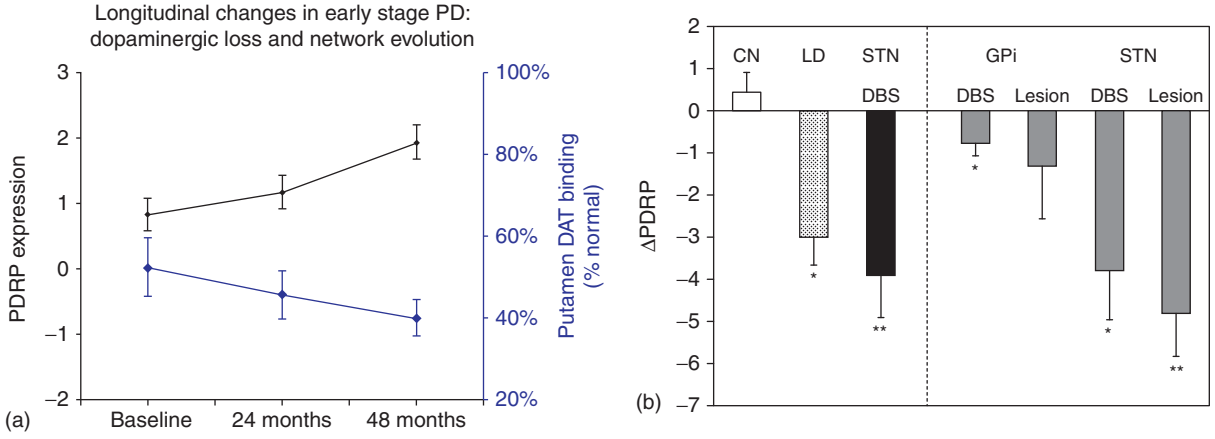

Figure 4 (a) *Top:* Mean expression of the PD-related metabolic covariance pattern (PDRP, see **Figure 2**) at baseline, and at the second (24 months) and third (36 months) time points as part of our longitudinal FDG PET study of early stage PD. PDRP values increased significantly over time ($p < 0.005$; repeated measures analysis of variance). *Bottom*: Mean putamen DAT binding measured by [^{18}F]-fluoropropyl βCIT PET in the same PD patients scanned longitudinally at the three time points. DAT binding was expressed as a percentage of the normal mean value for 15 age-matched control subjects. Unlike the longitudinal increases that occurred with PDRP expression, DAT binding declined over time ($p < 0.04$, reading a minimum of 30% normal for the putamen. Reprinted from Eckert T and Eidelberg D (2005) Neuroimaging and therapeutics is movement disorders. *NeuroRx* 2: 361–371. Copyright 2005, with permission from Elsevier and the American Society of Experimental Neuro therapeutics. (b) Bar graph illustrating treatment-mediated changes (±SE) in the expression of the PD-related metabolic covariance pattern (△PDRP). Difference in values from the levodopa infusion (LD; dotted), STN stimulation (DBS; black), and the test-retest control (CN; white) groups from the current study are presented in the left panel. These measures were compared to those computed on the basis of previous PET data (gray) from patient cohorts undergoing GPi and STN lesioning and stimulation. These comparison data are presented in the right panel. (△PDRP values were computed on a hemisphere-by-hemisphere basis for all treatment groups. For the unilateral surgical interventions, △PDRP reflects changes in network activity in the operated hemispheres. For the bilateral therapies, including levodopa infusion, PDRP changes were computed for each hemisphere and averaged. Asterisks represent p values with respect to the untreated condition (paired Student *t*-test). *$p < 0.05$, **$p < 0.01$ (paired *t*-test, ON versus OFF)). Modified reprint from *Brain* 129(Pt 10): 2667–2678. Copyright 2006, Oxford University Press.

GPi lesioning and DBS, with comparatively greater network modulation following the former intervention.

The metabolic effects of STN lesioning (subthalamotomy) were studied at 3 and 12 months following surgery. Compared to baseline, cerebral metabolism at 3 months following surgery was significantly reduced in the ipsilateral midbrain (larger than actual ablation site), GPi, ventral thalamus, and the pedunculopontine nucleus (PPN), regions in which metabolic activity has been shown to correlate with intraoperative recordings of STN firing rate. PDRP activity was reduced ipsilateral, but not contralateral to subthalamotomy, and remained stable at 12 months. These network changes correlated with improvement in limb bradykinesia and rigidity. The extent to which PDRP expression is reduced during stereotaxic surgery is dependent on the target and the mode of treatment (**Figure 4(b)**). Of note, RAC PET showed no change in striatal binding potential with STN stimulation, indicating that this intervention is unlikely to trigger endogenous DA release as its mode of action.

A recent Phase I study of unilateral subthalamic gene therapy for advanced PD utilized adeno-associated virus-glutamic acid decarboxylase (AAV-GAD) to convert the phenotype of STN projections to GPi/SN from glutamatergic (excitatory) to gabaergic (inhibitory). In this study, 12 subjects were scanned with FDG PET at baseline, and at 6 and 12 months following gene therapy. The data revealed a significant change in PDRP expression on the treated side, but not on the unoperated side. Changes in network activity correlated with improvement in concurrently measured clinical motor ratings. These results indicate the potential use of network quantification in the objective assessment of novel PD therapies. Moreover, imaging is likely to play a decisive role in determining the efficacy of other gene therapy strategies for movement disorders.

DA Cell Implantation

FDOPA PET has proved valuable in determining graft viability in the context of several blinded trials of embryonic nigral cell implantation. Although changes in FDOPA uptake at the graft site are only weekly correlated with clinical outcome following transplantation, this imaging approach has been critical in examining the basis for transplant-related dyskinesias. In five transplant recipients with this complication, FDOPA uptake was elevated in discrete regions of the putamen relative to their counterparts without dyskinesia. In addition to the posterodorsal zone of the putamen (in which a prominent reduction in uptake was present at baseline), the dyskinesia group also displayed a relative increase ventrally, in which preoperative dopaminergic input was relatively preserved. Further, technological development is likely to optimize DA cell implantation so as to prevent the occurrence of this undesirable complication of treatment. Future studies of stem cell implantation are likely to be carried out once these technical issues are satisfactorily addressed.

Cognitive Impairment in PD

Cognitive dysfunction in PD is a topic of great interest given its implications for patient quality of life. The underlying pathophysiology of PD dementia is thought to be the involvement of mesolimbic and mesocortical DA systems, Alzheimer-type pathology, cortical/limbic Lewy body deposition, and brain cholinergic dysfunction.

With FDG PET, we reported that neuropsychological performance in nondemented PD patients correlated with the expression of a distinct metabolic covariance pattern that was unrelated to the PDRP. This PD-related cognitive pattern (PDCP) is characterized by reduced metabolic activity in the prefrontal and parietal cortices with relative increases in dentate nuclei and cerebellar hemispheres (**Figure 5**). PDCP expression was found to correlate with impairment in memory and executive functioning in these patients, and unlike PDRP expression, it was not altered by the treatment of motor symptoms with either levodopa, STN DBS or STN AAV-GAD gene therapy.

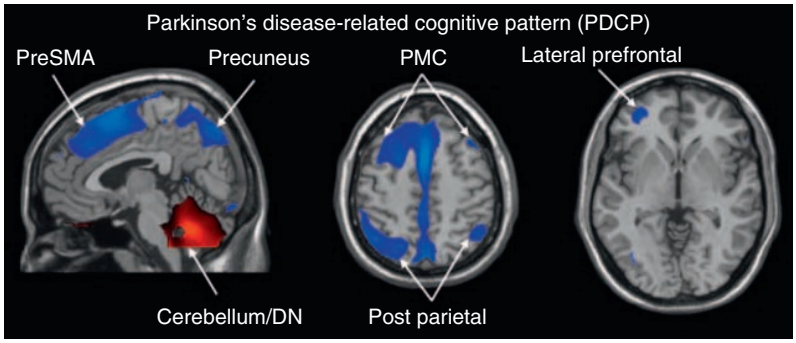

Figure 5 Parkinson's disease-related cognitive pattern (PDCP) characterized by hypometabolism of prefrontal cortex, rostral supplementary motor area (SMA), and superior parietal regions. Reprinted from Huang C, Mattis P, Tang C, Perrine K, Carbon M, Eidelberg D (2007) Metabolic brain networks associated with cognitive function in Parkinson's disease. *NeuroImage* 34: 714–723. Copyright 2007, with permission from Elsevier.

In a recent study, this pattern was found to be elevated in PD patients with clinically defined features of mild cognitive impairment (MCI) compared with patients of equivalent motoric severity who were cognitively intact. These findings suggest that the PDCP may be a useful biomarker of cognitive dysfunction at early stages of the disease.

Two novel radioligands developed for the clinical investigation of Alzheimer's disease (AD) have also provided insight into the mechanisms of cognitive dysfunction in PD. ^{18}FDDNP [2-(1-{6-[(2-[^{18}F]fluroethyl)(methyl) amino]-2-naphthyl}ethylidene)malononitrile] can be used to target neurofibrillary tangles and β-amyloid senile plaques. In a study of PD dementia with ^{11}C-PIB, there was evidence of prefrontal accumulation of radiotracer in the brainstem as compared to the cerebral cortex. Postmortem examination revealed ^{11}C-PIB uptake in Lewy bodies and in the neuromelanin of the substantia nigra in PD patients.

Other PET tracers to quantify brain acetylcholinesterase (AChE) activity (e.g., *N*-[^{11}C]-methylpiperidin-4-yl propionate (MP4P or PMP) or [^{11}C]-*N*-methylpiperidin-4-yl acetate (MP4A or AMP)) are also of interest. MP4P PET measures AChE activity in brain regions with low to moderate AChE activities such as cerebral cortex, thalamus, and cerebellum. Thalamic AChE reductions associated with relative preservation of AChE in cortex are a feature of PSP and MSA that may potentially be used for differential diagnosis in parkinsonism patients.

PET Imaging and Other Movement Disorders

Huntington's Disease

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder with pathological expansion of CAG/polyglutamine repeat that results in progressive impairments in behavior, motor function, and cognition. PET has provided important insights into understanding the pathological mechanism of HD. Decreased striatal D_2 receptor binding has consistently been demonstrated on RAC PET in HD patients and in presymptomatic HD (p-HD) gene carriers. A longitudinal study illustrated a progressive decrement of 6.3% per year. A negative correlation was found between age-normalized striatal D_2 receptor binding and CAG repeat length in both asymptomatic and symptomatic HD gene carriers. Network analysis of FDG PET scans from p-HD subjects and gene negative controls has indicated the presence of a significant reproducible disease-related spatial covariance pattern. This Huntington's disease-related metabolic pattern (HDRP; **Figure 6**) is characterized by covarying metabolic reductions in the caudate, putamen, and temporal cortex, with concurrent metabolic increases in the occipital lobe. Changes in HDRP expression with disease progression have been assessed in a longitudinal FDG PET study of 12 p-HD subjects. HDRP activity was found to increase between baseline and 18 months follow-up ($p < 0.003$), but interestingly declined at 44 months ($p < 0.04$). Striatal metabolism was abnormally low at all time points ($p < 0.005$). By contrast, thalamic metabolism was elevated at baseline ($p < 0.01$), but fell to subnormal levels in the p-HD carriers who subsequently developed hyperkinetic symptoms. Regional thalamic metabolic activity (and HDRP expression) may represent a compensatory mechanism in p-HD, which appears to fail as symptoms emerge.

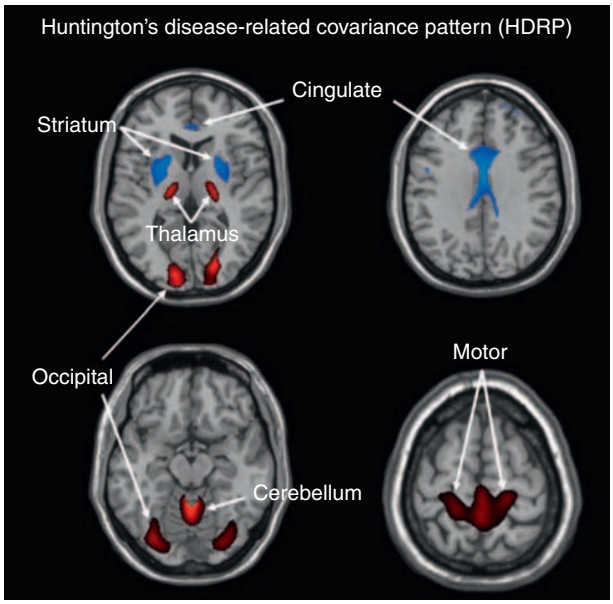

Figure 6 Huntington's disease-related spatial covariance pattern (HDRP) characterized by relative metabolic decreases in the striatum and cingulate cortex, associated with relative increases in the ventral thalamus, motor cortex, and occipital lobe. Reprinted from *Brain* 130 (Pt 11): 2858–2867. Copyright 2007, with permission from Oxford University Press.

Dystonia

Primary torsion dystonia is a chronic movement disorder manifested clinically by focal or generalized sustained muscle contractions and postures. FDG PET studies have indicated that *DYT1* gene carriers with and without clinical manifestations express an abnormal reproducible metabolic pattern characterized by covarying increases in the posterior putamen/globus pallidus, cerebellum, and supplementary motor area (SMA) (**Figure 7**). Indeed, elevated expression of this torsion dystonia-related pattern (TDRP) has been shown to persist following the suppression of involuntary dystonic movements by sleep induction. Abnormal TDRP expression is not specific for a particular primary dystonia genotype. It is present in carriers of the *DYT1* and *DYT6* mutations and in patients with blepharospasm. Despite these similarities at the network level, distinct differences in regional metabolism exist to distinguish dystonia subtypes based on genotype

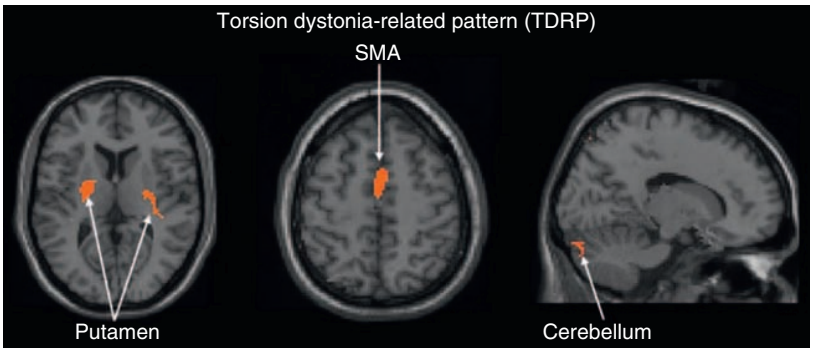

Figure 7 Torsion dystonia-related spatial covariance pattern (TDRP) characterized by relative metabolic increases in the putamen, extending into the globus pallidus (GP), the SMA, and the cerebellum. Reprinted from *Annuals of Neurology* 52: 853–856. Copyright 2002. Wiley-Liss, Inc.

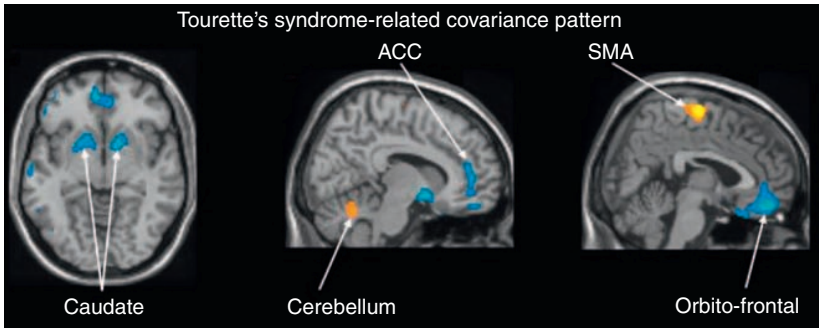

Figure 8 Tourette's syndrome-related pattern characterized by relative metabolic decreases in the caudate, anterior cingulate cortex (ACC), and orbitofrontal, associated with relative increases in the cerebellum and SMA. Courtesy of Dr. A. Feigin.

and phenotype. Interestingly, the TDRP network is not expressed in DRD, which is associated with a distinct spatial covariance pattern that is not expressed in *DYT1* or *DYT6* gene carriers. In spite of some clinical similarities with PD, that is, the presence of parkinsonian features and a marked response to levodopa, DRD patients do not express the PDRP network, in keeping with their intact presynaptic dopaminergic function. Striatal D_2 binding reductions are observed in both manifesting and nonmanifesting *DYT1* gene carriers, suggesting that this phenomenon is a trait feature of the *DYT1* genotype. By contrast, striatal D_2 binding in DRD is elevated in both nonmanifesting and manifesting subjects and was not affected by levodopa treatment.

Tourette's Syndrome

Gilles de la Tourette's syndrome (TS) is a chronic neurologic condition characterized by multiple motor and vocal tics of varying intensity, associated with behavioral disturbances. Network analysis has been applied to FDG PET data from TS patients revealing two distinct spatial covariance patterns in this disorder. The first metabolic pattern was associated with covarying increases in the lateral frontal cortex and paracentral regions, consistent with the presence of abnormal movements. A second TS covariance pattern was associated with metabolic reductions in the striatum, thalamus, and temporal lobe. The latter pattern correlated with the severity of TS symptoms, and relates the disorder to limbic CSPTC loops. A more recent network analysis using a voxel-based spatial covariance approach disclosed a similar metabolic pattern (**Figure 8**) in a subsequent population of TS patients. Given the absence of a specific neurochemical biomarker for TS, metabolic networks like these may prove useful as an adjunct to clinical evaluation in the assessment of new TS therapies.

Tremor Disorders

The pathophysiology of essential tremor (ET) is still poorly understood. Currently, ET assessment and diagnosis are established solely by clinical evaluation. No validated biomarkers are in use for the evaluation of this disorder. Striatal dopaminergic function in ET patients has been repeatedly demonstrated to be normal. Nonetheless, activation PET studies have provided valuable insights into the functional mechanism of ET and other tremor disorders. PET studies with ^{15}O-labeled water

($H_2^{15}O$) have revealed resting increases in cerebellar blood flow in ET, with abnormal red nucleus activation during arm extension. Cerebellar hyperactivation in ET can be reversed by ethanol ingestion with concurrent reduction of tremor. Interestingly, recent ECD-SPECT studies of ET patients and healthy controls conducted at rest have revealed that cerebellar–thalamocortical tremor-related networks identified in tremulous PD patients are similarly expressed in ET. That said, PDRP expression was elevated in the PD tremor cohort, but not in their ET counterparts.

High-frequency DBS of the ventral intermediate (Vim) nucleus of the thalamus can also alleviate tremor symptoms in ET patients. $H_2^{15}O$ PET has demonstrated increased cerebral blood flow during Vim stimulation and bilaterally in the anterior cingulate cortex (ACC). This was associated with decreased perfusion in the contralateral occipital cortex and ipsilateral inferior frontal cortex. Another $H_2^{15}O$ PET study of Vim DBS for ET revealed increased perfusion at the local surgical site and in the SMA, ipsilateral to stimulation.

Palatal tremor is thought to relate to the central inferior olivary nucleus, with hypersynchronous firing of dentatorubromedullary connections. FDG PET has demonstrated that medullary metabolism is increased in both primary and symptomatic palatal tremor patients.

Conclusion

Modern network-based approaches to functional imaging data have opened up new possibilities for the clinical investigation of PD and other movement disorders. In particular, these methods have allowed for high throughput image analysis to facilitate multicenter clinical trials of new therapies using network imaging biomarkers. Additionally, new radiotracers have been developed to quantify specific, localized neurochemical deficits in neurological disease. A combined *in vivo* imaging approach utilizing localized neurochemical assessments and whole-brain network measurements will help elucidate the abnormal structure–function relationships that underlie the various movement disorders. Quantifying changes in these relationships with therapy is likely to facilitate the development of new treatments for these disorders.

Acknowledgments

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See also: Basal Ganglia, Functional Organization; Choreiform Disorders; Deep Brain stimulation; Dementia, Movement Disorders; Dopamine; Dopamine Transporter: Aging and Parkinson's Disease; Dystonia; DYT1; DYT6, Mixed Phenotype Primary Dystonia; Generalized Primary Torsion Dystonia; Huntington's Disease; Levodopa; Movement Disorders: Overview; Neuroimaging, Parkinson's Disease; Pallidotomy for Parkinson's Disease; PARK1, Alpha Synuclein; Parkinson's Disease: Definition, Diagnosis, and Management; SPECT Imaging in Movement Disorders; Substantia Nigra; Subthalamic Nucleus; Thalamotomy; Tourette Syndrome; Tremor; Tremor, Essential (Syndromes).

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Pisa Syndrome

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Glossary

Cholinesterase inhibitors – Are drugs that block the activity of the cerebral enzyme cholinesterase. Thus, more acetylcholine is available. They are used to treat early stages of Alzheimer and Lewy body dementia.

Dystonia – A neurologic syndrome characterized by sustained muscle contractions, producing twisting and repetitive movements or abnormal postures, or positions.

Neuroleptics – Medications used to treat psychosis and blocking dopamine D2-like receptors. The older or typical neuroleptics show more Parkinsonian side effects than the newer, atypical neuroleptics.

Definition and History

Pisa syndrome (PS) is a dystonic lateroflexion of the trunk, or lean to the side, or pleurothotonus. The term was coined by Ekbom and colleagues in 1972. The authors described PS as a medication side effect in three elderly women taking butyrophenones. Thereafter, PS was mainly described as a side effect of typical and atypical neuroleptics, and in patients taking cholinesterase inhibitors. There has been some debate whether PS can also occur as an idiopathic syndrome and whether there may be some overlapping with scoliosis or lateral flexion frequently encountered in Parkinson's disease.

Pathophysiology

The PS is considered to be mostly a medication-induced truncal dystonia. The debate continues whether this dystonia has to be considered an acute or tardive dystonia. According to the most tempting hypothesis, PS is due to an imbalance of the dopaminergic/cholinergic system, with relative excess of cholinergic transmission and relative decrease of the dopaminergic transmission. Theoretically, this imbalance can be caused by the addition or the discontinuation of neuroleptics (typical or atypical), cholinesterase inhibitors, or dopaminergic drugs. Practically, pharmacological dopaminergic blockade and degenerative dopamine depletion seem to be the most frequent cause in predisposed patients, who are no longer able to compensate for the presupposed neurochemical imbalance. These are mainly elderly female patients with organic brain disorders (see below). Some authors have also hypothesized that dopaminergic hypersensitivity induced by neuroleptic treatment, or noradrenergic or serotoninergic dysfunction plays a role. Interestingly, a myopathic cause has never been proposed, although the PS has some similarities with camptocormia, in which such a cause has been proven in numerous cases.

Epidemiology and Risk Factors

There are no epidemiological data on the incidence of PS in the general population, but there have been studies in the psychiatric population under *neuroleptic treatment.* Stübner and colleagues studied the prevalence of PS in a population of 45 000 psychiatric patients, monitored by a multicenter drug safety surveillance program for 5 years. They identified 20 episodes of PS in 17 patients. Thus, the prevalence was 0.04%. However, Yassa and colleagues reported a prevalence rate of 8% in high risk psychogeriatric patients; in their carefully observed cohort of 133 patients, 11 developed PS in 2–120 days (mean 26 days) after neuroleptics were started. Several risk factors for PS have been identified: previous treatment with classical neuroleptics, combined pharmacologic treatment, previous episodes of tardive dyskinesia, female gender, old age, and the presence of an organic brain disorder, including marked brain atrophy. In one study, abnormal findings on brain CT were found in half of the patients. Given these risk factors, PS can even occur in patients taking atypical neuroleptics.

More recently, PS has been reported in demented patients taking *cholinesterase inhibitors*, such as donepezil, rivastigmine, or galantamine. Several patients were under concomitant treatment with atypical neuroleptics; other putative risk factors in this population are unknown. There are no epidemiological data, but the syndrome seems to be less frequent than in patients taking neuroleptics. Vanacore and colleagues have estimated that there may be an incidence of two cases per 10 000 patients per year. There are a few case reports on PS in patients taking metoclopramide, tricyclic antidepressants, selective serotonin (5-HT) reuptake inhibitors (SSRIs), valproate acid, or in patients being treated by pallidotomy.

Idiopathic PS and PS occurring in *neurodegenerative disease,* without drug induction, have also been described, but the differential diagnosis is challenging. PS has been

reported in patients with Parkinson's disease and multiple system atrophy (MSA). As proposed by Duvoisin and Marsden in 1975, the laterality of the basal ganglia abnormalities (i.e., asymmetric putaminal lesions) may be the main contributive factor, and a partial overlap with the common but less pronounced scoliosis in Parkinson's disease has to be discussed. Finally, PS can be the leading feature in axial predominant adult-onset *primary dystonia.*

Clinical Features

Bending to one side of the upper thorax, the neck, and the head are the main features of the PS syndrome. Additionally, the patient may show some rotation or twisting of the trunk to the same side. The syndrome, although permanent, often aggravates during walking or sitting, and diminishes in the supine position. It can be momentarily corrected by passive mobilization of the trunk, although the patient goes back to the initial trunk position after this maneuver. There are no other dystonic features, with the exception of a possible forward inclination (camptocormia). Interestingly, the patient is often unaware of the abnormal position and is unlikely to complain of it. The statuette by Richer (at the end of the nineteenth century) from Hôpital Salpétrière, Paris is a remarkable illustration of combined PS and camptocormia in an elderly patient (**Figure 1**).

Differential Diagnosis

The scoliosis or lateral flexion, primarily occurring in Parkinson's disease, is related to the laterality of the disease and worsens in an insidious way. In most cases, the concavity is contralateral to the side initially and most severely affected. When this scoliosis develops more rapidly and vigorously, it may be difficult to differentiate from the PS, especially if the patient is also taking dopaminergic drugs that can induce an axial dystonia of the PS type. However, it is also possible that such a PS-like dystonia worsens in the OFF period and improves after levodopa, thus reflecting a medication-sensitive motor fluctuation. In patients without Parkinson's disease, other differential diagnoses such as vertebral diseases (fractures and osteoporosis), conversion reaction, or malingering should be ruled out easily (**Table 1**).

Diagnostic Work-up

In most cases, a precise history of the present and past medications, a withdrawal trial, if needed, and in rare cases, complementary radiological exams of the brain and spine, should be sufficient to make the diagnosis.

Management and Prognosis

In medication-induced PS, reduction in dose or discontinuation of the offending antipsychotic drug or cholinesterase inhibitor is the first-line treatment. Importantly, the complete resolution of the PS can occur within 24 h but may also take weeks or months. In some patients, switching from a typical to an atypical neuroleptic or from one atypical to another atypical neuroleptic may also be

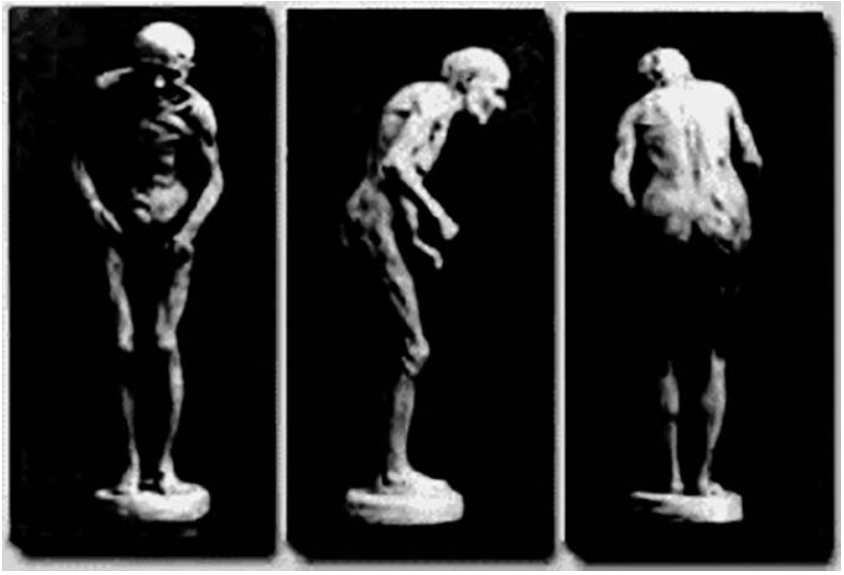

Figure 1 Reproduction of a photograph showing the 'Statuette pathologique' by Paul Richer (1895). The patient with Parkinson's disease shows a mild inclination of the trunk to the left and a more marked anteroflexion of the trunk (camptocormia). Reproduced from Hobbelen JSM, Koopmans RTCM, Verhey FRJ, Habraken KM, and de Bie RA (2008) Diagnosing paratonia in the demented elderly: Reliability and Validity of the Paratonia Assessment Instrument (PAI). *International Psychogeriatrics* 20: 840–852.

Table 1 Etiology of the Pisa syndrome

Medication-induced dystonia
Neuroleptics: typical neuroleptics more frequently than atypical neuroleptics; combination therapy more frequent than monotherapy; especially in (female) psychogeriatric patients
Cholinesterase inhibitors: rare
Antiemetics, valproate acid, selective serotonin (5-HT) reuptake inhibitors (SSRIs), tricyclic antidepressants: very rare
Dopaminergic medication in Parkinson's disease: very rare
Primary dystonia
Sporadic adult-onset axial dystonia: very rare
Within a neurodegenerative disease, but without induction by medications
Parkinson's disease, multiple system atrophy: possible overlapping with disease-inherent scoliosis, contralateral to predominantly affected side

helpful. According to small series, ~40% of the patients show an excellent therapeutic response to anticholinergics. Some of these patients, already on a small dose of triheyphenidyl (6 mg), showed this favorable response only when the dose was doubled. However, the cognitive side effects of these medications may not be tolerated by elderly patients.

See also: Camptocormia.

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Postpump Chorea

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Glossary

Chorea – Abnormal involuntary movements that are brief, random, usually distal, and without purpose.
Neuroleptics – Agents which block dopamine receptors.
Sydenham's chorea – Chorea resulting from autoimmune process triggered by β-hemolytic *Streptococcus*.

Definition and History

'Chorea' (derived from the Latin choreus meaning 'dance') refers to abnormal involuntary movements that are brief, random, usually distal, and without purpose. Postpump chorea (PC) is the term coined to describe chorea with onset within 2 weeks following cardiopulmonary bypass. The first cases were described in 1961 shortly after the introduction of the latter procedure under deep hypothermia to correct congenital heart disease. With

recognition of risk factors and improvement of technique, there seems to be a sharp decline in the number of cases of PC in the last years.

Etiology and Pathogenesis

Case–control studies have defined the existence of an association between PC with deep hypothermia, circulatory arrest, longer duration of the former two, age at surgery beyond early infancy, and cyanotic heart disease with systemic to pulmonary collaterals. The lack of vascular lesions on imaging studies suggests that there is a basal ganglia change related either to microemboli or a biochemical factor. It is presumed that these factors lead to hypoactivity of the subthalamic nucleus, which is well known to occur in patients with chorea, particularly of vascular cause.

Epidemiology

There are no recent epidemiologic investigations of PC. One study from a tertiary center active in the surgical treatment of congenital heart disease showed that this condition occurred in 1.2% of 668 children who underwent open cardiac surgery from 1983 to 1993. Based on the rarity of recent reports of PC in the literature, one may cautiously suggest that there is a decline in the incidence of this condition.

Clinical Features and Diagnostic Criteria

The typical features of PC are generalized chorea with onset 3–12 days following surgery. Other clinical features described in these patients are decreased muscle tone and cognitive decline. Age of onset is an important factor predictive of severity of PC: the older the patient, the more severe the chorea. Currently, there are no diagnostic criteria of PC. Diagnosis is based on the combination of the typical clinical features combined with the lack of alternative cause.

Differential Diagnosis

The close temporal relationship between onset of chorea and cardiopulmonary bypass with deep hypothermia is very specific of PC and renders unlikely diagnostic confusion with other conditions. Nevertheless, the most important differential diagnosis of PC is Sydenham's chorea (SC), the commonest cause of acute chorea in children where at least 60% of patients have cardiac lesions. In contrast to patients with PC, subjects with SC often have clinical and/or laboratory evidence of previous *Streptococcus* infection as well as of other rheumatic fever signs. Vascular lesions, which may also be a consequence of congenital heart disease, can cause chorea in children and are readily diagnosed with neuroimaging methods. Other alternative causes to be ruled out are systemic lupus erythematosus, primary antiphospholipid antibody syndrome, infections, acute disseminated encephalomyelitis, and exposure to drugs.

Diagnostic Work-up

Patients with de novo chorea whose onset is temporally related to cardiac surgery should undergo complete neurologic examination and diagnostic testing to investigate the number of causes of this hyperkinesia. Those are the tests helpful in the diagnostic workup of patients suspected to have PC: tests of acute phase reactants such as erythrocyte sedimentation rate, C-reactive protein, leukocytosis, rheumatoid factor, mucoproteins, protein electrophoresis, supporting evidence of preceding streptococcal infection (increased antistreptolysin-O, antiDNAse-B, or other antistreptococcal antibodies; positive throat culture for group A *Streptococcus*; recent scarlet fever); serologic studies for systemic lupus erythematosus and primary antiphospholipid antibody syndrome must be ordered to rule out these conditions; and neuroimaging, particularly magnetic resonance imaging, helps to define the vascular nature of chorea or if it is related to acute disseminated encephalomyelitis; spinal fluid analysis should be done if there is a possibility of central nervous system infection.

Management

Neuroleptics are the first choice of the pharmacological management of PC. Most of the experience refers to the use of haloperidol although any agent with powerful D2 receptor blocking action is expected to be useful in the symptomatic management of chorea.

Prognosis

The current evidence supports the notion that the long-term prognosis of PC is rather poor. In one series of eight patients, for example, five subjects had persistent chorea and one of them died. In another study there was a clear distinction between those eight patients with onset at earlier age (median 4.3 months), all of whom recovered fully, from 11 others, older (median age 16.8 months). Among the latter, four died and only one of the survivors

had a complete neurologic recovery. Other factors of poor prognosis are cyanotic heart disease and longer duration of the hypothermia during cardiac arrest.

See also: Chorea–acanthocytosis; Chorea Gravidarum; Choreiform Disorders; Subthalamic Nucleus; Sydenham's Chorea.

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Postural Tremor

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Glossary

Corticomuscular coherence – Electrical correlation between cortical brain activity and neuromuscular activity.
Deep brain stimulation – The surgical implantation of electrodes to specific targets deep within the brain as a treatment for various brain disorders.
Magnetoencephalography – A brain imaging technique used to measure the magnetic fields produced by electrical activity.
Postural tremor – Involuntary rhythmic oscillatory movement of a body part during maintenance of a particular posture.
Sensorimotor loop oscillations – Cyclical neuronal activity involving repetitive electrical impulse transmission between the sensory and motor systems of the brain through feedback loops.
Stereotactic thalamotomy – A minimally invasive surgical procedure using a three-dimensional coordinates system to lesion the thalamus used in the treatment of essential tremor.
Transcranial magnetic stimulation (TMS) – A noninvasive method to excite neurons in the brain using a strong magnet held outside the head.

Definition and Features

Postural tremor describes involuntary rhythmic oscillatory movement of a body part during maintenance of a particular posture. The regularity results from equal contraction of reciprocally innervated antagonist muscles. Variable frequency, amplitude, and direction can depend upon the location of involved muscles. Although tremor can simultaneously affect multiple body parts, physiologic evidence suggests that affected limbs on opposite sides demonstrate independent tremors.

Mechanisms

Postural tremor may be either pathologic or physiologic. Similar underlying mechanisms occur regardless of etiology and may be classified broadly into two groups:

1. mechanical-reflex or sensorimotor loop oscillations between the basal ganglia, thalamus, and cortex;
2. oscillatory central networks mostly involving cerebellar outflow pathways.

Awake mapping of the ventral thalamus prior to thalamotomy has been used to analyze neuronal activity. When postural tremor is present, more active neurons are typically observed in the ventral intermediate (VIM) thalamic nucleus receiving cerebellar fibers. Less neuronal activity is measured in the mostly sensory ventral caudal (VC) nucleus and the ventral oral posterior (VOP) nucleus receiving pallidal fibers. Advances in magnetoencephalography have lead to quantification and localization of these oscillatory networks with improved temporal and spatial accuracy.

Modifying Factors

Tremor parameters may be affected by internal perturbations, muscle-load mechanics, and neural feedback. The effects of internal perturbations often seem random and difficult to investigate but include cardiac rhythms and other natural postural fluctuations. The use of weighted

tools can often dampen the amplitude of disabling postural limb tremor, although the benefit appears less robust at greater amplitudes. Increasing muscle load in patients with very low amplitude postural tremor may actually increase tremor frequency. Although weights frequently dampen tremor frequency in patients with enhanced physiologic tremor, this change is not as obvious in essential tremor (ET) or Parkinson's disease (PD). Wrist splints used in conditions such as carpal tunnel syndrome also appear to diminish any significant effect of weight bearing on postural tremor. As younger adults are more likely to demonstrate healthy fluctuations in heart rate, pulsatile hormonal release, and variable electroencephalographic potentials, increasing age may be related to tremor due to progressive loss of neurophysiologic variability and therefore less adaptability to stress. Reduced motor adaptability may be associated with increased demand on task-specific motor output reorganization.

Measurement

One way to measure neural feedback from the neuromuscular system is to link cortical activity with electromyographic activity. These studies of corticomuscular coherence are based upon the observation that tremor amplitude increases proportionally with the square of electromyographic activity as related by a power function. Accelerometry can also measure the acceleration of a moving body part (mass) and its related force according to Newton's second law: [Force = mass × acceleration]. Because postural tremor by definition occurs with an affected body part maintained against gravity, the role of gravitational artifact should be considered particularly at lower tremor frequencies where results are more likely affected. Velocity time series can also be helpful in discriminating different types of postural tremor.

Causes

Enhanced Physiologic Tremor

An 8–12 Hz tremor is considered normal with the hands extended forward. The frequency often slows in people over 50 years old. Other body parts may have frequencies as slow as 6.5 Hz. Exercise, anxiety, stress, fatigue, and alcohol withdrawal can all increase the amplitude of physiologic tremor.

Essential Tremor

Essential tremor (ET) represents the most common pathologic cause of postural tremor. Although postural limb tremor is most frequent, postural tremor of the head, vocal apparatus, and trunk also occur. Voice tremor includes postural and/or kinetic tremor affecting muscles of the vocal cords, or transmitting from head or neck muscles.

Parkinsonism

While classic PD commonly presents with rest tremor, some patients have mild postural limb tremor for decades before other parkinsonian features appear. Postural tremor in PD may also indicate a genetic or shared hereditary mechanism; in one study, 70% of twins with postural or kinetic tremor had a twin with PD or were diagnosed themselves. Asymmetric postural tremor may be an early sign of unsuspected PD; one published review of 13 patients initially diagnosed with ET with a positive family history and alcohol sensitivity eventually met PD criteria.

Low amplitude postural tremor in PD may be due to multiple mechanisms as evidenced in one study by corticomuscular coherence at frequencies of 12–18 Hz, peaks in accelerometer frequency at 5–12 Hz unchanged with weight bearing, and peaks in accelerometer frequency at 5–8 Hz that shift with weight bearing. Although physiologic tremor in young and older people typically does not alter postural stance, PD patients with amplified postural tremor may have greater excursions from their center of gravity that might affect postural stability.

The term *benign tremulous parkinsonism* describes a group of patients who typically present with stable rest tremor and only mild progression of other parkinsonian features over at least 8–10 years. Over 80% of these patients have moderate to marked postural tremor and most do not respond as effectively to levodopa as classic PD patients. Dopamine agonists are often less effective than levodopa in treating PD postural tremor compared to rest tremor of the arms, head, or legs.

The term *'reemergent tremor'* describes postural limb tremor that resembles rest tremor in frequency but appears or 'reemerges' only after latency. This tremor typically responds to levodopa thereby suggesting that reemergent tremor and rest tremor have a similar pathophysiology. Quantification of hand and finger rest and postural tremor in PD patients showed similar characteristics in both tremor types suggesting that underlying neural mechanisms remain active despite postural change. Another study using a displacement laser transducer on the index finger found no significant difference in amplitude fluctuation, frequency dispersion, harmonic index, or proportional power between subclinical rest and postural tremor. When postural tremor without latency is observed in PD patients, the possibility of coexistent ET should be considered.

Although rest tremor is typically absent in vascular parkinsonism, postural limb tremor occasionally develops after one or more lesions in the basal ganglia, thalamus, or connecting pathways. Postural tremor is relatively infrequent in parkinson-plus syndromes possibly due to

extensive multisystem degeneration although some patients with progressive supranuclear palsy (PSP) can present with postural arm tremor with or without orthostatic tremor.

Axial Postural Tremor

Axial postural tremor refers to full-body oscillations in the standing position. This tremor can be distinguished from primary orthostatic tremor (14–16 Hz) by its typically lower frequency (8–12 Hz). Axial postural tremor may occur alone or in combination with palatal tremor and the frequent description of discrete cerebellar lesions in both axial postural and palatal tremor implicates cerebellar outflow pathways as the most likely sites of pathology.

Focal Lesions

Traumatic injury, brain tumors, abscesses, arteriovenous malformations, and other focal lesions that disrupt connections between the thalamus, cerebellum, basal ganglia, and cortex are capable of producing postural tremor.

Demyelinating and Autoimmune Disease

Multiple sclerosis (MS) and other autoimmune conditions can cause progressive destruction of cortical, subcortical, brainstem, and spinal cord white matter. Many patients with one or more lesions to central pathways involved in tremor develop rest or postural tremor. In one study, proximal and distal postural tremor was noted in 88% of MS patients that had tremor. Antiphospholipid antibody syndrome can present with movement disorders including tremor although chorea is a more common finding.

Neurodegenerative Ataxias and Dystonia

The heterogeneous clinical presentation of spinocerebellar atrophy type 2 (SCA2) yields many patients with postural tremor alone or parkinsonism responsive to levodopa. Despite phenomenological overlap between ET and SCAs, one study of 177 patients diagnosed with ET found only one patient (0.5%) with positive genetic evidence of SCA3 and no patients with SCA2. Children and young adults with SCA27 have a fibroblast growth factor 14 gene mutation and may have postural tremor, progressive ataxia and dyskinesia. More than 30% of Friedreich ataxia patients have postural tremor. Generalized and focal dystonia patients can have irregular, coarse head, or limb postural tremor. Wilson's disease patients may have postural hand tremor and dystonia along with behavioral changes and psychosis. A common presentation of Fragile X tremor ataxia syndrome (FXTAS) is that of a man between 40- and 60-year old with postural tremor, ataxia, and gait instability while his daughter may have premature ovarian failure and his grandson may have mental retardation.

Neuromuscular Disorders

Peripheral neurological conditions can present with postural tremor. In one study, six of seven patients with hereditary sensorimotor neuropathy (HSMN) had postural tremor. Roussy–Lévy syndrome is a dominantly inherited neuropathy that can present with gait ataxia, pes cavus, areflexia, and postural tremor but an otherwise good prognosis. X-linked bulbospinal neuronopathy (Kennedy disease) is a polyglutamine disorder characterized by slowly progressive bulbar and proximal limb weakness, muscle atrophy, fasciculations, gynecomastia, and postural tremor. Postural tremor can also be seen in other acquired causes of neuropathy including diabetes, porphyria, uremia, and immunoglobulin M paraproteinemias.

Drug-induced Postural Tremor

Several sympathomimetic drugs associated with increased noradrenergic activity tend to worsen physiologic and pathologic postural tremor. These include stimulants such as methylphenidate and amphetamines and β-adrenergic agonists such as albuterol and terbutaline. Similar exacerbation of tremor can be seen with methylxanthine derivatives such as caffeine and theophylline, which act on adenosine receptors although the clinical extent of this has been debated. The immunosuppressant drug cyclosporine can cause tremor in transplant patients.

Many anticonvulsant and psychotropic medications commonly cause postural tremor. Lithium may worsen postural tremor in more than half of patients taking normal therapeutic doses. Postural tremor is more commonly noted in patients receiving conventional valproic acid compared to a continuous release form despite equivalent dosing and plasma concentrations. In one study, of 201 epilepsy patients treated with valproate, 45% had postural tremor. Selective serotonin reuptake inhibitors are associated with dose-dependent tremor in 4–11% depending on the patient population investigated. Neuroleptic drugs are known for symmetric rest tremor but parkinsonian postural tremor can also occur. One randomized, placebo-controlled trial of amantadine in ET patients found 6 of 16 patients taking the drug had increased postural tremor.

Metabolic and Toxic Disorders

Hypoglycemia frequently exacerbates tremor. Thyrotoxicosis should be suspected in patients with postural tremor associated with nervousness, rapid heartbeat, heat intolerance, fatigue or weight loss or evidence of a goiter, exophthalmos, thinning hair, or smooth skin.

Hepatic encephalopathy patients develop postural tremor due to pathologic disruption of corticomuscular coherence and thalamocortical loop synchronization.

Cyclosporine causes tremor more often in liver (55%) than cardiac (31%) or kidney (21%) transplant patients.

While manufacturing prosthetic dental appliances, dental technicians may be exposed to numerous toxic solvents like *n-hexane* and heavy metals such as mercury, iron, chromium, cobalt, and nickel. One study of 14 dental technicians found four with postural tremor and one with parkinsonism. Workers with manganese toxicity often develop persistent postural tremor for 12 months after serum levels normalize. High amplitude postural hand tremor occurs with chronic paint sniffing along with kinetic hand tremor, mild dysmetria, dysdiadochokinesia, and positional nystagmus.

Psychogenic Tremor

Psychogenic tremor may present with a complex combination of rest, postural, or kinetic tremors. Distinguishing features often include distractibility with complex volitional movements, suggestibility and inconsistent frequency, amplitude and direction.

Treatments

Medications

Postural tremor due to pathologic conditions such as autoimmune or thyroid disease is most likely to respond to successful treatment of the underlying disorder. Treatment of drug-induced tremor usually begins with discontinuation of the provoking drug after considering the risks and benefits. If possible, an offending drug may be switched to a different class of medication that is not associated with tremor. Enhanced physiologic tremor patients frequently improve with various β-blockers. ET postural limb tremor often responds to propranolol, other β-blockers or primidone. Other options to consider include topiramate, benzodiazepines, gabapentin, and clozapine. While many with ET experience tremor resolution with alcohol, withdrawal may cause rebound tremor. Numerous medications have been used individually but larger trials are needed to determine efficacy. Head and voice tremor in ET are often resistant to medication. Axial postural tremor has been reported to respond to topiramate.

Botulinum Toxin Injections

A small randomized, double-blinded placebo-controlled trial of botulinum toxin type A injections for hand tremor in 25 patients with ET found no significant improvement on functional rating scales. A larger multicenter randomized, double-masked controlled trial of botulinum toxin type A injections in 133 patients with ET found evidence of significant improvement in postural tremor but not kinetic tremor at both low and high doses at 4 and 16 weeks follow-up.

Stereotactic Thalamotomy

Thalamotomy and similar surgeries can control ET postural tremor but this procedure has largely been replaced by deep brain stimulation (DBS) in order to circumvent permanent tissue destruction. Patients with MS who receive thalamotomy for postural tremor may initially experience improvement, but progressive demyelination can reduce effectiveness at long-term follow-up.

Deep Brain Stimulation

DBS of the thalamic ventral intermediate nucleus (VIM) can safely and effectively treat postural tremor in ET with greater functional improvement over patients who received thalamotomy. High amplitude motor evoked potentials from the motor cortex noted on transcranial magnetic stimulation (TMS) might indicate that VIM DBS activates rather than inhibits the target area. A nearly linear response between stimulation frequencies and tremor acceleration is noted between 45 and 100 Hz with graded benefit rather than all-or-nothing improvement. Maximal benefit is typically achieved at stimulation frequencies of 100–130 Hz. Using higher frequencies likely only shortens pulse generator battery life with little or no additional tremor improvement.

Subthalamic nucleus (STN) DBS is used for rest and postural tremor in PD. Patients with postural tremor who undergo STN-DBS often have reduced amplitude and increased frequency, suggesting the importance of STN in PD postural tremor pathogenesis. This unique frequency increase can improve patient function when compared to using medications alone. One SCA2 patient with rapid-onset disabling postural tremor had markedly improved function with STN-DBS. A recent small study of subthalamic area DBS shows greater tremor improvement over ventrolateral thalamic DBS. Another small study of bilateral caudal zona incerta DBS in MS saw postural tremor reduced by almost 60%.

Repetitive Transcranial Magnetic Stimulation (rTMS)

Although not widely used, postural cortical tremor has been reported to improve with 1 Hz rTMS over the premotor cortex but similar stimulation of primary motor cortex is ineffective.

See also: Botulinum Toxin; Cortical Tremor; Deep Brain stimulation; Essential Tremor: Animal Models; Harmaline Tremor Model; Primary Orthostatic Tremor; Rest Tremor; rTMS; Thalamotomy; Tremor; Tremor, Essential (Syndromes); Tremor, Essential: Genetics; Tremor, Holmes; Tremor: Drug-induced.

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http://www.ninds.nih.gov/disorders/tremor/detail_tremor.htm – National Institute of Neurological Disorders and Stroke: Tremor Fact Sheet.

http://www.tremoraction.org/ – Tremor Action Network.

http://www.wemove.org/ – WE MOVE (Worldwide Education & Awareness for Movement Disorders).

Press-while-licking Task

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Glossary

6-Hydroxydopamine – A neurotoxin that, when administered into the brain, produces selective degeneration of catecholamine neurons. The 6-hydroxydopamine depleted rat is the most widely used preclinical model of Parkinson's disease.

Electromyography (EMG) – The measurement of electrical signals that are involved in activating motor units and muscle contractions. EMG can be conducted at the individual muscle fiber level by inserting needle electrodes into a muscle, or at a population level by attaching a surface electrode to the skin.

Fourier analysis – A set of operations for mathematically decomposing a time series of complex waveforms into combinations of separate, simple periodic components. In doing so, Fourier analysis extracts frequency (rhythmic) information from the data.

Instrumental – A measurement method that requires no direct human contact and is, therefore, not subject to bias.

Isometric force – Force resulting from contraction of a muscle or limb without a visible change in joint angle. Measurement of isometric force typically involves an immovable force transducer.

Ordinal data – Data ranked according to a scale that reflects intensity, with differences between values containing no information (e.g., ranking degree of satisfaction using a scale from 1 to 5).

Tremor – Involuntary rhythmic muscle contractions that produce oscillations of body parts. Tremors often indicate a pathophysiological state, but are also present in healthy organisms.

Definition and History

The press-while-licking task is a sensitive and clinically-analogous means to measure forelimb force control and tremor in rats. Like primates, rats use their forelimbs to manipulate objects. The same neural and muscular structures that play a role in limb use in primates are also involved in rats' limb use. More importantly, rats can be trained to produce desired movements, allowing measures of forelimb function that are analogous to those used in human studies. Although operant lever pressing has a long history in preclinical research, the biophysical properties of the press itself have generally not been of interest to the investigator. An underlying thesis of our work is that these properties can be exploited to reveal neuromuscular function.

Grip force is often used to assess muscle strength in rodents, while tremor assessment typically involves visual observation or the use of electromyography (EMG). Commercially available grip force measures can provide valuable information and are relatively simple to implement. However, testing usually requires direct experimenter involvement, and is, therefore, subject to investigator bias and other confounds unrelated to muscle strength. Tremor measurements typically involve visual observation and scoring intensity along an ordinal data scale, or the use of EMG. The press-while-licking task was developed as an alternative way to measure forelimb force and tremor in a noninvasive but instrumental manner.

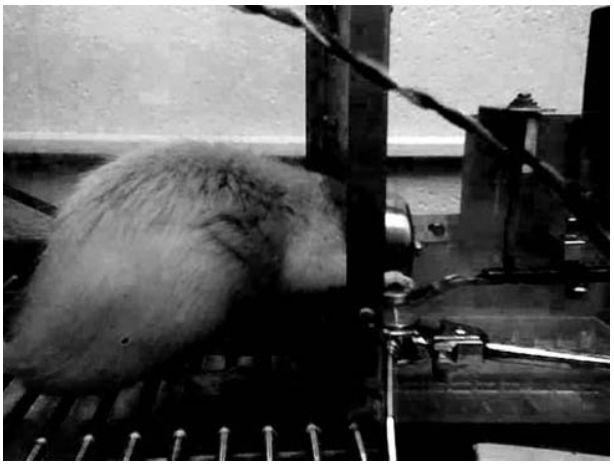

Figure 1 Photograph of a rat performing the press-while-licking task. When the force criterion is exceeded, the solenoid-operated dipper raises, providing access to 0.5 ml water. The dipper remains up as long as a threshold force is maintained. The duration of the press-hold-release bout is determined primarily by the amount of time it takes for the rat to empty the dipper cup. During an 8 min session, a well-trained rat typically produces between 40 and 60 press-hold-release bouts.

Press-While-Licking Method

The press-while-licking task is analogous to isometric force tasks used in human studies. The apparatus consists of an operant chamber enclosed in a sound-attenuating cubicle. The front panel of the chamber has a cylindrical recession that provides access to a 0.5 ml solenoid-operated dipper cup. To the side of the recession is a rectangular opening positioned so that a rat can reach the operandum located outside the chamber using its forelimb (see **Figure 1**). The operandum is an 18-mm diameter disc attached to an isometric force transducer that continuously measures the force exerted on the disc. The spatial arrangement allows a trained rat to press the operandum with a single extended forepaw and drink from the dipper cup at the same time. An interface receives the analog signals from the transducer, converts them to digital form, and routes them to a computer. Signal output is recorded at 100 samples per second with a force resolution of 0.33 g equivalent weights. Contingencies are programmed so that when a rat produces a specified criterion force (we typically use 20 g), the dipper is activated (raised) and the cup is presented through a hole in the cylindrical recession. We usually employ a second, lower force threshold for deactivating the dipper (typically 6.7 g). This inequality results in discrete press-hold-release bouts (see **Figure 2**). Under these conditions, force output peaks early in the first second of the response, and then decreases and plateaus until the disc is released. The duration of a press-hold-release bout is determined primarily by the amount of time it takes the rat to lick the water from the dipper cup. However, durations can also be influenced by drugs, lesions, and age, making duration an interesting dependent variable.

A computer program parses raw force-time data into individual 'response' bouts. We have defined these responses as press and hold bouts that exceed force criteria for at least 4.36 s, with the last 3.36 s used for spectral analysis of tremor (the force variation during the first second of the response precludes its use in spectral analysis). This duration was selected based on sampling requirements (the resulting 336 samples is a compatible sample) and assumptions of a stationary signal for Fourier analysis. Because almost all trained rats produce responses that are longer than this, we discard the remaining portion of the response before ensemble averaging the waveforms. This provides waveforms of equivalent length and without the nonstationary component associated with the release of the operandum. We derive a peak force measure from the first second of the response. The power spectrum and a mean hold force measure are derived from the remaining 3.36 s. Area under the curve of specific portions of the power spectrum is used to quantify tremor and other measures.

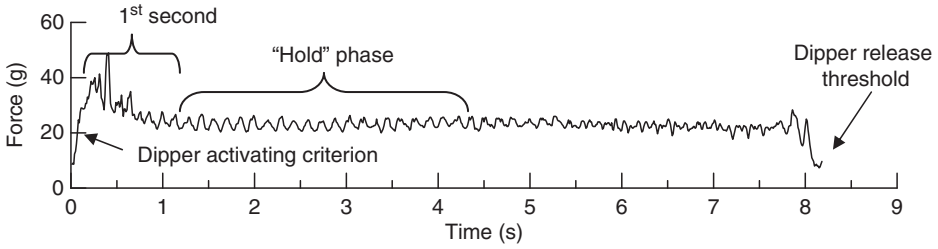

Figure 2 Representative force-time waveform recorded during a behavioral session. The higher dipper-activating criterion results in a peak in the waveform during the first second of the response. Force then decreases and plateaus for the remainder of the bout. Mean force and power spectra are derived from the hold portion of the bout. The prominent oscillations in the hold phase of the waveform are produced by the rat's licking as it is reflected through the forelimb muscles.

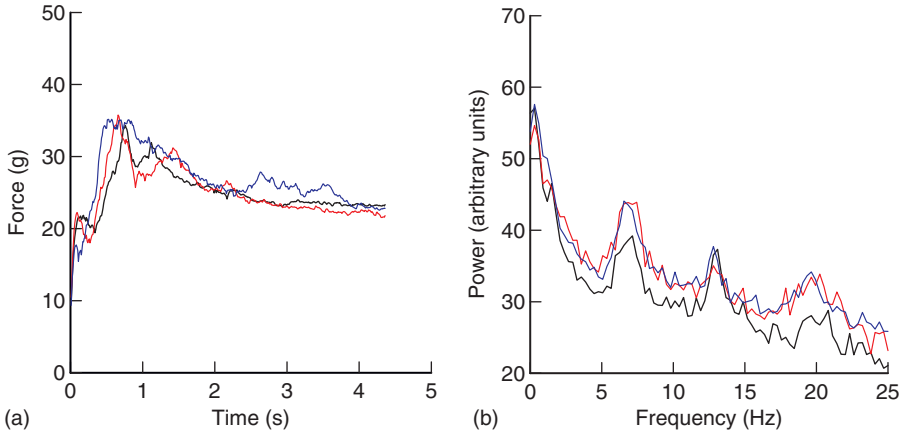

Figure 3 Averaged force-time waveforms and corresponding frequency power spectra from an 18-month-old Sprague-Dawley rat prior to (black lines), and 2 (red lines) and 4 (blue lines) weeks following infusion of 6-hydroxydopamine into the contralateral striatum. This animal sustained a 30% depletion of striatal dopamine. Note that although overall force was not substantially affected by the lesion, isometric force-related tremor was elevated at both the postlesion time points. Note also that because the waveforms were cut off at 4.36 s, the increased response durations are not reflected in this figure.

Research Applications

The press-while-licking task has been used to study the effects of dopamine depletion, drugs, and force training on isometric forelimb force and tremor in rats. Following is a brief synopsis of findings from these studies.

Nigrostriatal Dopamine Depletion

Nigrostriatal dopamine depletion in Parkinson's disease (PD) produces bradykinesia, muscle rigidity, and tremor. Rats with advanced unilateral 6-hydroxydopamine-induced dopamine depletion exhibit severe contralateral forelimb deficits. In order to model early stage PD, we produced a mild (30%) dopamine depletion by injecting 6-hydroxydopamine into the striatum contralateral to the trained forelimb of a rat. The lesion did not affect the overall force output in this rat but did increase isometric tremor (10–25 Hz band) at 2 and 4 weeks postlesion (see **Figure 3**). This may model the enhanced postural tremor observed in patients. The lesion also increased the duration of press-hold-release bouts and power in low frequency portions of the power spectrum. These effects are analogous to deficits in task disengagement and diminished isometric force control observed in clinical studies.

Drug Effects

'Typical' antipsychotic drugs such as haloperidol produce Parkinson's-like motor side effects, including bradykinesia and muscle rigidity. Newer 'atypical' antipsychotic drugs produce fewer motor side effects. Consistent with these clinical phenomena, haloperidol increased isometric force-related tremor in the press-while-licking task. This effect, which was reversed by coadministration of the anticholinergic drug atropine, likely reflects increased muscle rigidity. The atypical antipsychotics clozapine and risperidone attenuate force-related tremor in the task.

We compared the effects of physostigmine and harmaline, two drugs known to produce whole body tremor through different pharmacological mechanisms. Physostigmine increases the amount of acetylcholine in the

synapse, resulting in enhanced muscle contraction. Harmaline, which is used to model essential tremor, activates cells in the inferior olive and induces rhythmic activation of cerebellar Purkinje cells via the climbing fiber pathway. At doses that are too low to produce visually observable tremor, both drugs elevated force-related tremor in the press-while-licking task. The tremor profiles of the two drugs were different, as physostigmine elevated power in a wider portion (10–25 Hz) of the power-frequency spectrum than harmaline (8–12 Hz).

Dantrolene sodium is a skeletal muscle relaxant that inhibits calcium release at the sarcoplasmic reticulum. Because it also possesses neuroprotective potential, we tested dantrolene and found that it attenuates isometric force-related tremor at doses that do not appreciably affect operant responding or force output. This suggests that dantrolene affects neuromuscular function at doses that do not produce muscle weakness (a common side effect of the drug).

Force Training

We subjected rats to a training protocol in which they were required to press and hold with 20 g force, then 40 g, and then 60 g, practicing at each force level for ~2 weeks. Force-related tremor increased with each new force requirement, and force output increased with practice from the beginning to the end of each stage. However, force-related tremor decreased within both the 20 and 40 g stages, reflecting training effects that have been observed in human subjects.

Summary

Although the press-while-licking task involves a substantial amount of operant training, the behavioral control it affords provides advantages over other measurement techniques. Using sensitive isometric load cells, we have measured tremor at doses below those typically required to produce visually observable tremor in rats. We have also measured changes in isometric force that are analogous to those reported using isometric-based force tasks in humans. The press-while-licking task is therefore a valuable tool with translational appeal for preclinical research into motor function.

See also: Dopamine; Dopamine Depletors and Movement Disorders; Essential Tremor: Animal Models; Harmaline Tremor Model; Parkinson's Disease: Animal Models.

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Primary Orthostatic Tremor

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Glossary

Orthostatic tremor (OT) – A form of tremor that occurs when the subject stands.

Pathognominic EMG pattern – Pathognomic EMG pattern can be found only for orthostatic tremor (high frequency, 13–18 Hz) and asterixis (pauses of EMG-activity in antagonistic muscles).

Clinical Presentation

Orthostatic tremor (OT) is a unique tremor syndrome characterized by a subjective feeling of unsteadiness during stance, and in severe cases, during gait. Some patients experience sudden falls. By definition, patients do not have problems when sitting and lying. The only clinical finding is visible, more often only palpable fine-amplitude, regular, rippling of leg muscles. Thus, this form of tremor is suspected mainly based on the complaints of the patients rather than clinical findings. The diagnosis can be confirmed with surface electromyography (EMG, e.g., from the quadriceps femoris muscle) while the patient is standing. In OT, pathognomonic 13–18 Hz burst pattern will be detected. All leg, trunk, and even arm muscles will show this pattern, which is in many cases absent during sitting and lying.

OT is a relatively rare condition, and only small case series have been published adding up to <200 cases. Epidemiological data are lacking, but the condition has only been described in patients above 40 years and in one series, the mean age of onset was lower for women (50 years) compared with men (60 years). So far, it is not considered as a hereditary disease, but one familial case has been reported.

OT is considered as an idiopathic condition, but several other movement disorders often occur with it for unknown reasons: Parkinson's disease, vascular Parkinsonism, and Restless Legs Syndrome have all been described in OT, but because OT is so uncommon, none of these conditions appears to be pathophysiologically related to OT. It is of special interest that dopaminergic terminals are significantly reduced in this condition, but clinical trials with L-dopa and dopamine-agonists have been largely unsuccessful.

Arm tremor may occur in roughly half of the patients and is usually more evident during standing up. Because the typical high-frequency EMG tremor pattern is detected in all the muscles of the body. The hypothesis that a bilaterally descending system underlies OT is widely accepted. Such projections presumably originate in the brainstem or cerebellum and not the hemispheres or subcortex. The differential diagnosis is broad, as other idiopathic tremors like essential tremor, and also cerebellar tremors can present with similar complaints. The most important test to separate them is electromyography.

Treatment

OT is responsive to clonazepam and primidone. Valproate and propranolol have been used in single published cases with variable success. Abnormalities of dopaminergic innervation of the striatum have been described, although levodopa has not consistently shown efficiency. Pramipexole, a dopamine agonist, was successful in one case. According to small double-blind studies gabapentine may have an excellent and sustained beneficial effect confirmed by objective measurements. In the author's experience, this is the drug of first choice for OT (1800–2400 mg daily). Surgical therapies were not considered to be helpful until recently. However, one case responded to spinal cord stimulation at thoracic level and three cases have just been reported to respond successfully to deep brain stimulation of the thalamus (Vim).

Summary and New Research Directions

OT is a specific tremor condition that occurs when subjects stand. It has a distinctive pattern that can be detected with surface electromyography. Further research efforts will be aimed at defining its anatomical locus and developing treatments with greater specificity.

See also: Rest Tremor; Tremor; Tremor, Essential (Syndromes); Tremor, Holmes.

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Primary Progressive Freezing Gait

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Primary progressive freezing gait (PPFG) was described, in 1993, in Israel, as a single-sign disorder. From a clinical point of view, PPFG is similar or identical to syndromes of 'gait ignition failure' and 'isolated gait ignition failure,' meaning a marked difficulty in initiation of walking. PPFG can be considered as a higher level gait disorder, most probably associated with pathology involving the frontal lobes and their connections with other cortical regions, basal ganglia, and brain stem. It was described as 'pure akinesia' in Japan as a variant of progressive supranuclear palsy (PSP), where the predominant and initial motor symptom was freezing of gait (FOG). The pathogenesis of FOG remains unknown. It seems to originate from dynamic alteration of the normal cortical (premotor)–basal ganglia-thalamic–cortical (SMA) neuronal network at the level of the basal ganglia or the cortex. We hypothesized that 'unexpected' information reaching the basal ganglia possibly through the frontal–limbic–caudate nucleus network, involved in parkinsonian gait in a hypodopaminergic state, 'jams' the normal locomotion network to cause hyper or dys-synchronization at the level of the basal ganglia outflow. As a result, normal locomotion is no longer possible in the automatic mode, and an alternative but inefficient locomotion network, with an internal rhythm of 4–6 Hz (instead of 1 Hz in the normal gait network) is activated unintentionally. The result of activation of the 'alternative' locomotion network is dys-synchronization and abnormal scaling of leg muscles, which probably causes the feeling of the feet being 'glued' to the ground. The dys-synchronization and abnormal scaling is self-limited in nature but can intentionally be overcome by switching to an 'externally' driven gait (using cues), which bypasses the inefficient gait network.

Epidemiology and risk factors for PPFG are unknown.

Phenomenologically, FOG describes intermittent episodes of inability to initiate or maintain locomotion or to perform a turn that last seconds (rarely exceeding 30 s). Most episodes are associated with a subjective feeling that the feet are 'glued' to the ground. Patients either accept the situation and wait for its spontaneous disappearance or actively try to overcome the block, an effort that frequently causes tremor-like movements of both legs. Typically, most episodes can be overcome by motor, sensory, or mental tricks but habituation has been described. Freezing may occur while walking, passing through tight quarters (entering an elevator), reaching the destination (approaching a chair), or in stressful situations, such as crossing the street ('open space'). Movement during FOG can be divided into three categories: small steps forward, trembling in place, or complete akinesia.

PPFG begins around age 70 years (range 55–85) without gender differences. At early stages of different diseases, PPFG can be the main and, sometimes, the only symptom lasting as such for many years. Ninety percent of PPFG patients first complain about clumsiness, awkwardness of leg movements while walking, initially at sudden changes of a walking pattern, for instance, when suddenly stopping to avoid an obstacle or during a sudden change of walking direction and while turning. About 60% of PPFG patients experience at one stage the typical start or turn hesitations. Nearly one-third of patients experiences bradykinesia at disease onset, usually in the legs. About 20% of patients characterize beginning PPFG as subjectively impaired coordination, retropulsion or festination, gait ataxia, short-step walking, and shuffling though balance usually remains preserved and postural reflexes are normal. No abnormalities in eye movements or apraxia of eyelid opening are usually seen at early

stages of PPFG. Cognitive decline is usually mild and of limited significance at early stages of the disease.

Diagnostic criteria for PPFG, as offered by Factor et al. are: (1) PPFG is the primary feature the disease; (2) No clinical findings consistent with the diagnosis of PD or a known Parkinson plus syndrome; (3) No clinical or laboratory data to suggest other diagnoses such as cerebro-vascular disease; (4) Lack of dyskinesia or motor fluctuations from levodopa therapy. With disease progression, the majority of PPFG patients develop various parkinsonian features such as bradykinesia, micrographia, hypomimia, and mild rigidity, while tremor is less frequent. In the advanced stage of PPFG, the basic complaint is instability of gait and recurrent falls classically with no significant fear of falling.

The main differential diagnosis for PPFG in its early stages is subcortical arteriosclerotic encephalopathy of Binswanger which is classically associated with early falls while falls are less common in the early stages of PPFG. Cerebrovascular disease is frequently associated with basal ganglia and white matter lesions and extrapyramidal features (lower body parkinsonism), in addition to FOG. In most neuroimaging studies, performed to patients with PPFG, using SPECT, MRI, or PET scanning, no striatal abnormalities were observed.

Another important differential diagnostic option is Parkinson's disease (PD), which can be associated with FOG relatively early on. However, most FOGs in earlier stages of PD are short in duration and with limited functional importance as they rarely cause falls. Very significant FOGs in the first years after the onset of motor symptoms are rare in PD and should raise the question of atypical parkinsonism.

Evidence-based information about treatment of the PPFG is nonexistent. Anecdotal case reports have been published describing positive symptomatic effect of rasagiline $1\,mg\,day^{-1}$, and selegiline in greater doses (up to $20\,mg\,day^{-1}$) with reduction of gait blocks and restoration of ambulation. In the USA, the FDA does not recommend the use of selegiline at doses exceeding $10\,mg\,day^{-1}$.

After a mean of 4 years from motor symptom onset, postural instability becomes more prevalent and falling increases in frequency, ultimately leading to a wheelchair-bound state. Time to wheelchair stage ranges from 3 to 10 years after symptom onset.

In conclusion, PPFG is a late onset (60–70 years), slowly progressive syndrome, where FOG is the initial symptom and slowly progresses as years go by. Falling begins, on average, after 2.6 years (range: 1–10 years), retro- and propulsion after 3.2 years (range: 1–10 years) and wheelchair-dependency after a mean of 4.1 years (range: 1–10 years).

See also: Anticholinergics and Movement Disorders; ATM Gene; Cognitive Assessments and Parkinson's Disease; Cortical Sensory Dysfunction and the Parietal Lobe; Friedreich's Ataxia Rating Scale (FARS); Mercury; Palatal Myoclonus; Pseudobulbar Symptoms.

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Primidone and Movement Disorders

Mitra Habibi

Glossary

Allosteric binding site – A binding site other than the active site.

Cys-loop superfamily – Family of ligand-gated ion channels; examples include: Nicotinic ACh (acetylcholine), 5-HT_3 (5-hydroxytryptamine), glycine, $GABA_A$, and $GABA_C$ receptors.

Enzyme induction – An increase in the synthesis of hepatic metabolizing enzymes causing a decrease in the plasma concentration and elimination half-life of the affected drug.

Half-life – The time required for 50% of a drug to be eliminated from the body.

Metabotropic receptors – G-protein-coupled receptors; examples include: Muscarinic ACh (acetylcholine), $GABA_B$, dopamine, and most of serotonin receptors.
Pyrimidinedione – A chemical compound consisting of a pyrimidine ring substituted with two carboxyl groups.

Introduction

Primidone is an anticonvulsant drug that was first synthesized in 1949. It is the 2-deoxy analogue of phenobarbital and is of the pyrimidinedione class. It is indicated for the treatment of simple and complex partial and secondary and primary generalized tonic–clonic seizures. In addition to epilepsy, it is indicated as the first line of therapy for treatment of essential tremor.

Pharmacokinetics

Primidone is well absorbed and distributed throughout the body. Maximum plasma concentration is reached in about 2 h after administration of a 250 mg tablet. Primidone is metabolized in the liver to active metabolites: phenobarbital and phenylethylmalonic acid (PEMA). Phenobarbital is further metabolized to *p*-hydroxyphenobarbital. Several other minor metabolites of primidone have been identified but there is no evidence that they have a significant therapeutic role. Human studies estimate that on average 24.5% of primidone is converted to phenobarbital. The plasma concentration ratio of primidone to phenobarbital in patients on monotherapy is about 1:1. This ratio is increased to 1:3–5 with the addition of other enzyme inducing medications. Other factors influencing this ratio include age and pregnancy. Primidone and its metabolites are primarily excreted in urine and it has been estimated that about 40–50% of primidone is excreted unchanged. The mean plasma half-life of primidone varies between 6 and 18 h depending on the presence of other enzyme inducing medications. Phenobarbital has a much longer half-life compared to primidone, ranging between 72 and 96 h, while the half-life of PEMA is estimated between 10 and 25 h. It is also important to note that primidone has low protein binding and only about 20% binds to plasma proteins.

Mechanism of Action

Several studies have suggested a synergistic effect of primidone and its two active metabolites. It has been proposed that primidone and its active metabolite, phenobarbital, exert their anticonvulsant activity by enhancing inhibition via the $GABA_A$ receptor. Phenobarbital enhances the activity of $GABA_A$ receptor by increasing the duration of Cl^- channel opening, without affecting the frequency of ion channel opening or its conductance. Phenobarbital can also activate $GABA_A$ receptor in the absence of GABA; this has been linked to its sedative properties.

The antitremor mechanism of primidone is not known; however, there is evidence that GABAergic system and the $GABA_A$ receptors play a major role in regulating motor activity.

GABA Receptors

GABA (γ-aminobutyric acid) is the major inhibitory neurotransmitter and is widely distributed throughout the central nervous system (CNS). GABA receptors are divided into $GABA_A$, $GABA_B$, and $GABA_C$ receptors. $GABA_B$ receptors are metabotropic receptors that couple to K^+ and Ca^{2+} ion channels and activate a second messenger system via G proteins. Like $GABA_A$ receptors, $GABA_C$ receptors are ligand-gated receptors linked to chloride ion channels. However, unlike $GABA_A$ receptors that are composed of variable combinations of different types of subunits, these receptors are only composed of ρ_1–ρ_3 subunits and mostly found in neurons of the retina. The inhibitory effects of GABA are primarily mediated through $GABA_A$ receptors.

$GABA_A$ Receptors

$GABA_A$ receptors are fast ligand-gated chloride ion (Cl^-) channel receptors and are members of the cys-loop superfamily. $GABA_A$ receptors are expressed in most brain neurons. They are transmembrane receptors composed of five subunits. These subunits are identified as α_1–α_6, β_1–β_3, γ_1–γ_3, δ, ε, π, θ, and ρ_1–ρ_3. Each subunit has a large extracellular N-terminal domain, four transmembrane domains (TM_1–TM_4) and a large cytoplasmic loop between TM_3 and TM_4. The Cl^- channel pore is part of TM_2 domain of each subunit. These subunits can be assembled in different compositions to form a large variety of $GABA_A$ receptor subtypes in the brain.

These subunits are wildly distributed in the brain. The α_1 subunit is predominantly found in cerebellum and α_{2-5} subunits are mainly present in the hippocampus. There are intermediate levels of α_{1-4} subunits and low levels of α_5 subunits in the cerebral cortex; α_6 subunit is found in the cerebellar granule cells. The distribution pattern of β_1 and β_3 subunits is as follows: hippocampus > cortex > cerebellum, while the β_2 subunits have the opposite pattern and are mainly found in cerebellum > cortex > hippocampus. In contrast, the mRNA of the γ_1 subunit is mainly found in amygdale and septum. The γ_2 subunit

is found in every part of the brain and γ_3 subunits are distributed mostly in cortex and basal nuclei.

The subunit composition of $GABA_A$ receptors subtypes influences their physiological and pharmacological characteristics. Most common pentameric combinations in the brain consist of two α, two β, and one γ_2 subunits or two α, two γ, and one β subunits. A fully functional $GABA_A$ receptor requires the presence of these three subunits; however, only α and β subunits are considered the essential part of the receptor and $GABA_A$ receptors with less functionality can be formed without the expression of γ subunits. Studies have shown that functional $GABA_A$ receptors were assembled in mice devoid of γ_2 subunits, but they lacked the benzodiazepine receptor binding site. The other subunits, δ, ε, π, θ, are thought to substitute γ in less commonly expressed receptor subtypes.

The GABA binding site is located at the interface of α and β subunits. The binding of GABA results in a conformational change in the receptor, opening the intrinsic Cl^- channel and allowing a rapid flux of Cl^- ions; this causes hyperpolarization and inhibition of the action potential.

$GABA_A$ receptors are pharmacological targets of several important drugs such as anticonvulsants, benzodiazepine, barbiturates, neurosteroids, and general anesthetics. Instead of binding to the GABA binding sites, these drugs exert their action by binding to their allosteric binding sites on the $GABA_A$ receptors.

Physiological Properties

The exact antitremor mechanism of primidone and its two active metabolites is not known; however, the efficacy of primidone in essential tremor has been confirmed in several controlled studies. Its major active metabolite, PEMA does not seem to possess any antitremor properties. In one study, no significant difference in tremor magnitude was noted between patients receiving 400 and 800 mg day^{-1} of PEMA and placebo.

Several studies suggest the involvement of $GABA_A$ receptors in controlling motor functions. In addition, patients with essential tremor show lower concentrations of GABA in their cerebral spinal fluid (CSF). In an animal study, $GABA_A$ receptors with α_1 subunits were deleted. This resulted in the loss of 50% of all $GABA_A$ binding sites throughout the brain, including motor pathways in the brainstem, thalamus, and basal ganglia. Mice with this deletion showed postural and kinetic tremor, characteristics very similar to essential tremor in humans. Drugs used in the treatment of essential tremor, such as primidone, were efficacious in reducing tremor in mice by 45–70%.

In another study, significant reduction in tremor was observed after 2 weeks of therapy and primidone maintained its efficacy for at least 1 year. Several other studies suggest an initial 40–50% reduction in tremor amplitude in about 70% of patients treated with primidone.

In an open-label study, after 4 weeks of therapy with primidone, 82% of patients showed 25% reduction in their tremor. About 63% of these patients maintained the same benefit at 12 months, indicating that some patients develop tolerance to therapy. In these patients, dose of primidone can gradually be increased to see if similar efficacy can be obtained with higher doses.

Tolerability is an important issue with primidone and about 20–30% of patients discontinue therapy because of intolerable adverse effects. The most common CNS side effects are somnolence, ataxia, vertigo, nausea, fatigue, and dizziness. Rare idiosyncratic reactions such as hematological abnormalities, hepatotoxicity, and skin rash have also been reported with primidone.

To minimize the occurrence of initial adverse effects, primidone is usually initiated at a low dose of 25–50 mg day^{-1} and is gradually titrated up based on patient's tolerance and response. The efficacy of 250 versus 750 mg day^{-1} of primidone was compared in patients with essential tremor. The patients receiving 250 mg day^{-1} showed similar or better response, maintained the same efficacy at 12 months and experienced less side effects compared to the higher dose of 750 mg day^{-1}.

Side effects at the initiation of therapy are due to the parent drug, primidone, as they are reported before the active metabolites are formed. However, some of the adverse effects experienced later in therapy may be due to its long lasting active metabolite, phenobarbital. As noted earlier, the concentrations of phenobarbital can be higher than those of primidone and may limit dose increases later in therapy even in those individuals who initially tolerated primidone. There have been reports of less neurotoxicity with PEMA compared to phenobarbital. In one study, patients taking 400 and 800 mg day^{-1} of PEMA reported no side effects. These doses produced plasma steady concentrations expected to be reached by taking 1500 mg day^{-1} of primidone.

See also: GABA and Movement Disorders; Postural Tremor; Tremor; Tremor, Essential (Syndromes); Tremor, Essential: Genetics.

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Progressive Supranuclear Palsy

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Definition and History

Progressive supranuclear palsy (PSP) is the term J. Clifford Richardson first used in 1964 to describe a group of patients he had been studying in Toronto. All of his patients had progressive gait disturbance and falls, ophthalmoplegia, pseudobulbar palsy, and mild dementia, without prominent Parkinsonism. The pathological examination of these patients by John Steele and Jerzy Olszewski confirmed a common underlying pattern of extensive subcortical neurofibrillary degeneration, which was distinct from other known pathologies. This pattern of pathological change has subsequently been observed in a number of other clinical syndromes that expand on Richardson's original observations, and hence the emphasis of this terminology has changed from a clinical to a pathologically defined entity. Accordingly all clinical syndromes associated with pathologically defined PSP will be considered in this article (**Figure 1**).

In 1955, Richardson was visited by a good friend and 52 year old business executive because of clumsiness, trouble in seeing, and mild forgetfulness. During the next 4 years, Richardson was puzzled as his friend progressively developed an unusual constellation of signs that included supranuclear ophthalmoplegia affecting chiefly vertical gaze, pseudobulbar palsy, dysarthria, dystonic rigidity of the neck, and mild dementia.

As he was observing the evolution of this illness, Richardson serendipitously identified similar symptoms in three other middle-aged men. The first was a West Indian laborer, who immigrated to Canada in 1913 and developed unsteady walking in 1954. The second patient was a truck driver who came from England when he was a child and who had been well until his personality changed and he started to fall at the age of 49. The third veteran had come from Ukraine in 1913 and had worked as a laborer until 1956 when he developed difficulty with vision, his speech became slurred, and he had trouble in swallowing. Richardson recognized that despite different presentations, these four patients had the same hitherto unrecognized disorder.

During the next few years, Richardson came across three further patients with what also appeared to be the

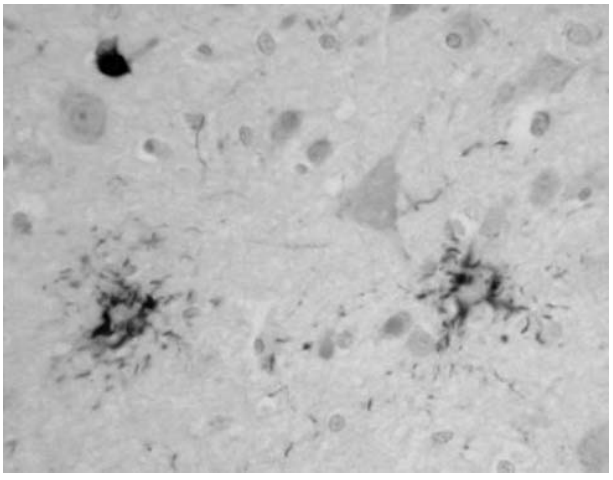

Figure 1 Pathology in the frontal cortex of patient with PSP (Richardson's disease). AT8 positive pathological tau accumulation. Neurofibrillary tangle, tufted astrocytes and neuropil threads (x20 magnification).

same condition. In 1962, he recommended that Dr. John Steele assist Professor Jerzy Olszewski, to thoroughly evaluate the pathology of his cases. In June 1963, at the American Neurological Association meeting in Atlantic City, Richardson presented the first clinical report of eight cases of 'Heterogeneous System Degeneration' with supranuclear ophthalmoplegia, pseudobulbar palsy, nuchal dystonia, and dementia. He observed that this disorder presented in the seventh and eighth decades of life and was relentlessly progressive with death occurring within 9 years.

Olszewski described the anatomy and histopathology of the disease and the detailed localization of the lesions in four cases and presented the findings to the American Association of Neuropathologists in 1963.

The following year, Richardson and Olszewski, together with Steele, published their seminal paper titled 'Progressive supranuclear palsy' (PSP) describing the clinical and pathological features of the disease. The highly specific clinical picture Richardson had observed was, with considerable foresight, dependent on the similar localization of lesions among their cases. Furthermore, they predicted that 'it is possible that further observations may broaden the clinical spectrum of the disease. In other cases, the distribution of pathological changes may be different, and therefore, the clinical picture would be modified.'

In their 1963 reports, Richardson and Olszewski had called the condition heterogeneous system degeneration, a term first used by W. J. C. Verhaart for a similar case he described in 1958. However, as they were not certain that the disease was a primary degeneration or that it was related to other system degenerations, it was agreed that they shouldchoose another term. They briefly considered 'Can't look down disease', and 'Toronto disease.' In the summer of 1963, Richardson proposed that it be called progressive supranuclear palsy, a clinical designation and the name by which the disease is now known, particularly in Europe. Some also refer to it as the Steele–Richardson–Olszewski syndrome, an eponym which was first used by the Montréal neurologist Andre Barbeau in 1965.

Pathophysiology

PSP is considered as one of the primary tauopathies, in which tau dysfunction is regarded as central to its pathogenesis, and neuronal and glial accumulation of abnormal filamentous tau is a characteristic. The postmortem diagnosis of PSP is dependent on the identification of neurofibrillary tangles and neuropil threads in basal ganglia and hindbrain structures. The presence of coiled bodies, and in particular, tufted astrocytes and the predominance of 4-repeat (4R) tau isoforms in both neuronal and glial tau inclusions, are now also recognized as characteristic features of PSP, although they are not included in the current operational diagnostic criteria. Pathological heterogeneity of PSP has been reported and it is as yet unknown whether the pathology in PSP follows a consistent topographical progression or whether a disease 'footprint' of regional susceptibility is established early with subsequent uniform progression of pathology in all affected structures. Serial imaging studies suggest that the brainstem, in particular the midbrain, and frontal lobes bear the brunt of the disease and natural history studies support the notion of a progression of pathology. Different degrees of pathological tau burden have been identified in the different clinical phenotypes. The relatively more benign clinical syndrome of pure akinesia with gait freezing has a less severe and more restricted tau pathology than patients with Richardson's syndrome. Furthermore, patients with corticobasal syndrome or progressive nonfluent aphasia presentations of PSP-tau pathology have a relatively more cortical pathology than patients with Richardson's disease.

A PSP-tau grading system has been proposed to summarize the severity of tau pathology in these cases. The proposed scale uses grade of severity of coiled body and thread lesions in the substantia nigra, caudate, and dentate nucleus. This 12 tiered grading system has been shown to be reliable and repeatable and correlates well with the severity of clinical features throughout life (PSP-tau score: 0 – mild tau pathology, restricted distribution; >8 – severe, widespread tau pathology) and was negatively correlated with disease duration.

Epidemiology

Richardson was surprised that the clinical syndrome he reported had not been reported earlier and in 1963, suggested that 'a good many cases of the same disease will be identified in other areas'. In fact, historical studies had identified reports of the clinical PSP at least 100 years before. It is likely that these patients were considered by physicians of the day to be formes frustes Parkinson's disease, vascular disease, or progressive ophthalmoplegia.

PSP has subsequently been described in most regions around the world, although epidemiological data and clinical reports from Africa are scarce. Geographical clusters of PSP have been reported, in conjunction with high rates of unclassifiable Parkinsonism, motor neuron disease, and dementia, in the Japanese peninsula of Kai, Guam, Guadeloupe, New Caledonia, and East Papua. Pathological studies from some of these regions have identified important pathological differences from PSP, and therefore despite the clinical similarities, currently, these patients are classified separately.

Determining the prevalence of PSP is difficult because of the limitations of clinical diagnostic accuracy. In addition, methods of case finding and population size can result in 20-fold variations in crude prevalence rate estimates.

The best studies of prevalence are community-based, derived from primary care, utilizing sensitive inclusion criteria, personal examination, and validated diagnostic criteria. Two studies in the United Kingdom that satisfy these requirements report a crude prevalence rate of 6.5 per 100 000 and an age-adjusted prevalence of 5.0 per 100 000. Another study using similar methodology estimated crude and age adjusted prevalence in Yonago, Japan to be 5.8 and 5.0 per 100 000 respectively. Studies designed primarily to determine the prevalence of Parkinson's disease (PD) in Northwest Italy and the Faroe Islands estimate the prevalence of PSP to be 3.2 and 4.6 per 100 000 respectively.

These clinical studies used clinical criteria that emphasize Richardson's classic syndrome and therefore probably underestimated the true prevalence of PSP-tau pathology in the community. Overall, however, these rates are similar to prevalence rates reported in motor neurone disease, where disease duration is shorter and more than 25 times less than the rates in PD, where disease duration is almost twice that in PSP.

Table 1 Clinical diagnostic criteria for the diagnosis of PSP

Clinically definite PSP
Gradually progressive disorder
Onset at age 40 or over
Prominent postural instability with falls in the first year of disease onset AND vertical (up or down) supranuclear palsy
Probable PSP
Gradually progressive disorder
Onset at age 40 or over
Vertical (up or down) supranuclear palsy OR
Prominent postural instability with falls in the first year of disease onset AND slowing of vertical saccades
Exclusion criteria
History compatible with encephalitis lethargica
Alien hand syndrome, cortical sensory deficits, focal frontal or temporaparietal atrophy
Hallucinations or delusions unrelated to dopaminergic therapy
Cortical dementia of Alzheimer's type (severe amnesia, aphasia or agnosia)
Prominent cerebellar symptomatology or unexplained dysautonomia (early prominent incontinence, impotence or symptomatic postural hypotension)
Neuroradiologic evidence of relevant structural abnormalities (basal or brainstem infarcts, lobar atrophy)
Whipple's disease, confirmed by polymerase chain reaction, if indicated

Clinical Features and Differential Diagnosis

Richardson's Disease

Richardson's disease is the prototypic clinical manifestation of PSP-tau pathology. The first clinical symptoms usually develop in the seventh decade (median age of onset 63–68), but the age of onset of disease can range from the fifth to the ninth decade.

Richardson's classic description has been validated in different clinicopathological series and is reflected in the operational clinical diagnostic criteria. The NINDS-SPSP criteria for 'possible' PSP require the presence of a gradually progressive disorder with onset at age 40 or later, either vertical supranuclear gaze palsy or both slowing of vertical saccades and prominent postural instability with falls in the first year after onset (**Table 1**). 'Probable' PSP is defined by the presence of vertical supranuclear gaze palsy, prominent postural instability, and falls in the first year of onset, as well as the other features of possible PSP. In many cases, falls or postural instability dominate the early clinical picture. A proportion of patients first present with cognitive and behavioral change or nonspecific visual disturbance.

Falls associated with Richardson's disease (RD) are often seemingly unprovoked and can appear out of context with gait disturbance. Patients often describe their falls as 'if the wind blew' them over. In many cases, gait becomes unsteady and is described by some as a 'drunken' gait. Unlike Parkinson's disease, the initial complaint is rarely of gait slowing, rather a lack of balance and confidence while walking. In almost half of patients, the falls are only backwards, in contrast to Parkinson's disease where falls are more often forwards. Soft tissue injuries and fractures, particularly of the hip, trunk, and head, are a common accompaniment of the postural instability. The median time to first fall in RD is around 12 months. Motor recklessness is another feature, where the patient seems unaware of their imbalance, misinterprets their center of gravity, and attempt to execute movements they are incapable of completing safely. This combination of impulsiveness, apraxia, and bradykinesia contributes to the risk of falling and can be seen in the clinic as the 'rocket sign' where patients sit en bloc, falling back into the chair without appropriate knee and hip flexion.

The diagnostic eye movement abnormalities are the most distinctive clinical feature of Richardson's disease. In 20% of patient's nonspecific visual disturbance are early features, including blurred vision, irritated dry eyes, diplopia, and ocular discomfort or blepharospasm. It is not uncommon for patients to frequently visit their optometrists for new corrective lenses. Patients usually develop subtle slowing of the vertical saccades as the first abnormal eye signs. This slowing can be difficult to measure but may manifest itself as the 'round the houses' sign where horizontal deviations are seen in subtly slow vertical saccades. The saccadic velocities progressively deteriorate and vertical saccadic movements become hypometric and then eventually limitation of the extents of gaze can be seen. Horizontal eye movements are relatively less affected and deteriorate after vertical movements. The gaze paresis can be overcome by activating the vestibulo-ocular reflex using the Doll's head maneuver.

The early cognitive features of RD can be subtle, and the insidious progression often goes unnoticed by patients

Table 2 Clinical pointers (green flags) for the diagnosis of PSP

Early instability with falls
Absent or poor, or waning response to L-dopa
Marked slowing of vertical (up or down) gaze (commonly precedes the limitation of vertical gaze palsy that enables the diagnosis of PSP to be made)
Eyelid abnormalities (e.g. eye lid apraxia)\Severely decreased blink rate
Stuttering or pallilalia as an early feature
Early dysphagia or dysarthria
Axial more than limb rigidity
Retrocollis
Deep inspiratory sighs

Table 3 Non-PSP causes of eye movement abnormalities, postural instability and Parkinsonism

Dementia with Lewy bodies (28)
Multiple system atrophy (29)
Cerebrovascular disease (30)
Aortic surgery and hypoxic damage (31, 32)
FTDP-17 (33)
Ubiquitin positive frontotemporal lobar degeneration (34)
Neuropsyphilis (35)
Motor neuron disease/congophilic angiopathy (36)
Amyotrophic lateral sclerosis (37)
Antiphsopholipid syndrome (38)
Prion disease (39)
Bodig (40)
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (41)
Whipple's disease (42)
Neimann–Pick type C (43)

and their families. Patients can present with bradyphrenia, frontal type disinhibition, and personality change that can precede the postural instability and other motor manifestations of PSP-tau pathology and dominate the early clinical picture.

In the original descriptions of PSP, Richardson described the absence of Parkinsonism as an important clue to the diagnosis. Although the first symptom was different in all of his patients, they all developed postural instability and falls within the first few years of the disease. The most exceptional clinical feature was the progressive supranuclear gaze palsy that initially affected vertical gaze and progressed to complete ophthalmoplegia in most patients. This characteristic clinical syndrome is helpful in diagnosis, but alternative pathologies should be considered (**Tables 2** and **3**).

Progressive Supranuclear Palsy – Parkinsonism

Richardson stated that none of the patients he described had 'the characteristic Parkinsonian features, and none had tremor'. While hypomimia or hypophonia may be considered as signs of hypokinesia and 'rubbery' rigidity might be thought of as extrapyramidal tone, in isolation, these findings are insufficient to diagnose Parkinson's disease or even vascular Parkinsonism.

Pathological series of PSP have consistently identified a small group of patients who do not fit the classic clinical description and who have 'atypical' clinical features, including normal eye movements, rest tremor a positive-levodopa response, and focal dementia. Clinicopathological studies have consistently identified the classic syndrome described by Richardson as well as a smaller group where Parkinsonism (rigidity, tremor, bradykinesia and L-dopa responsiveness) dominates the early clinical picture. This has provisionally been referred to as PSP-Parkinsonism (PSP-P).

These patients present with bradykinesia, rigidity, and in some cases, tremor to movement disorder clinics and are commonly labeled as Parkinson's disease. Asymmetry of limb signs is more common in this group, and although axial rigidity was often striking early, limb rigidity is more common and severe than in Richardson's syndrome, where muscle tone may be normal. Tremor is included in the mandatory exclusion criteria of some diagnostic guidelines for PSP but jerky postural tremor and even a 4 to 6Hz rest tremor are relatively common in PSP-P. The tremor can diminish over time and may disappear even in the absence of dopaminergic treatment. A 'moderate' or 'good' improvement in bradykinesia and rigidity follows initiation of L-dopa in a proportion of patients with PSP-P, although the response is rarely 'excellent'. In most cases, the beneficial effects wane over a few years although sustained responses have been reported.

The PSP-P phenotype is difficult to differentiate from Parkinson's disease early in the disease. Early helpful pointers may include rapid progression with relatively poor response to L-dopa, and more frontolimbic cognitive deficit and axial symptomatology. Falls and cognitive function occur later in PSP-P than Richardson's syndrome and perhaps as a consequence disease duration is about 3 years longer.

Most patients eventually go on to develop falls and the eye movement abnormalities and cognitive dysfunction characteristic of Richardson's syndrome. In many cases, the transformation from clinical Parkinson's disease to PSP-P occurs five to ten years after disease onset. In a small number of patients, the purely parkinsonian syndrome predominates until death, and eye movement abnormalities or other characteristics of Richardson's disease never appear. A sustained response to L-dopa, drug-induced choreic dyskinesias and a longer disease duration appear to characterize these patients.

Pure Akinesia with Gait Freezing

The syndrome of pure akinesia with gait freezing (PAGF) appears to be highly predictive of PSP-tau pathology and represents a third, clinical presentation. Pure akinesia was

first described in 1974 in two patients, who developed freezing of gait, writing and speech with paradoxical kinesia. At presentation, these patients were cognitively intact, had no eye movement abnormalities, and in many, there was a long disease duration without the development of other parkinsonian features. Clinical diagnostic criteria have recently been proposed for this syndrome and include progressive onset of gait disturbance with start hesitation and subsequent freezing of gait, speech or writing in the absence of rigidity; tremor; dementia or eye movement abnormality during the first 5 years of disease. There is no benefit from L-dopa therapy; and no clinical or radiological evidence of lacunar infarcts of diffuse deep white ischemia.

When these criteria were applied retrospectively to a pathologically diagnosed series of 759 cases with Parkinsonism, seven cases were identified, including 6 with PSP-tau pathology and the other had Lewy body disease. These patients presented gait disturbances and postural instability, for up to 24 months before developing freezing start hesitation and gait initiation failure. Phonation difficulties, facial immobility, and a reduction in the size of handwriting were additional early signs. Axial rigidity with marked neck stiffness in the absence of limb rigidity was a distinctive feature.

A supranuclear downgaze gaze paresis and blepharospasm developed late in the majority of cases, but in contrast to Richardson's syndrome, fronto limbic cognitive deficits and bradyphrenia are not prominent. The median duration of disease is 11 years.

Corticobasal Syndrome

Corticobasal syndrome is characterized by progressive, asymmetric dyspraxia, cortical sensory loss including an alien limb, a jerky dystonia of the limb with rigidity, and bradykinesia unresponsive to levodopa and was first described in patients with corticobasal degeneration (CBD). Pathological series have indicated that only 50% of cases with corticobasal syndrome have CBD pathology, and cerebrovascular disease, Alzheimer's disease, and progressive supranuclear pathology account for the majority of other cases.

Corticobasal syndrome appears to be a rare presentation of PSP-tau pathology, with only 5 cases from a pathological series of 160 patients with progressive supranuclear palsy, identified with asymmetric limb dystonia, apraxia, and alien limb phenomena. Cortical sensory loss and aphasia were seen in some cases. None of these patients developed postural instability or falls within the first year of disease and dysarthria, dysphagia, and axial rigidity were also absent in the early stages. Most patients with PSP-CBS eventually do develop postural instability but it occurs much later than in Richardson's syndrome. An increase in saccadic latency is the most common eye movement abnormality, and typically, it is more marked on the side where the apraxia predominates. The distinction between this and the typical saccadic slowness in Richardson's disease can be difficult early on. In advancing disease, these patients may also develop some mild slowing of saccadic velocity, although never as severe as is seen in Richardson's syndrome.

Progressive Non-Fluent Aphasia

Progressive nonfluent aphasia (PNFA) is a disorder of language characterized by nonfluent spontaneous speech, with hesitancy, agrammatism, and phonemic errors, requiring significant effort in speech production. It fits within the spectrum of frontotemporal dementia syndromes and may be seen with a corticobasal syndrome. There are several components to speech and language difficulties in PNFA, including 'apraxia of speech', which describes errors in timing, coordination, and initiation of speech secondary to disorders of motor command. Clinically, this is evident when patients perform serial repetition, and although it usually accompanies agrammatism, it has been reported as an isolated, early sign of PNFA. Interestingly, in a pathologically diagnosed series, five of seven patients who presented with PNFA and prominent early apraxia of speech were found to have underlying PSP-tau pathology. The other two cases had Pick's disease and CBD diagnosed pathologically. The apparent specificity of prominent early apraxia of speech for tauopathies, and in particular PSP-tau pathology, has lead to the suggestion that this syndrome be considered as a clinical subtype of PSP. Patients who presented in this way were not found to be different at ages of onset or disease duration to patients with Richardson's disease. In other patients, PNFA with a less prominent apraxia of speech was more likely to be due to CBD or frontotemporal lobar degeneration with tau negative and ubiquitin positive inclusions.

Diagnostic Investigations

The diagnosis of PSP relies almost completely on clinical acumen and ancillary tests are only used to exclude other pathologies such as cerebrovascular disease. Some clinical and radiological tools show some promise in differentiating PSP from Parkinson's disease and multiple system atrophy, but differences early in the disease are relatively poorly studied. A therapeutic trial of levodopa typically results in little improvement of clinical symptoms, including the frequency of falls or axial rigidity and can be used as a pointer to non-Lewy body Parkinsonism.

Olfactory testing in small groups of patients with established disease showed a relatively preserved sense of smell among nondemented patients with PSP compared with Parkinson's disease. Although these findings probably apply also to early disease, the sensitivity and specificity for the diagnosis of PSP have not been calculated.

Cardiac metaiodobenzylguanidine (MIBG) scintigraphy measures the postganglionic sympathetic innervation of the cardiac muscle and is abnormal in the majority of patients with idiopathic Parkinson's disease. The test is normal in the majority of patients with PSP and multiple system atrophy, although the results can be difficult to interpret in patients taking certain medications, diabetes, or heart failure.

Electrophysiological studies of the auditory startle response and acoustic blink reflex have shown significant abnormalities in PSP compared with Parkinson's disease. These studies have shown qualitative and quantitative differences in patients with clinically established disease. The findings in patients with early, difficult-to-diagnose disease are uncertain, but in patients with PSP-P and PAGF, the findings are not sufficiently different from those of Parkinson's disease to be diagnostically useful.

Neuroimaging can give clues to the diagnosis of PSP, and typical patterns of regional atrophy can be seen. Midbrain atrophy is most prominent and has been variously described as resembling a hummingbird or penguin on mid-saggital cuts or morning glory flower on axial cuts. The ratio between the area of the midbrain and the pons measured on mid-saggital MRI is decreased in PSP (mean 0.124) compared with MSA (mean 0.266) and controls (0.237), suggesting that quantitative measures may improve diagnostic accuracy (Oba et al., 2005). Atrophy of the superior cerebellar peduncle is severe in PSP and can be identified in the trained observer. Nonspecific T2 hyperintensities or uncertain significance are commonly seen in the brainstem.

Diffusion-weighted MR imaging is a practical and efficient way for changes of PSP to be identified. Regional apparent diffusion coefficient (rADC) is increased in the basal ganglia compared with Parkinson's disease and in the frontal and parietal cortices compared with controls.

Management

The vast majority of neurotransmitter replacement studies in PSP have been negative, and hope of developing a treatment akin to levodopa in Parkinson's disease has gone. More radical breakthroughs in PSP therapeutics will come from a greater understanding of the pathophysiology of the condition and the development of animal models in which to test new disease-modifying treatments. Some symptomatic treatments have beneficial effects in a small proportion of patients, but on the whole, adverse side effects limit there usefulness and randomized placebo-controlled trials have not been done. Amitriptyline appears to be helpful in some patients, particularly in improving speech and swallowing. In a minority of patients, amantadine has improved gait and balance. The hypnotic zolpidem has been reported to be of transient benefit to the motor symptoms of PSP, but often associated with extreme somnolence and confusion. It is recognized that L-dopa is effective in some patients, although the extent of benefit is moderate and transient at best. Coenzyme Q10 has been evaluated in one small pilot study showing mild, nonclinically significant improvement in disease severity associated with significant alterations in cerebral energy metabolism. Botulinum toxin may be effective as a treatment of disabling blepharospasm. Extreme cervical dystonia, and characteristically retrocollis, may also be alleviated with botulinum toxin injection, but the risk of pharyngeal weakness is high. Gastrostomy feeding should be considered when feeding becomes difficult.

Good management of PSP centers on expert palliative care, and charitable support groups are available to support patients and families in North America, Europe, and Australia. Assistance with difficulty in feeding, mobilizing, and self care can be addressed with the help of experienced physiotherapy, speech therapy, and occupational therapy.

See also: Corticobasal Degeneration; Parkinson's Disease: Definition, Diagnosis, and Management; Parkinsonism: Vascular; Primary Progressive Freezing Gait; SCA27; Tauopathies.

Further Reading

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Relevant Websites

http://www.psp.org
http://www.pspeur.org

Propionic Acidemia

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Glossary

Basal ganglia – Anatomic region located at the base of the brain composed of four clusters of neurons. This area of the brain is involved in body movement and coordination.
Excitotoxicity – Pathological process by which neurons are damaged and killed by glutamate and similar substances. This occurs when receptors for the excitatory neurotransmitter glutamate such as the *N*-methyl *D*-aspartate (NMDA) receptor and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor are overactivated.
Intoxication type neurological distress – Acute or rapidly progressive neurologic symptoms due to the accumulation of toxic compounds proximal to the metabolic block.
Metabolic acidosis – Disruption of the body's acid/base (pH) balance in which the accumulation of a particular acid occurs associated with not enough bicarbonate to effectively neutralize the effects of the acid. It can be due to starvation, gastrointestinal disorders, diabetes, or to those inborn errors of metabolism in which an enzymatic block leads to the accumulation of toxic acids.
Stroke – The sudden death of some brain cells due to a lack of oxygen. The most common cause is a blockage or rupture of a blood vessel to the brain (cerebrovascular accident). 'Metabolic strokes' are present in diverse inborn errors of metabolism and are due to bioenergetic abnormalities that finally lead to a poor oxygen consumption and cell death.

Definition

Propionic acidemia (PA) is a disorder in which a defective enzyme, propionyl-coenzyme A (CoA) carboxylase (PCCA), results in an accumulation of propionic acid. This autosomal recessive disorder is a branched-chain organic aciduria, a class of disease involving the catabolism of the branched-chain amino acids valine and isoleucine (**Figure 1**), and other propiogenic substrates such as methionine, threonine, odd-chain fatty acids, and cholesterol.

Pathophysiology

PCCA, which requires biotin as a cofactor, catalyzes the conversion of propionyl-CoA to methylmalonyl-CoA. Genetic mutations in two subunits of the PCCA gene (PCCA and PCCB) may cause varying levels of PCCA functioning. The A subunit of 72 KD is encoded by the PCCA gene on chromosome 13q32, while the B subunit of 56 KD is encoded by the PCCB gene on chromosome 3q13.3–q22. To date, more than 40 mutations in PCCA and 60 in PCCB have been reported, mostly missense variants.

Defects in the metabolic pathway produce toxic metabolites and it is a cause of the so-called 'intoxication type' neurological distress with acute or rapidly progressive neurologic symptoms due to the accumulation of toxic compounds proximal to the metabolic block. Oxidative stress, mitochondrial dysfunction and excitotoxicity are presumably pathomechanisms related to neurodegeneration in organic acidurias. In the particular case of PA, basal ganglia are especially involved giving rise to abnormal movements. Metabolites of the dysfunctional propionic acid and methylmalonic acid pathways may be selectively toxic to the endothelial cells in the basal ganglia. On the other hand,

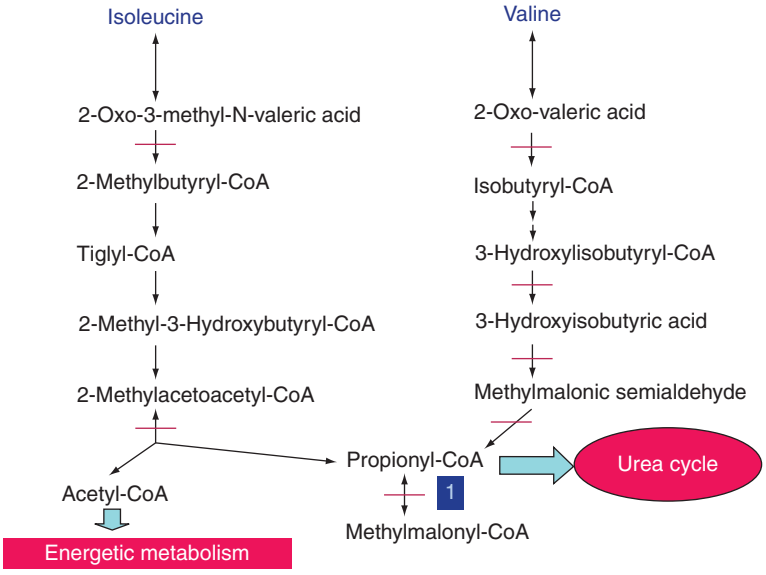

Figure 1 Pathways of the brain chain amino acids, isoleucine and valine. Main metabolic steps are marked by solid red bars. Bar number 1: propionyl-CoA carboxylase. This metabolic pathway is related to urea cycle (the accumulation of propionyl-CoA shown in PA leads to urea cycle inhibition) and energetic metabolism.

mitochondrial dysfunction due to an accumulation of propionic acid apparently results in an abnormal cytochrome *c* oxidase and energetic deficiency. Another hypothesis states that hyperammonemia, which is often associated with PA, leads to an accumulation of glutamine and/or glutamate in astrocytes. This excess glutamate may be excitotoxic to neuronal cells in the basal ganglia. Moreover, free radicals can affect glutamate transporter activity and therefore induce excitotoxicity via increased glutamate concentrations in the synaptic cleft. Probably, a combination of all these intracellular mechanisms produces neuronal damage and the consequent neurological signs.

Epidemiology

The prevalence of PA ranges from 1:165 000 in Italy to 1:277 000 in Germany, and 1: 35 000–75 000 in the United States. Mild forms of the disease due to differences in the mutations of PCCA or PCCB may exist in different parts of the world, and prevalence may be as high as 1 case in 18 000 people. There are no prevalent PCCA alterations in Caucasian patients. Three mutations, namely 922–923insT, 1644–6C > G, and p.Arg399Gln, account for more than 50% of PCCA chromosome in Japanese children. A limited array of PCCB mutations is associated with PA in both Caucasian and Asian populations. It is unclear whether these differences are related to biological factors other than the population specific genetic background. In a study of 65 patients, a slight female predominance was found, with a female-to-male ratio of 1.4:1. Patients present in the neonatal period or during early infancy. Patients with mild forms of the disease may present later in life.

Clinical Features

Patients with PA can be dividend into two subgroups: most of them present in the neonatal period; a less common group has late-onset disease with appearance of symptoms during the first years of life.

1. *Neonatal forms*: The most common clinical picture is a full term baby born after normal pregnancy and delivery, who rapidly deteriorates after an initial symptom-free period (from hours to the first week). Feeding refusal, vomiting, and abdominal distension can be the first signs. Neurological manifestations rapidly appear, including abnormal posturing and movements, hypotonia, lethargy, and seizures, that often present a burst-suppression EEG. Without appropriate treatment, the patient evolves toward brain edema, coma, and death or permanent brain damage.
2. *Late-onset forms*: They have a more variable presentation, including intermittent neurological signs such as ataxia, movement disorders and behavioral abnormalities, recurrent vomiting, and failure to thrive with selective refusal of protein-rich foods. The relapsing episodes are normally triggered by metabolic stressing factors that stimulate catabolism such as infections, fasting, and chirurgical procedures, or can be due to a high-protein intake. Between attacks patients may appear without any symptom. In other cases, the child presents chronic symptoms mainly characterized by psychomotor delay, failure to thrive, and vomiting.

Abnormal Movements

Newborns manifest high-amplitude tremors in the extremities that appear spontaneously or triggered by

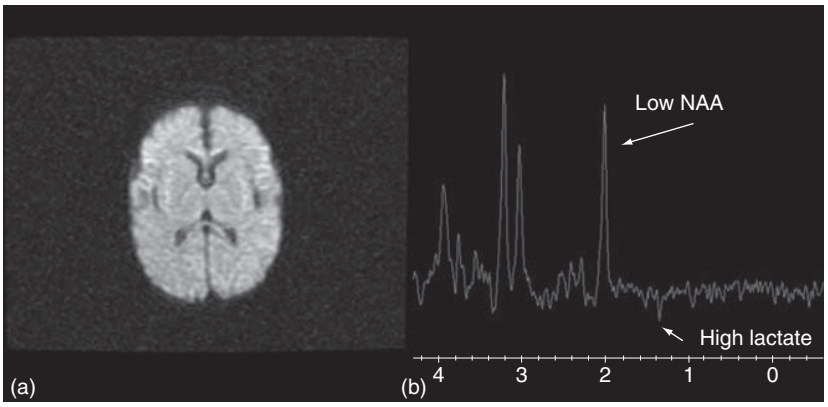

Figure 2 (a) Diffusion brain MRI of a newborn at the onset of the disease showing normal results. (b) Despite normal brain MRI high lactate and low *N*-acetylaspartate (NAA) peaks are pointing toward metabolic decompensation.

stimulation. Nonepileptic multifocal myoclonus is also common. Late-onset forms can present with dystonia, choreoathetosis, and rigidity. Brain MRI may show high-intensity basal ganglia lesions, especially in the globus pallidus. In general, these lesions are localized bilaterally and usually appear during acute episodes of metabolic decompensation or due to long-term poor metabolic control over time. Accumulation of toxic metabolites such as propionyl-CoA can inhibit the mitochondrial respiratory chain and tricarboxylic acid cycle and produce an energetic stroke. Diffusion-weighted images show in the acute phase bilateral pallidus high intensity (putamen and caudate may also be affected). MR spectroscopy may show a decrease of *N*-acetylaspartate (which reflects neuronal loss) and an increase of lactate in decompensation episodes (**Figure 2**). These images may translate basal ganglia infarction. More recently, positron emission tomography has been used to show decreased glucose uptake in the basal ganglia.

Other organs involved are heart (rapidly fatal hypertrophic cardiomyopathy) and pancreas (acute pancreatitis, which is a rare complication).

Differential Diagnosis

In neonatal forms: Sepsis and different causes of metabolic ketoacidosis such as other organic acidurias and some primary hyperlactacidemias (mitochondrial diseases).

In late-onset forms: Different causes of MRI bilateral basal ganglia involvement associated with encephalopathy (mitochondrial cytopathies, organic acidurias, infectious encephalitis, homocystinuria, urea cycle disorders, biotinidase deficiency, creatine deficiency).

Diagnostic Workup

1. *First line laboratory tests*: Metabolic acidosis with ketonuria, haematological abnormalities (leukopenia, thrombocytopenia, anemia), hyperammonemia, and hyperuricemia are the most common routine laboratory findings. They often lead to the wrong diagnosis of sepsis.
2. *Brain MRI*: will provide helpful information especially in late-onset forms with neurological signs.
3. The diagnosis of PA is based on the presence of characteristic compounds detected by gas *chromatography/mass spectrometry* organic acid analysis in urine and blood acylcarnitine profile by tandem mass spectrometry. Methylcitric acid, 3-hydroxypropionate, propionylglycine, tiglylglycine, 3-hydroxy-2-methybutyrate, and 2-methyl-cetoacetate acids are usually elevated. Enzymatic and genetic studies confirm the diagnosis.

Management

Therapeutic approach in acute decompensations must be considered as an emergency and is based on the avoidance of protein intake and the inhibition of endogenous catabolism by providing enough energy (80–120 kcal kg^{-1} day^{-1} in a newborn). Insulin has an anabolic effect and can be added. Acidosis is corrected by rehydration and bicarbonate. Carnitine is used to buffer the intramitochondrial accumulation of propionyl-CoA. In the neonatal period during the refeeding phase, valine intake is progressively increased to 220–250 mg day^{-1} over a period of 5–7 days.

Long-term treatment is based on protein restriction and additional intake of amino acid mixtures free of valine, isoleucine, leucine, methionine, and threonine, to prevent protein deficiency, oral administration of L-carnitine (100 mg kg^{-1} day^{-1}) and metronidazole to reduce the microbial propionate production (10–20 mg kg^{-1} day^{-1} for 10 consecutive days each month).

Prognosis

The use of most accurate and early therapeutic strategies has improved survival over time but has not modified

neurodevelopment. The late-onset forms have a better prognosis compared with the neonatal/early-onset ones. However, neurocognitive deterioration is almost invariably present. Relapsing episodes of acute metabolic decompensation are associated with a high risk of basal ganglia stroke, responsible for severe motor disabilities. Decreased early mortality, less severe symptoms at diagnosis, and more favorable short-term neurodevelopmental outcome were recorded in patients identified through expanded newborn screening.

See also: Aromatic Amino Acid Decarboxylase Deficiency; Parkinson's Disease: Definition, Diagnosis, and Management.

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Propriospinal Myoclonus

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Glossary

Myoclonus – Shock-like muscle jerks.
Propriospinal myoclonus (PSM) – A type of spinal myoclonus characterized by involvement of muscles innervated by different segments of the spinal cord.
Spinal myoclonus – A form of myoclonus with origins of the movements in the spinal cord and its pathways.

Clinical Syndrome

Propriospinal myoclonus (PSM) is a type of spinal myoclonus characterized by involvement of muscles innervated by different segments of the spinal cord. The muscles activate sequentially through the propriospinal tract or pathway, which is a spinospinal fiber system interconnecting multiple spinal levels. These fibers are found mainly as a thin shell of small, mostly nonmyelinated fibers surrounding the spinal gray matter. The conduction

speed in the propriospinal tract is ~5–15 m s^{-1}, and is considered to be relatively slow when compared to the corticospinal tract (25–70 m s^{-1}). PSM involves spread of muscle jerks rostrally and caudally along spinal segments from a point of origin, typically in the mid-thoracic region, sometimes referred to as the 'pattern generator.' The timing of muscle activation remains relatively fixed.

PSM primarily involves axial muscles with spread often to proximal limbs, but usually spares cranially-innervated muscles. Clinically, it presents with truncal flexion or extension jerks, with neck, arm, hips, and knee flexion, usually bilateral in distribution. The myoclonus may be rhythmic or irregular, spontaneous, or stimulus-induced. When measured with electrophysiologic testing, the electromyographic (EMG) burst in PSM is longer than in cortical myoclonus, usually ranging from 150 to 300 ms. The electrophysiological characteristics of slow conduction and selective recruitment of truncal and proximal limb muscles can help differentiate PSM from spinal segmental myoclonus or generalized cortical myoclonus. However, it is hard to differentiate PSM from psychogenic/functional movement disorders without the help of electrodiagnostic studies.

PSM was first described in 1988 by Bussel and colleagues, when they reported a patient who developed spontaneous and stimulus-sensitive, rhythmic truncal and lower extremity extension jerks after suffering a complete lower cervical cord transaction from a severe C7 vertebral fracture. They postulated that the myoclonus was due to partial release of a spinal stepping generator. Brown and colleagues did extensive work as well, describing in detail the clinical and electrophysiological characteristics of several patients with predominant abdominal flexion contractions serving as an originating source with spread to neck, arm, and leg muscles. The conduction velocity was quite slow, ~5 m s^{-1}. In the majority of their patients, the myoclonus was stimuli-sensitive, and in several cases, the jerks persisted in sleep and were most prominent when lying supine. Brown and colleagues also suggested that spinal cord damage leads to the release of pattern generators that result in these involuntary movements.

Anatomical Localization

Similar to spinal segmental myoclonus, various spinal cord structural and pathologic processes may cause PSM, including arteriovenous malformations, tumors and cysts, infections, multiple sclerosis plaques, spondylitic myelopathy, cervical disc herniation, inflammatory processes, and trauma. A case report described a patient with new onset PSM following a T11 vertebral fracture, who subsequently experienced an episode of severe myoclonic activity and respiratory arrest. There appear to be idiopathic forms of PSM as well, and in many cases, magnetic resonance imaging of the spinal cord appears normal. Several cases of PSM related to nonstructural pathogenic factors have been reported, including presentation as a paraneoplastic syndrome related to breast cancer, related to ciprofloxacin use, and as the result of an enteropathogenic toxin. One case report described a patient with probable psychogenic PSM, despite having an electrophysiologic profile consistent with PSM. Another study showed that healthy volunteers could simulate PSM clinically and electrodiagnostically but with prolonged EMG burst durations. These two reports appear to indicate that electrodiagnostic studies play an important diagnostic role in PSM but are not full-proof.

Pathophysiology

The pathophysiologic mechanisms for PSM are not fully understood, but in general spinal interneuron dysfunction is thought to be a primary cause, via reduced inhibitory mechanisms. In some cases, dysfunction in motoneurons in the spinal cord has been suggested to be the cause of repetitive muscle jerks. And as postulated by Brown and Bussel, a pattern generator in the spinal cord that is abnormally released may be the initiator for abnormal hyperexcitability in the cord. It is unclear what factors determine whether a structural lesion will lead to segmental involvement only or to caudal–rostral spread via the propriospinal pathway.

Treatment

Treatment of PSM should first be directed at any primary treatable causes if possible. Symptomatic treatments have included clonazepam, which is considered the medication of first choice, as well as diazepam, levetiracetam, valproic acid, tetrabenazine (currently not approved in the United States), baclofen, 5-hydroxytryptophan, and carbamezapine.

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Relevant Websites

www.movementdisorders.org – Movement Disorder Society.

Proteasome Function in Movement Disorders

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Glossary

Macroautophagy – A process in which double membrane structures engulf cytoplasmic constituents, which are then degraded within lysosomes, following autophagosome–lysosome fusion.
Proteasome – A multicatalytic protein complex that degrades the majority of intracellular proteins.
19S proteasome – A multicatalytic protein complex responsible for recognition of polyubiquitinated proteins, and for threading them into the 20S core.
20S proteasome – A barrel-like structure comprising the enzymatic core of the proteasome.
Ubiquitin – A 76 amino acid protein which is responsible for tagging protein substrates for proteasomal degradation.

Definition and History

Proteasomes, together with lysosomes, are the main systems of intracellular protein degradation. In recent years, dysfunction of the proteasomal pathway of protein degradation has been proposed as a major pathogenetic mechanism underlying Parkinson's disease (PD) and other neurodegenerative conditions. Targets for degradation by the proteasome include rapidly turning over, misfolded, damaged, or oxidatively modified proteins, and, consequently, in many cell types the bulk of total intracellular protein degradation occurs through this system. In most cases, protein substrates are tagged with multiple adducts of a small molecule, ubiquitin, in order to be degraded through the proteasomes, hence the term 'ubiquitin proteasome system' (UPS). Ubiquitination begins with the ATP-dependent activation of ubiquitin by a universal E1 ubiquitin-activating-enzyme. Activated ubiquitin is then transferred to a member of the E2 ubiquitin conjugating enzyme (UBC) family. E2s then transfer ubiquitin to a complex formed between a member of the E3 ligase family and the particular protein substrate, leading to the covalent attachment of ubiquitin to a lysine residue of the substrate, via the catalytic activity of the ligase. The cycle is then repeated to attach further ubiquitin moieties, thus forming a polyubiquitin chain on the substrate. In some cases, E4 enzymes are involved in the stacking of ubiquitin molecules on each other. E2s and, especially, E3s and E4s are specific for a substrate or a group of substrates.

The polyubiquitinated proteins that are formed are subsequently recognized and degraded by the proteasome. Natively unfolded proteins may not need ubiquitin tagging, and thus, ubiquitin-independent proteasomal degradation also occurs. The 26S proteasome contains a core catalytic component, the 20S proteasome, flanked on both sides by a 19S cap, also termed PA700. Polyubiquitinated proteins signaled for degradation are recognized by and bind to components of the 19S cap. Four or more ubiquitin adducts are required for recognition. Following the detachment of the polyubiquitin chain, substrates enter the cylindrical pore formed by the 20S proteasome, which is a barrel-like structure that consists of two identical outer rings of seven α subunits each and two identical inner rings of seven β subunits each. Within the 20S core, substrates are degraded by three sets of enzymes, with chymotrypsin-like, trypsin-like, and peptidylglutamyl-like activity. Proteasomal proteolysis is ATP-dependent and leads to the production of small peptides that are further degraded in the cytosol. The polyubiquitin chains are hydrolyzed to monomeric ubiquitin through the action of de-ubiquitinating enzymes, which include, amongst others, ubiquitin C-terminal hydrolases (UCHs). The released monomeric ubiquitin is reactivated by E1 in order to act on further substrates.

The function of the proteasome is assessed by measuring the three enzymatic activities present within the 20S core by incubating cell lysates or tissue extracts with artificial fluorogenic substrates. Alternatively, the levels or half-lives of particular substrate proteins that are proteasomal targets can be assessed. Such artificial substrates have been created and tagged to fluorescent proteins, so that their accumulation can be monitored in living cells. A method that can be used to assess accumulation of proteasomal targets more globally is Western immunoblotting for ubiquitin. In the case of impairment of the proteasomal system, there is accumulation of polyubiquitinated proteins. However, lysosomal impairment and, in particular, inhibition of macroautophagy may also lead to such accumulation.

Genetic Data Linking the UPS with PD

Genetic data support the idea that defects in the UPS may lead to PD. The product of the *Parkin* gene, which is mutated in early onset autosomal recessive parkinsonism, is an E3 ligase. Mutations in the *Parkin* gene may lead to

diminution or loss of E3 activity, but also to the loss of function through altered stability or solubility. *Parkin* overexpression can ameliorate proteasomal function, and may act as a general facilitator of the degradation of misfolded proteins, in part through binding to the proteasome. Thus, the loss of function of *Parkin*, apart from its effects on the build-up of its specific protein substrates, may lead to more generalized UPS defects. The function of *Parkin*, however, may not be restricted to the UPS, as it may connect to endosomal or lysosomal pathways through monoubiquitination. Furthermore, in seeming contradiction to its facilitatory role in protein degradation as a classical E3 ligase, it may ubiquitinate substrates via the K63 (instead of the classical K48) ubiquitin residue, thus leading to substrate stabilization, instead of degradation. *Parkin* may, thus, have a role in inclusion formation, which may help explain the general lack of inclusions in Parkin-related parkinsonism.

A mutation in UCH-L1, I93M, has been found in one family with autosomal dominant PD, but its pathogenicity is questioned. Whether the S18Y UCH-L1 polymorphism actually offers protection against PD development, as initial studies indicated, is also questionable. UCH-L1 is an abundant neuronal-specific protein, which belongs to the family of UCHs, thus is expected to be a cleaver of ubiquitin, usually monomeric. However, a main function of UCH-L1 is the maintenance of free cellular ubiquitin levels. UCH-L1, similar to Parkin, may also function in a dimeric form, as an aberrant E3 ligase, binding to protein substrates such as α-synuclein and ubiquitinating them via K63, leading to their build-up in the cell. Whether the genetic alterations identified are linked to PD through a loss or gain of function is contested. In sporadic PD, decreased brain levels and oxidative modifications of UCH-L1 have been identified. An unexpected finding from our laboratory has been that the S18Y polymorphism conferred a novel function to UCH-L1, that of a potent antioxidant that prevented oxidative stress-induced ROS generation and death in neuronal cells.

SNCA, the first gene found to be linked to PD encodes for the presynaptic protein α-synuclein, which is also a major component of Lewy bodies (LBs). A number of links between α-synuclein and the proteasome have been proposed. Initial reports suggested that α-synuclein is degraded via the UPS, but we and others have failed to confirm this. Instead, we have found that only very specific soluble α-synuclein oligomeric species, comprising a very small proportion of total α-synuclein, are degraded by the proteasome, and, at the same time, inhibit its function, likely by 'clogging' the 26S proteasome. The A53T mutant appears to have a greater tendency than the WT protein to cause this effect. Certain reports suggest that α-synuclein interacts directly with proteasomal components. It remains to be seen whether the effect of α-synuclein on UPS function represents a significant component of its toxicity.

Studies in Human PD

Ubiquitin within LBs represents polyubiquitinated proteins, and therefore, if there is dysfunction of the UPS in PD, this should be at a level beyond polyubiquitination, at the level of the proteasome. Two groups have reported a decrease of enzymatic proteasomal activity in substantia nigra (SN) of PD patients compared to controls, whereas activities in other CNS regions were unaltered. The specificity of the effect appears to confirm the UPS dysfunction hypothesis in PD, however, a note of caution is needed. The SN is severely depleted of dopaminergic neurons in terminal PD, and therefore, the enzymatic assay is mainly measuring the activity generated from nondopaminergic cells, particularly glia. Furthermore, these studies cannot exclude UPS dysfunction at other levels beyond the 20S proteasome in nonnigral brain regions.

In any case, these studies collectively show that there is a regional impairment of enzymatic activity of the proteasome at the level of the SN in PD (and diffuse Lewy body disease (DLBD)) patients. Studies in incidental Lewy body cases would be needed to establish whether such impairment occurs early in disease pathogenesis, prior to overt nigral cell loss and gliosis.

The accumulation of aberrant soluble oligomeric species of α-synuclein may be the factor leading to proteasomal dysfunction in PD. Alternatively, changes in the levels of select proteasomal subunits, such as the α subunits of the 20S proteasome, have been reported in PD, and other factors such as aging, oxidative, nitrosylative stress, or mitochondrial dysfunction may also be contributory. Application of mitochondrial toxins, in particular, leads to proteasomal impairment in experimental cell and animal models.

Models of UPS Dysfunction in Cell Culture

If UPS dysfunction is a significant factor in PD pathogenesis, proteasomal dysfunction in experimental cell models would be expected to generate a PD-like phenotype. We and others have, therefore, applied relatively selective pharmacological proteasomal inhibitors to cultured neuronal cells, and have detected formation of cytoplasmic ubiquitinated inclusions and neuronal death. Inclusions stain positively for many components of LBs, including for Thioflavin S, which detects fibrillar, β-amyloid-like structures. We have furthermore mapped the pathways involved in these two phenomena, neuronal death and inclusion formation. We have found that proteasomal inhibition may lead to morphologically apoptotic or non-apoptotic neuronal death. In both cases, there is participation of caspases and the apoptotic machinery. Aberrant activation of cell cycle components and p53

nuclear translocation are involved in death, but not the inclusion formation. Formation of inclusions is an active, transcription-dependent process, which also requires ubiquitination. α-synuclein, present within the inclusions in a monomeric and oligomeric conformation, is not required for initial ubiquitinated inclusion formation, but for fibrillar elaboration. Interestingly, the lysosomal pathway of macroautophagy is activated in response to proteasomal inhibition and contributes to the clearance of the inclusions, providing evidence for cross-talk between the two main pathways of intracellular protein degradation. Overall, there is dissociation between inclusion formation and death, suggesting that these phenomena occur in parallel, largely independently of each other.

Although the issue is somewhat controversial, most studies, including our own, have found that cultured nigral dopaminergic neurons are selectively sensitive to death induced by proteasomal inhibition. This could be due to the contribution of oxidative products of dopamine metabolism and the relative lack of a protective HSP70 upregulation response in these neurons.

Models of UPS Dysfunction in vivo

In an attempt to model proteasomal dysfunction in vivo, direct intrastriatal or intranigral injections of pharamacological proteasomal inhibitors in rodents have led to relatively selective nigrostriatal degeneration, with formation of rather ill-defined inclusions in the remaining nigral neurons. McNaught and colleagues applied pharmacological proteasome inhibitors systemically, via the intraperitoneal route, and observed selective neuronal degeneration and ubiquitin/α-synuclein/thioflavin-S-positive inclusions in various brainstem structures, including the SN. Proteasomal function, measured by the enzymatic assay, was only decreased in the nigra and in other affected regions, which may not have the reserve capacity to withstand such insults. They suggested that systemic exposure to the natural proteasomal inhibitors may underlie certain forms of sporadic PD. However, most laboratories have not been successful in replicating this original model.

A very exciting development has been the generation of the first genetic mammalian model of brain proteasomal dysfunction. In this model, regional ablation in the forebrain or in catecholaminergic neurons of Psmc1, a subunit of the 19S proteasome, led to neuronal degeneration and inclusion formation. The inclusions contained α-synuclein and resembled pale bodies identified in PD patients as possible precursors of LBs. Beyond doubt, this model proves that 26S proteasomal dysfunction can lead to a PD-like phenotype in rodents and will be very useful in preclinical studies, if UPS dysfunction turns out to be a major pathogenetic factor in PD.

Huntington's and Related Polyglutamine Repeat Diseases

Mutant huntingtin and other expanded polyglutamine repeat proteins are degraded, at least in part, by the proteasome. Ron Kopito et al., by expressing truncated forms of such proteins in cells carrying a reporter for proteasomal function, made the seminal observation of the link between protein aggregation and UPS dysfunction, which may play a significant role in the pathogenesis of these disorders. Mutant huntingtin has been shown, using reporters of UPS activity targeted specifically to the synapses, to cause UPS impairment both presynaptically and postsynaptically. The UPS normally regulates synaptic function and plasticity, and its dysfunction may underlie the synaptic aberrations that occur in these triplicate repeat disorders and in other neurodegenerative diseases.

However, mutant huntigtin expression in cells does not always cause UPS dysfunction, in part because of compensatory upregulation of proteasomal components or accelerated proteasomal biogenesis, which underlines the dynamic nature of the system. Similarly, it has been controversial whether expression of mutant huntingtin causes UPS impairment in vivo. Using a novel mass-spectrometry-based method, Kopito et al. have shown that there is indeed accumulation of polyubiquitinated proteins in the human disease, as well as in the well characterized R6/2 transgenic and knockin mutant huntingtin mouse models.

Actually, in Huntington's disease (HD) tissues, proteasomal dysfunction is more widespread than expected. Unaffected brain regions and even patient fibroblasts showed impairment of enzymatic proteasomal activity compared to controls. Patients from the very early stage of the disease, with little neuronal loss, also showed proteasomal dysfunction. Therefore, in contrast to the situation in PD, altered cellular composition cannot account for the observed changes. These data suggest that a decrease of proteasomal activity may not be directly toxic, and that issues of selective vulnerability or additional aggravating factors may play a role in determining whether a cell can withstand proteasomal impairment.

Given that no obvious inclusions are present in many of the tissues assessed, the inference is that prefibrillar forms of mutant Huntingtin may be responsible for such proteasomal dysfunction, 'clogging' the system in a similar way to that mentioned for α-synuclein. Alternatively, the large amount of aggregated protein may overwhelm the system by consuming ubiquitin or other elements of the pathway such as proteasomal components themselves, or molecular chaperones. Furthermore, isolated mammalian proteasomes cannot degrade the regions with the polyglutamine repeats, and release them without processing them further. The accumulation of these

super-aggregated species may have further detrimental effects, feeding into a vicious cycle.

There is evidence that some of the polyglutamine repeat proteins, such as Ataxin-3 and -7, may normally serve functions within the UPS pathway. They interact directly with polyubiquitinated proteins, the proteasome, and other UPS components, and may assist in the presentation of polyubiquitinated substrates to the proteasome.

Inhibition of ubiquitination leads to decreased inclusion formation but enhanced toxicity induced by huntingtin or other polyglutamine repeat proteins in cellular and animal models. Therefore, ubiquitination appears necessary for inclusion formation, and inclusions may be protective. Alternatively, there may be something inherently protective in the process of ubiquitination itself, and disrupting that may lead to enhanced toxicity in these conditions. This latter possibility is supported by the recent finding that reduction of free ubiquitin leads to neurodegeneration in vivo.

There is also other indirect evidence for the existence of UPS dysfunction in HD brains. Ubiquitin B (UBB^{+1}) is an aberrant form of ubiquitin caused by molecular misreading at the mRNA level. Under normal circumstances, its protein levels are nondetectable, and they only accumulate in situations of proteolytic stress. Elevated protein levels of UBB^{+1} have been detected in brains of patients with HD or SCA3, suggesting that in these conditions the UPS is impaired. Accumulation of UBB^{+1} can lead to further proteasomal inhibition, and may be a contributing factor to neurotoxicity in these disorders.

Conclusions

Genetic, biochemical, and pathological data suggest that UPS dysfunction may be an important pathogenetic factor in PD, HD, and other movement disorders. More work needs to be done before UPS dysfunction may be considered as a target for therapeutic interventions in these conditions.

See also: Alpha-synuclein; Ataxin; Huntington's Disease: Genetics; PARK1, Alpha Synuclein; PARK2, parkin; PARK5, UCH-L1.

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Pseudoathetosis

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Glossary

Athetosis – A writhing involuntary movement characterized by inability to maintain the limbs in a posture.

Pseudoathetosis – Writhing involuntary movements caused by severe loss of proprioceptive input to the striatum.

Definition and History

The term 'athetosis' is derived from the Greek word for 'without fixed position.' The description of athetosis is attributed to Hammond: 'Under the name of athetosis I propose to describe an affection which is mainly characterized by an inability to retain the fingers and toes in any position.' The term 'pseudoathetosis' was introduced by Dooling and Adams, and refers to athetotic movements that result from loss of proprioceptive input.

Pathogenesis/Pathophysiology

Pseudoathetosis generally occurs in patients with severe sensory loss in the context of normal motor function. The movements seem to relate to difficulty with integration and control of motor function consequent to loss of proprioceptive input to the striatum.

Epidemiology/Risk Factors

Pseudoathetosis is considered rare, though there are no data on epidemiology or risk factors.

Clinical Features and Diagnostic Criteria

Pseudoathetotic limbs exhibit continuous slow writhing movements that may be worse with posture-holding and action, external stimuli, mental stress, as well as when the eyes are closed. Movements are most prominent in the distal limbs, and are confined to limbs affected by the sensory disturbance. While their onset often coincides with the onset of significant proprioceptive loss, published reports of spinal pseudoathetosis suggest that involuntary movements may first appear after the sensory loss has been present for some time and in association with a painful crisis during the disease course.

There are no validated diagnostic criteria for pseudoathetosis. In 1994, Sharp et al. described seven cases and suggested the following clinical features: (1) the duration of the movement disorder is the same as the duration of the underlying sensory abnormality; (2) the distribution of the movement disorder is the same as the distribution of the sensory loss; (3) if the sensory abnormality resolves, the movement disorder also resolves; (4) lesions at all levels of the sensory pathways may be involved.

Differential Diagnosis

Pseudoathetosis must be distinguished from chorea, athetosis, and dystonia.

Once the movements are correctly identified, the differential diagnosis depends on the localization of the underlying lesion or disease process. Pseudoathetosis can result from a lesion anywhere along the sensory pathways that carry proprioceptive information. The differential diagnosis is broad and includes: peripheral nerve diseases such as neuropathy and leprosy; disease of the dorsal root ganglion such as that associated with diabetes mellitus; spinal cord pathology such as multiple sclerosis, subacute combined degeneration associated with Vitamin B12 deficiency, myelitis, infarct, trauma, tumor, syringomyelia; and brainstem disease such as central pontine myelinolysis, thalamic damage due to tumor or stroke, and motor cortex diseases.

Diagnostic Work-up/Tests

The diagnostic work-up depends on clinical localization of the underlying lesion and may include nerve conduction velocity studies and electromyography, somatosensory-evoked potentials, neuroimaging studies of the spinal cord or brain, and cerebrospinal studies.

Management

The primary focus is on treating the underlying etiology of the illness. There is no proven treatment for the movements themselves.

Prognosis

Prognosis is generally linked to that of the underlying lesion or disease process.

See also: Athetosis; Dystonia.

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Pseudobulbar Symptoms

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Background and Clinical Features

Sudden outbursts of involuntary, difficult-to-control, exaggerated laughter and/or crying have long been known to occur in patients with neurological disorders. In a 1924 paper, Kinnier Wilson described the core features of the "pseudobulbar affect" (PBA) syndrome and its association with focal and diffuse brain pathology across widely distributed networks. He noted that patients' emotional displays were often disproportionate to the stimuli that evoked them, inappropriate to the context in which they occurred, and out of synchrony with their subjective feelings. Wilson hypothesized that the anatomical basis for this syndrome was the loss of voluntary, cortical inhibition from brainstem centers that produce the faciorespiratory functions associated with laughing and crying.

PBA occurs on a spectrum of severity and can significantly impair social and occupational function. PBA may be associated with aspiration risks and contribute to medical morbidity.

Several different terms have been used for the clinical syndromes related to PBA. Clinicians have also used terms such as pathological laughing and weeping, emotional lability, emotional incontinence, pathologic emotionality or affect, and emotionalism to refer to these disorders. PBA has been reported in association with stroke, brain trauma, motor neuron disease, multiple sclerosis, and other neurodegenerative disease.

Measurement Instruments

Standardized scales exist, which may be used to screen for PBA, or to follow the severity of PBA over time. Two such scales are available.

Robinson and colleagues developed the Pathological Laughter and Crying Scale (PLACS), an interviewer-rated instrument, which is both valid and reliable in quantitatively assessing the severity of PBA symptoms in stroke patients. The PLACS rates sixteen items to quantify the aspects of laughter and crying, and scores the severity of each symptom on a 0–3 point scale. Scores on all items are totaled to obtain an overall score. A score of 13 or higher was reported to distinguish those with PBA.

Moore and colleagues developed and validated the Center for Neurologic Study-Lability Scale (CNS-LS), a self-report measure of "affective lability" in patients with amyotrophic lateral sclerosis (ALS). The CNS-LS quantifies perceived aspects of PBA, including frequency, intensity, lability, degree of voluntary control, and inappropriateness to context. It consists of two subscales: one for laughter (4 items) and one for tearfulness (3 items). Each item asks respondents to indicate on a five-point scale (where 1 = applies never and 5 = applies most of the time) how often they experience symptoms of PBA. A score of 13 on the CNS-LS, as on the PLACS, is thought to be the threshold for significant PBA.

Neural Substrates of the Disorder

The PBA syndrome occurs in patients with some structural disease of the central nervous system, capable of disturbing the functional neural networks of emotional display. These networks are distributed through prefrontal, temporal-amygdala, brainstem, and cerebellar systems. The neurochemistry of these systems is also complex, involving various receptor networks mediated by serotonin, dopamine, acetylcholine, histamine, γ-amino butyric acid, glutamate, *N*-methyl-D-aspartate, and opioids. The central neurophysiologic concept concerning the neurobiology of PBA is that there occurs an interruption of one or more inhibitory neural networks related to brainstem nuclei that affect the complex physiologies of laughter and weeping. No single anatomic site seems necessary or sufficient for the expression of the PBA syndrome. Lesions may occur in subfrontal systems, connector systems in the brainstem, or in the cerebellum.

Treatment

There are clinical reports of therapeutic benefit for the PBA syndrome from both antidepressants and dopaminergic agents. Comparative trials, case series, and individual reports suggest that tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitor (SSRI) antidepressants have efficacy. Dopaminergic agents have also been reported to benefit the PBA syndrome. Psychotherapy is not considered helpful in the treatment of PBA. A novel therapeutic option is under investigation for the treatment of the PBA syndrome, consisting of a fixed combination of dextromethorphan and quinidine. Dextromethorphan is a well-known antitussive agent with pharmacological activity as a potent sigma-1 agonist and as a noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist. Rapid metabolism of dextromethorphan is blocked by quinidine, a cytochrome P450 2D6 inhibitor, resulting in an increased availability of dextromethorphan. This product was proved effective and safe for PBA in two multicenter, controlled trials, one in amyotrophic lateral sclerosis patients and one in multiple sclerosis. Since dextromethorphan has agonist action on sigma receptors in brainstem and cerebellar neural networks, these efficacy studies suggest the possibility that there may be a selective neurochemistry to the PBA syndrome and to its treatment.

See also: Dementia, Movement Disorders; Progressive Supranuclear Palsy.

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Psychogenic Movement Disorders

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Definition and History

Psychogenic movement disorders (PMDs) are physical manifestations of an underlying psychiatric illness or malingering and cannot be attributed to any known structural or neurochemical diseases. Clinically, PMD often present with complex movements of various phenomenology. Symptoms can mimic the full spectrum of organic abnormal involuntary movements, affect gait and speech, or present as bizarre undifferentiated movements. From a psychiatric perspective, most PMD fulfill criteria for somatoform disorders, and more specifically, conversion disorders of the motor subtype. The first descriptions of somatoform disorders, found in the medical literature of ancient Egypt, date back to 2000 BC. Hippocrates first introduced the term 'hysteria' (Greek for uterus)

into the medical literature. Hysteria was looked at as a disorder of the uterus, until Galen first described it in men and attributed its cause to sexual abstinence. In the nineteenth century, the French neurologist Jean-Marie Charcot took a major interest in the study of hysteria and described the clinical features in detail in his lectures and manuscripts. The modern concept of a psychiatric origin of hysteria and psychotherapy as a treatment modality were finally introduced in 1893 by the Austrian physicians Josef Breuer and Sigmund Freud.

Pathophysiology

The pathophysiology of PMD and other somatoform disorders remains unclear, but initial steps to understand the underlying mechanisms have been undertaken with the use of functional neuroimaging. Spence et al. used positron emission tomography (PET) to investigate the pathophysiology of psychogenic paralysis. They studied two men with psychogenic left-arm weakness, two healthy individuals feigning arm weakness, and six normal controls. Measurements of regional cerebral blood flow showed a relative hypoactivity of the left dorsolateral prefrontal cortex when attempting to move the affected right limb in subjects with psychogenic paralysis compared with feigners and normal controls. Marshall and colleagues evaluated a patient with left-sided psychogenic paralysis, using PET scanning and found failed activation of the right primary motor cortex and overactivation of the right orbitofrontal and anterior cingulate cortex. A study by Vuilleumier and colleagues aimed at differentiating imaging findings secondary to the somatoform disorder itself from findings attributable to coexisting psychiatric disorders such as depression and anxiety. The investigators compared Tc-99m single-photon emission computerized tomography (SPECT) imaging data from patients with psychogenic sensorimotor paralysis before and after recovery by measuring cerebral blood flow at rest and with an activation procedure of passive vibratory stimulation of both hands. There was a decreased regional cerebral blood flow in the thalamus and basal ganglia contralateral to the deficit in each subject. Importantly, these abnormalities resolved with clinical recovery, suggesting that conversion disorders may entail functional disorders in striatothalamocortical circuits controlling sensorimotor function and voluntary motor behavior.

Epidemiology/Risk Factors

PMD account for approximately 2–3% of cases seen in movement disorders clinics. Estimates for the prevalence of psychogenic disorders in the general neurology population vary, but range between 1% and 9%, depending on the applied definitions and methods for case ascertainment. The mean age of onset of PMD ranges between 37 and 50 years and women are predominantly affected. There are no data in the literature on racial distribution, but a transcultural comparison between PMD subjects in Spain and the United States found essentially similar demographic and clinical characteristics. Risk factors for PMD include major emotional stressors such as divorce or death of a family member, history of sexual abuse or rape, previous surgery, or other physical trauma.

Clinical Features and Diagnostic Criteria

Typical characteristics of PMD are abrupt onset, history of a precipitating event, rather fast progression to maximal symptom severity, distractibility, and variability of the movement disorder. The movement phenomenology can mimic the whole spectrum of movements seen in movement disorders of organic origin (tremor, dystonia, chorea, bradykinesia, myoclonus, tics, athetosis, ballism, cerebellar incoordination), and also affect speech and gait. Tremor and dystonia are most common, whereas parkinsonism is only rarely seen. When evaluating patients for psychogenic tremor, the presence or absence of entrainment and coactivation are useful clinical indicators. Entrainment is tested by having the patient execute voluntary movements at a given frequency with the extremity contralateral to the side under evaluation. The psychogenic movement will assume the frequency of the contralateral voluntary movement if entrainment is present. Coactivation refers to an increased muscle tone in the tremulous extremity affected by PMD that is inconsistent during the examination and can be overcome with passive movement. Typical features of psychogenic dystonia include fixed dystonic postures, excessive pain, or unusual distribution of symptoms such as limb dystonia in an adult.

Patients with PMD often exhibit multiple movement phenomena, have bizarre undifferentiated movements, or present with dysfunction of gait and speech in addition to other PMD symptoms. Psychogenic gait disorders often present with exaggerated effort and slowness, bizarre uneconomic postures, convulsive shaking episodes, sudden knee buckling, and near falling. Psychogenic speech disturbances can present with excessive slowness of speech output, stuttering, or even mutism. Symptoms may fluctuate drastically and sometimes resolve completely when the patient is unaware of being observed. The movement disorder is often accompanied by other psychogenic neurological symptoms such as false weakness, excessive pain and tenderness, or coexisting psychiatric illnesses.

Based on these clinical features, Fahn and Williams have defined four diagnostic categories of PMD:

1. *Documented PMD:* Movements relieved by psychotherapy, suggestion, or placebo, or spontaneous symptom resolution when the patient feels unobserved.

2. *Clinically established PMD:* Movements incongruent with organic disease or inconsistent symptoms, in addition to the presence of other false neurological signs, multiple somatizations, or a documented psychiatric illness.
3. *Probable PMD:* Movements are incongruent with organic disease or inconsistent, but no other supportive features are present.
4. *Possible PMD:* Suspicion for PMD, based on the patient's obvious emotional disturbance alone.

According to the DSM IV, there are three pertinent diagnostic categories for the psychiatric classification of PMD: somatoform disorders, factitious disorders, and malingering. Somatoform disorders encompass conversion disorders (physical symptoms that are brought on by psychological stressors), as well as somatization disorders (a multitude of physical, nonorganic symptoms). Factitious disorders refer to symptoms that are intentionally produced with the purpose of achieving some psychological gain, whereas malingering is the intentional symptom production for a material (e.g., financial) gain. The most commonly encountered psychiatric diagnosis of PMD is conversion disorder, followed by somatization disorder, factitious disorder, and malingering. PMD are commonly associated with other axis I psychiatric disorders; most commonly depression and anxiety.

Differential Diagnosis

The differential diagnosis of PMD consists of ruling out the organic counterpart of the type of PMD in question. By means of careful history taking, detailed physical examination and ancillary testing, clues to organic disorders will be elicited. A slowly progressive course without a precipitating event, associated organic abnormalities such as pathological reflexes, and electrophysiological findings suggestive of organic disease will make a diagnosis of PMD unlikely. Organic dystonia as well as paroxysmal dyskinesias are organic movement disorders that are quite often mistaken for PMD, highlighting the importance for expert evaluation.

Diagnostic Workup/Tests

Ancillary testing in the form of neuroimaging and spinal fluid examination is often undertaken to exclude organic diseases. In addition, there are several neurophysiological tests that positively reinforce the diagnosis of PMD. In cases of psychogenic tremor, electromyography (EMG)-based tremor analysis can demonstrate entrainment, an increase of tremor amplitude and frequency with weight loading of the tremulous extremity, variability in tremor frequency, and coactivation of antagonist muscles. EMG evaluation of psychogenic myoclonus is used to demonstrate an abnormally long and variable latency between stimulus and the myoclonic response, variable patterns of muscle recruitment within each jerk, and prolonged duration of myoclonic bursts, as well as significant habituation with repeated stimulation. In difficult-to-diagnose cases of psychogenic parkinsonism, functional neuroimaging with [^{123} I]β-CIT SPECT or [^{18}F]DOPA-PET has been used, confirming the absence of striatonigral degeneration in PMD.

Management

The management of PMD contains three important steps: (1) Clear and sensible delivery of the diagnosis by the neurologist, (2) avoidance of iatrogenic harm from unnecessary tests and medications, and (3) treatment by a psychiatrist, often in conjunction with a psychologist and physical therapist.

It is important for the treatment success that the patient understands the diagnosis of PMD. The specific movement disorder based on the primary movement phenomenology (e.g., tremor, dystonia, myoclonus) should be disclosed, and the underlying etiology (PMD) clearly discussed in layman's terms. Some physicians prefer the term 'functional movement disorder' as the term 'psychogenic' might be perceived as pejorative by the patient. On the other hand, 'psychogenic' seems to be more meaningful and easier to grasp, and 'functional' might be somewhat artificial and abstract. In any case, the concept of physical expression of emotional problems should be explained, as well as the potential for better outcome of PMD compared with organic neurodegenerative diseases. A referral to a psychiatrist will be made who will first establish the pertinent diagnostic category for PMD (somatoform disorder, factitious disorder, or malingering) and define secondary psychiatric illnesses. Treatment of the psychiatric comorbidities, most often depression or anxiety, can improve physical symptoms. Clear guidance as to the best psychiatric treatment modality specific to PMD is lacking, but a combination of psychodynamic psychotherapy and antidepressants or anxiolytics is often used, sometimes in conjunction with a rehabilitative physical or occupational therapy program. Cognitive behavioral therapy aimed at the reduction of perceived stress and disability and limiting the inappropriate use of medical care has also been shown to be of value in the management of functional somatic symptoms.

Prognosis

The outcome of patients with PMD is highly variable and mostly dependant on the duration of symptoms by the time of diagnosis. If left untreated, PMD are often chronic and disabling, persisting in 65–95% of patients. A treatable comorbid psychiatric condition such as depression or

anxiety has been found to be a positive prognostic factor. Negative prognostic value has been associated with long-standing symptoms, insidious onset of movements, and primary psychiatric diagnosis of hypochondriasis, factitious disorder, or malingering. Other commonly encountered obstacles to treatment are patient resistance toward the diagnosis of psychogenicity, and lack of willingness to engage in psychiatric treatment. If PMD are recognized early and appropriate psychiatric treatment is administered, functional status could be completely restored.

See also: Factitious Disorders; Malingering; Somatoform Disorders.

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Relevant Websites

www.mentalhelp.net/poc/center_index.php?id=112

Psychosis in Parkinsonism

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Glossary

Acetylcholinesterase inhibitors – Pharmacological agents that inhibit the acetylcholinesterase enzyme from breaking down the neurotransmitter acetylcholine.

Atypical antipyschotics – Heterogeneous group of pharmacological agents used to treat psychiatric conditions that differ from traditional antipsychotics in chemical composition and/or side effect profile.

Delirium – A transient mental state characterized by confusion and disorientation, sometimes associated with psychotic phenomena.

Delusion – A false belief often firmly held in light of evidence to the contrary that is not explained by cultural or religious doctrine.

Hallucination – A disturbance in the perception of reality consisting of a sensory experience without an external percept. Can manifest in a variety of modalities (i.e., visual, auditory, olfactory, tactile, gustatory).

Illusion – A sensory distortion resulting from incorrectly perceiving or misinterpreting an external percept.

Psychosis – A mental disorder characterized by a compromised ability to recognize reality consisting of hallucinations and/or delusions.

Definition and History

Psychosis in PD is characterized by hallucinations that are primarily visual, delusions, and 'minor' sensory disturbances such as illusions, 'passage,' and 'sense of presence' hallucinations. The understanding of psychosis in PD has expanded markedly from an initial interpretation of symptoms as dopaminergic drug side effects to the current view of a complex interplay of extrinsic and disease-related factors.

Dopaminergic medication use was the first risk factor implicated in PD psychosis. However, hallucinations in PD patients were reported prior to the introduction of levodopa. Evidence that dopaminergic medications are neither necessary nor sufficient to account for psychotic symptomatology is accumulating, and the underlying pathophysiology of psychosis is a rich area of research.

Pathophysiology

The Role of Dopaminergic Medications

All PD medications have been implicated in the appearance of psychotic features, and these features often remit after drug therapy has been reduced or eliminated. Dopaminergic agonists (e.g., cocaine and amphetamine) can induce psychotic symptoms. Conversely, the mechanism of action of atypical antipsychotics (AAs) used to reduce the occurrence of these symptoms is thought to involve dopamine (D2) receptor occupancy. A prominent theory for the mechanism by which PD drugs increase susceptibility to psychosis involves hypersensitization of dopamine receptors following chronic stimulation, which may lead to dysfunction of limbic structures that assign emotional and hedonic significance to sensory input. This dysfunction may result in misattributions of internal stimuli as having originated from the external sensory world.

However, studies have failed to find a clear relationship between medication dosage and the occurrence or severity of psychosis in PD. Psychotic symptoms have also been found to be associated with nondopaminergic agents, such as anticholinergics and amantadine. Intrinsic, disease-related processes combine with anti-PD medications to contribute to the emergence of PD psychosis. Recent research implicates visual processing abnormalities, sleep dysfunctions, and structural and neurochemical changes.

Visual Processing Abnormalities

PD patients who experience visual hallucinations may also suffer from deficits in visual processing. Compared with nonhallucinating PD patients, hallucinators exhibit a lower visual acuity, deficits in color and contrast recognition, and a greater ocular pathology, including cataracts, retinal disease, and glaucoma. Disease-related dopamine deficiency at the level of the retina has been linked to the occurrence of visual hallucinations in both PD and dementia with Lewy bodies (DLB). These deficits may facilitate the onset of visual hallucinations.

While structural MRI studies of hallucinating PD patients have not revealed specific occipital lobe or deep white matter lesions, studies using fMRI have identified functional abnormalities in visual processing. Hallucinating PD patients appear to exhibit a more frontal (i.e., BA 44, 6), visual association cortex (i.e., BA 19), and subcortical (i.e., caudate nucleus) activation coupled with a less occipital activation than do nonhallucinating PD patients. Hallucinators exhibit deficient reality monitoring in that they are more likely to believe that mental images represent real external stimuli. Such findings may indicate disinhibition of 'top-down' processing and the subsequent release of internally generated images into areas that normally represent externally generated percepts, perhaps resulting from the weakening of retinal–striatal–cortical signals.

Sleep Dysfunction

Psychosis in Parkinson's has also been linked to sleep disturbances. Although the 'continuum hypothesis,' which asserts that sleep disturbances in PD lead to altered dream phenomena and then to frank daytime hallucinations and delusions, has not been fully supported, these phenomena do appear to overlap. A prominent view of the relationship between sleep disturbances and PD psychosis involves disruption in rapid eye movement (REM) sleep. Polysomnographic studies of Parkinson patients have found a relationship between visual hallucinations and short, fragmented REM sleep. Specifically, patients experiencing hallucinations evidenced lower sleep efficiency and reduced total REM sleep time and percentage, compared with nonhallucinating patients. Some purport that visual hallucinations in PD represent a narcolepsy-like phenomenon in which REM dream imagery intrudes into the waking state, perhaps due to a reduction in acetylcholine. Moreover, sedating antipsychotic drugs such as quetiapine and clozapine have shown a greater efficacy in controlling psychosis than nonsedating agents such as olanzapine.

Neurochemical Abnormalities

Of the brain's neurotransmitters, dopamine is most consistently linked to psychosis in PD as described earlier. However, serotonin, acetylcholine, and the interaction between these and dopaminergic systems may also play a role in psychosis emergence. Several pharmacological agents (including nonpsychotropic medications) that reduce serotonergic activity improve psychotic symptoms. PD involves a cholinergic deficit, which is even more apparent in cognitively impaired and demented

PD patients who are at higher risk for psychosis. A cholinergic deficit has been linked to psychosis in DLB. Anticholinergic drugs used to treat motor symptoms can lead to the emergence of psychotic symptoms, while cholinesterase inhibitors may represent an alternative to AAs to treat PD psychosis. Overall, it appears that PD psychosis involves the dysregulation of a combination of neurotransmitter systems.

Structural Abnormalities

Lewy body deposition is associated with dementia in PD, which is a risk factor for PD psychosis. Researchers have documented strong correlations between the distribution of Lewy bodies in the temporal lobe, specifically in the amygdala and parahippocampus, and well-formed visual hallucinations in Lewy Body diseases such as DLB and PD dementia. These Lewy bodies may also be associated with an earlier onset of hallucinations.

Epidemiology and Risk Factors

It has been estimated that psychotic symptoms occur in 20–40% of PD patients, and they typically occur later in the disease (i.e., 10 or more years after initial diagnosis). While all anti-PD medications have been associated with psychosis, it appears that dopamine agonists in particular and the use of multiple drugs put patients at highest risk. While drug therapy is a risk factor for psychosis, neither duration nor dose has been found to be. Multiple other risk factors have now been identified, including cognitive impairment and dementia, increased age, disease duration and severity, depression, and various sleep disturbances.

Clinical Features and Diagnostic Criteria

Psychosis in PD comprises a specific constellation of clinical features that are different from those typical of other psychotic disorders such as schizophrenia. Psychosis in PD usually takes the form of visual hallucinations, which most commonly start in the evening hours during periods of low stimulation, although they can eventually occur at any time of the day. The content of visual hallucinations typically involves people or animals but may also feature inanimate objects. Visual hallucinations last seconds to minutes at a time and tend to be chronic, occurring at least once a week, often much more frequently. Unlike schizophrenia, auditory hallucinations occur less commonly in PD, and they typically cooccur with visual hallucinations. They consist more often of whispers or music, as opposed to the threatening voices reported in schizophrenia; however, some cases of threatening auditory hallucinations have been documented in PD. Tactile, olfactory, and gustatory hallucinations have also been reported in PD psychosis, but they are not common and tend to cooccur with visual hallucinations.

'Minor' phenomena such as illusions, 'passage,' and 'sense of presence' hallucinations have been included in the literature on PD psychosis. Illusions are disturbances in perceptual experience, such as mistaking a plant for a person. 'Sense of presence' refers to the feeling that a person or animal is in close physical proximity to the patient. A typical 'passage' hallucination is described as seeing shadows or quick fleeting objects (e.g., cockroach) passing through the peripheral visual field. As these features are less likely to disrupt patients' daily lives, they are less likely to be spontaneously reported.

Delusions and disorganized thinking may also emerge, although they are not as common as visual hallucinations. Paranoid thoughts (e.g., spousal infidelity) are a common theme, although, rarely, grandiose, somatic, persecutory, and religious delusions have also been reported.

While there are no standardized diagnostic criteria for PD psychosis, the NINDS and the NIMH recently gathered a work group to promote discourse on provisional diagnostic criteria forming an inclusive constellation of clinical features, not shared by other psychotic syndromes. PD psychosis was conceptualized as involving at least one psychotic symptom (i.e., illusions, false sense of presence, hallucinations, or delusions) that emerges *after* the onset of PD (defined by UK brain bank criteria) that lasts at least 1 month and cannot be better accounted for by another cause. In addition, associated features, such as the presence or absence of insight, dementia, and pharmacological treatment, should be noted.

Differential Diagnosis

The differential diagnosis of psychosis in PD first involves excluding delirium as the cause of symptoms. Psychotic symptoms may emerge as part of a delirium caused by infection, toxins, metabolic disturbance, or acute drug intoxication from sudden changes in antiparkinsonian drug doses and newly prescribed narcotics. Other neurodegenerative disorders involving parkinsonism may also produce psychotic features, such as progressive supranuclear palsy, corticobasal degeneration, DLB, and various psychiatric disorders (e.g., schizophrenia, psychotic depression, brief psychotic disorder).

The main distinction between DLB, which is defined as a progressive cognitive decline with at least two additional features (i.e., fluctuating cognition, recurrent, well-formed visual hallucinations, and spontaneous parkinsonism), and PD psychosis with dementia lies in the temporal course of symptoms. If dementia occurs within the year before or concurrently with parkinsonism, then a diagnosis of DLB is more appropriate.

Psychosis related to PD can be distinguished from that due to a primary psychiatric disorder by considering the history of symptoms. If symptoms arise very early (i.e., first 3 months) in the course of PD, involve fear and/or prominent paranoia with nonvisual hallucinations, and do not fluctuate during the course of a day, the psychosis may be due to a psychiatric disorder. Psychosis onset in late adolescence and early adulthood, a progressive clinical course, signs of grossly disorganized speech, and the presence of negative symptoms are highly suggestive of schizophrenia. While some negative symptoms (e.g., apathy, affective flattening) are common among PD patients, they may fluctuate with medication. Psychosis lasting more than 1 month, which is characteristic of PD psychosis, is, by definition, not considered as a brief psychotic disorder. If psychosis appears in the context of prominent affective symptoms and manifests in mood congruent symptoms such as delusions of guilt or worthlessness, it may result from a mood disorder. The average age of onset of delusional disorder is middle or late life, and unlike those seen in schizophrenia, delusions are typically not bizarre or accompanied by hallucinations. If present, hallucinations are more often olfactory or tactile in mood disorders with psychotic features, in contrast to prominent visual hallucinations characteristic of PD psychosis.

Assessment Instruments

Psychosis in PD can be assessed with a variety of instruments, most of which were originally designed for use in non-PD populations. Scales vary in information source (patient, caregiver, or clinician), necessity for trained raters, inclusion of psychiatric symptoms other than psychosis, and original validation population. The most commonly used instruments include the Neuropsychiatric Inventory (NPI) and the Brief Psychiatric Rating Scale (BPRS). The NPI is a caregiver-based interview comprising 12 queries aimed at characterizing psychopathology in patients with dementia. While this instrument assesses hallucinations and delusions, it may not be very sensitive to change in PD populations. The BPRS was specifically designed to measure clinical change in schizophrenia and is the most commonly used rating scale in clinical trials of antipsychotic agents in patients with PD despite lacking a formal validation study in this population. The BPRS comprises 18 items scored on a 7-point Likert-type scale. Six items are scored based on clinical judgment, and the remaining 12 are scored based on the content of a patient interview. This instrument appears to be sensitive to change in PD psychosis; however, it requires well-trained raters. Other recommended scales include the Positive and Negative Syndrome Scale (PANSS) and the Schedule for Assessment of Positive Symptoms (SAPS).

Several scales have been developed specifically to assess psychotic symptoms in PD, including the Parkinson Psychosis Rating Scale (PPRS), the Parkinson Psychosis Questionnaire (PPQ), and item two from the Mood, Mentation, and Behavior section (Part I) of the Unified Parkinson Disease Rating Scale (UPDRS). The PPRS comprises seven total items rated on a 4-point Likert-type scale and includes a global assessment item based on family report. While this scale was specifically developed in PD, it may not capture the heterogeneity of symptoms seen in the disease, and applicability appears limited. The PPQ was developed as a screening measure and consists of initial probes followed by detailed questions and separate frequency and severity ratings. This scale may not assess the range of PD hallucinatory phenomena and may overemphasize a link between sleep phenomena and psychotic symptoms. The single 'thought disorders' item (item 2) from the UPDRS, which combines dream phenomena, hallucinations, and delusions, constitutes a screen rather than a measure of psychosis severity and is scored on a 5-point Likert-type scale. This item assumes a continuum from dream phenomena to frank psychosis and may exhibit floor effects. The Movement Disorder Unified PD Rating Scale, a revision of the original UPDRS, has one question on hallucinations and psychosis with reference to other scales in its Appendix.

Management

Reduction/Simplification of PD Medications

General consensus and clinical practice support a reduction in anti-PD medications as the most appropriate first-line treatment for PD psychosis. If a patient is on multiple medications, most authorities would recommend the gradual removal of anti-PD medications in the following order: anticholinergics, amantadine, MAO-B inhibitors, dopamine agonists, catechol-O-methyltransferase (COMT) inhibitors, and lastly, levodopa. Furthermore, the short-acting formulation of levodopa, compared with the continued-release version, may mitigate the accumulation of adverse side effects. Aside from these medications, polypharmacy has been identified as an independent risk factor for psychosis in PD. It should be noted that various commonly prescribed agents (e.g., narcotics, hypnotics, antidepressants, anxiolytics) can lead to psychotic symptoms.

Due to adverse side effects, the addition of an antipsychotic agent should be considered only if medication reduction to the lowest tolerated dosages causes significant motor worsening or does not improve psychosis. Since reducing medications will likely lead to a reemergence of motor deficits, the clinician and patient are faced with a difficult challenge (see **Table 1**).

Table 1 Summary of pharmacological treatment of psychosis in Parkinson's disease

Agent	*Class*	*Dosages reported (mg day^{-1})*	*Empirical support*	*Extrapyramidal side effects*	*Other considerations*
Clozapine	Atypical antipsychotic	24.7–36	+++	Minimal	Monitoring for agranulocytosis required
Risperidone	Atypical antipsychotic	0.7–1.9	−	Significant	Prolactin elevation
Olanzapine	Atypical antipsychotic	4.1–6.5	−	Moderate	
Quetiapine	Atypical antipsychotic	54–200	++	Mild	
Aripiprazole	Atypical antipsychotic	1–12	−	Variable	
Ziprasidone	Atypical antipsychotic	N/A	−	Moderate	Effects on electrical cycle of the heart
Tacrine	Cholinesterase inhibitor	40–60	+	Variable	Hepatic toxicity
Donepezil	Cholinesterase inhibitor	5–10	+	Minimal	
Galantamine	Cholinesterase inhibitor	4–8	+	Unclear	
Rivastigmine	Cholinesterase inhibitor	1.5–8.9	++	Minimal	
Ondansetron	Antiemetic	12–24	−	Minimal	Cost

+++, Fully recommended; ++, Moderate support, further trials warranted; +, Minimal support; −. Little to no support.

Atypical Antipsychotics

After simplifying a patient's medication regimen, prescribing an AA represents the most common clinical response to PD psychosis. Since differences between the six AAs currently marketed in the US lie in their relative tendencies to lead to motor dysfunction, the choice of an agent is based largely on its distinct side effect profile.

Clozapine is the only AA fully recommended for the treatment of PD psychosis, according to a 2007 meta-analysis. In addition to two well-designed, randomized, controlled and numerous open-label trials that demonstrated acute efficacy and tolerability of clozapine in PD populations, longitudinal studies have shown it to be well-tolerated and effective long term. Despite these results, clozapine is often avoided by clinicians because of the requirement of cumbersome monitoring for agranulocytosis, which has been shown to occur in only 0.38% of a sample of over 99 000 US patients with schizophrenia. WBC count monitoring is required weekly during the first 6 months and bi-weekly thereafter. Other adverse side effects (e.g., sedation, orthostatic hypotension, sialorrhea) may also occur. Therefore, research is moving toward identifying more practical agents.

Although released in the United States as an AA, risperidone may more closely resemble 'typical' neuroleptics due to the dose-dependent incidence of extrapyramidal side effects and prolactin elevation. While most studies in PD demonstrate significant improvements in psychosis, the majority are open-label, which may partly contribute to the variability in reports of motor side effects. Due to numerous reports of motor worsening and the agent's documented 'typical' antipsychotic behavior, it is often avoided by clinicians combating PD psychosis.

Olanzapine is estimated to lead to motor worsening in about 40% of PD patients and is generally considered to be a poor choice for treating PD psychosis.

Among the AAs, quetiapine is most chemically similar to clozapine, but it does not show a risk of agranulocytosis. Despite results from numerous open-label studies involving more than 400 patients in which it was well-tolerated and efficacious in the treatment of PD psychosis, two double-blind trials reported no significant improvements in psychosis. A third, in which 40 patients were randomized to either quetiapine or clozapine, did show quetiapine efficacy in treating psychosis. The discrepancy between open label and double-blind studies is puzzling, but quetiapine remains a commonly prescribed AA in patients with PD and hallucinations.

The use of ziprasidone has been limited due to its effects on the heart's electrical cycle (i.e., prolongation of the QT interval), but there have been no reported cases of *torsades de pointes*. Case reports and series suggest that ziprasidone may be a relatively safe treatment for psychosis in PD, especially when other AAs have proved ineffective or caused intolerable side effects. However, after reviewing data on ziprasidone for the treatment of schizophrenia, a panel of expert psychiatrists concluded that its extrapyramidal side effects profile is 'better than risperidone, the same as olanzapine, but not quite as good as quetiapine or clozapine.'

Unlike other AAs, aripiprazole is a 'partial agonist' at both D_2 and 5-HT_1 receptors and is believed to carry a relatively low risk of extrapyramidal side effects. Data from case reports and two open-label trials in PD suggest that its efficacy and tolerability in PD patients are variable. While aripiprazole may be efficacious for some patients, it carries a considerable risk of adverse effects, and there is a need for further controlled trials of aripiprazole in the PD population.

While AAs continue to be the most commonly prescribed pharmacological agents in the treatment of PD psychosis, the US Food and Drug Administration (FDA)

has mandated that all manufacturers provide a boxed warning on product labels stating that AAs have been found to be associated with a higher risk of mortality when used in elderly patients with dementia. This finding is particularly relevant to the management of PD psychosis due to the age and frailty of the late-stage PD patients who typically exhibit psychosis. Since the mechanism by which AAs cause increased mortality is not well understood, they will likely continue to be used in the treatment of PD psychosis, especially when the consequences of inaction are considered. However, studies involving alternative therapies such as cholinesterase inhibitors are ongoing.

Cholinesterase Inhibitors

The first published report of a cholinesterase inhibitor in PD was an open-label trial of tacrine in which psychotic symptoms completely resolved in five out of seven demented patients and improved in the remaining two. Despite a previous account of exacerbated parkinsonism in one patient treated with tacrine, no motor worsening was reported in this trial. Today, tacrine is rarely used for the treatment of PD psychosis due to its tendency to cause hepatic toxicity.

While many open-label studies using donepezil in PD patients have shown improvements in psychosis, motor side effects have been variable. In addition, placebo-controlled trials published to date have shown nonsignificant improvements in psychosis, perhaps as a consequence of small sample sizes and/or low baseline symptom severity.

Unlike other cholinesterase inhibitors, galantamine also acts on nicotinic receptors, activity at which may prevent the downregulation of acetylcholine that accompanies treatment with cholinesterase inhibitors. In the striatum, increasing activity at nicotinic receptors on presynaptic dopamine neuron terminals may facilitate the release of dopamine, thereby improving motor symptoms. Only one study using galantamine in PD psychosis has been published, and it reported that three out of nine patients experienced a complete resolution of hallucinations, and four additional patients reported an improvement. While parkinsonism improved in six of the patients, the remaining three experienced a worsening of tremor. Further studies are necessary to determine the utility and safety of galantamine in treating PD psychosis.

Rivastigmine, the only one in its class now FDA approved for the treatment of PD dementia, is unique among cholinesterase inhibitors in that it inhibits not only acetyl, but also butyryl cholinesterase. One open-label trial showed that caregiver distress, Mini-Mental State Exam scores, and scores on the NPI hallucinations and sleep disturbances subscales improved. Also, rivastigmine was well-tolerated, and motor symptom severity remained stable. A large, double-blind, placebo-controlled trial using rivastigmine to treat patients with PD and dementia showed that it better alleviated symptoms in the subset of hallucinating patients. A significant improvement in both total NPI score and the agitation/aggression item was noted. Additional double-blind, controlled trials using this promising agent for the treatment of visual hallucinations in PD are warranted and are underway.

Ondansetron

Ondansetron, an antiemetic, was tested in schizophrenia because of its antagonism of 5-HT_3 receptors, but it has not been found to be efficacious for this purpose. However, several early reports suggested that it may be efficacious in the treatment of psychosis in PD without worsening motor symptoms, presumably due to its high selectivity. Two open-label trials conducted by one group reported improvements in psychosis with limited side effects; however, these positive results have not been reproduced by others. Furthermore, the cost of the drug has kept it from being tested further in the PD population.

Prognosis

Once hallucinations appear, they tend to become a chronic and progressive condition. While treatment with AAs has been shown to provide some degree of symptom relief, data regarding long-term treatment effects have been variable. Some studies document no long-term outcome differences between patients who received treatment and those who did not, and many treated patients still experience psychotic symptoms. Other reports suggest that many patients receiving antipsychotic treatment experience continued efficacy, especially those who responded to medication early on.

After patients initiate antipsychotic therapy, continued treatment may be necessary to maintain symptom control and avoid psychosis exacerbation. One study that attempted to wean psychosis-free PD patients off their antipsychotic medications was aborted because five of the six subjects experienced 'rebound psychosis.' Furthermore, three of these five patients experienced an exacerbation (compared with the original psychotic episode that prompted antipsychotic use) in the form of paranoid delusions or threatening auditory hallucinations. Additional research is needed to confirm the utility and necessity of continued antipsychotic treatment.

Psychotic features may be prognostic of additional complications such as cognitive impairment and weight loss, as well as negative outcome variables such as caregiver distress, nursing home placement, and mortality. Data appear to support the clinical observation that PD patients who present with visual hallucinations are more likely to develop cognitive impairments later on.

Psychosis and cognitive decline often cooccur, and both have been related to the development of the other. When psychosis and dementia coexist in PD, it is perhaps the greatest limiting factor for the optimal treatment of motor symptoms. These symptoms severely impact on caregiver burden and patients' quality of life and may partly explain these patients' increased risk of nursing home placement and related mortality. A case-control study controlling for motor and cognitive impairment identified hallucinosis as the primary factor differentiating PD patients who were placed in a nursing home from those who were not. The finding that hallucinations and other psychotic phenomena are predictive of negative outcome has been well-replicated and underscores the importance of treating PD psychosis.

See also: Cholinesterase Inhibitors in Parkinson's Disease; Dementia, Movement Disorders; Hallucinations and Movement Disorders; Neuroleptics and Movement Disorders; Parkinson's Disease: Definition, Diagnosis, and Management; REM-behavior Disorder.

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Relevant Websites

www.movementdisorders.org – Movement Disorder Society.

Punding (PD)

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Glossary

Dopamine dysregulation syndrome (DDS) – A troublesome condition, close to addiction, consisting of motor and behavioral disturbances caused by an intake of DRT at doses well beyond those required to control motor symptoms of Parkinson's disease (PD). It is also reported as hedonistic-homeostatic dysregulation syndrome (HHDS).

Dopamine-related compulsions (DRCs) – A group of motivational disorders related to abnormal activation of the reward mechanisms, caused by DRT. Some authors include in this group: DDS, ICDs, and punding behaviors.

Dopaminergic replacement therapy (DRT) – A therapeutic category that includes levodopa and dopaminomimetics and that represents the cornerstone of pharmacotherapy in PD.

Impulse control disorders (ICDs) – A set of psychiatric disorders including intermittent explosive disorder (hot-headedness), kleptomania (stealing), pathological gambling, pyromania, trichotillomania (pulling one's hair out),

dermatillomania (skin picking), and compulsive shopping. Impulsivity, the key feature of these disorders, can be thought of as seeking a small, short-term gain at the expense of a large, long-term loss. ICDs may be caused by DRT: among the DRT-induced ICDs, some authors include DDS and hypersexuality.

LEDD – The acronymic of 'levodopa equivalent daily dose' that means all the pharmacologic therapy taken in 1 day (24 h) for PD converted in levodopa, as follows: levodopa (100 mg) = 130 mg controlled-release levodopa = 70 mg levodopa + COMT inhibitor = 1 mg of pergolide = 1 mg of lisuride = 1 mg of pramipexole = 5 mg of ropinirole = 10 mg of bromocriptine = 10 mg of apomorphine = 20 mg of dihydroergocriptine.

Obsessive–compulsive disorder (OCD) – The essential feature is recurrent obsessional thoughts or compulsive acts. Obsessional thoughts are ideas, images, or impulses that enter the patient's mind again and again in a stereotyped form. They are almost invariably distressing, and the patient often tries, unsuccessfully, to resist them. They are, however, recognized as his or her own thoughts, even though they are involuntary and often repugnant. Compulsive acts or rituals are stereotyped behaviors that are repeated again and again. They are not inherently enjoyable, nor do they result in the completion of inherently useful tasks. Their function is to prevent some objectively unlikely event, often involving harm to or caused by the patient, which he or she fears might otherwise occur. Usually, this behavior is recognized by the patient as pointless or ineffectual, and repeated attempts are made to resist. Anxiety is almost invariably present. If compulsive acts are resisted the anxiety gets worse.

Punding behaviors – Punding is a complex, prolonged, purposeless, stereotyped behavior (such as collecting or arranging objects) observed in drug addicted individuals and in patients treated with dopaminergic drugs.

Definition and History

Punding refers to a complex, stereotypical behavior characterized by an intense fascination with repetitive and purposeless activities. The term originates from Swedish slang ('block-head'), and was first used to define a stereotyped behavior in amphetamine and cocaine addicts in California and in Denmark. Since the first description in the 1970s, this phenomenon came to the attention of neurologists when punding was reported in a patient with Parkinson's disease (PD), triggered by dopaminergic replacement therapy in 1994.

Epidemiology

Punding is probably underreported and underestimated for several reasons, one being that repetitive behaviors have been reported under the label of 'obsessive–compulsive behavior' or 'hypomania.' Prevalence data from the medical literature are conflicting, as it was observed in only 1.4% of 291 PD patients by Miyasaki, while Evans and colleagues reported that 14% of 123 unselected PD were punders, and that the percentage increased to 30% in patients treated with large doses of dopaminergic drugs (>800 levodopa equivalent daily dose – LEDD).

Clinical Presentation

Punding is a peculiar stereotyped behavior characterized by an intense fascination with a complex, excessive, nongoal oriented, repetitive activity such as manipulation of technical equipment, handling, examining, or sorting through common objects, grooming, hoarding, and engagement in extended monologues devoid of content. Men tend to repetitively tinker with technical equipment such as radio sets, clocks, watches, and car engines, the parts of which may be analyzed, arranged, sorted, and catalogued but rarely put back together. Women, by contrast, incessantly sort through their handbags, tidy continuously, brush their hair, or polish their nails. The behavior is reported as soothing/calming and associated with an intense curiosity; while involved in their chosen activity, punders withdraw into themselves, become tacit and unresponsive, and give the impression of absent-mindedness, becoming irritable when distracted from their tasks. Punders are normally aware of the inapposite obtuse nature of the behavior, and recognize that time and money spent on their behaviors are excessive and inappropriate; despite the consequent self-injury, they do not abort such behavior. Therefore, they can have devastating psychosocial consequences.

Nosology and Psychiatric Comorbidity

In the last decade, a set of complex behaviors related to excessive or aberrant dopaminergic stimulation have been recognized in PD patients. These include pathological gambling, hypersexuality, compulsive shopping, compulsive eating, hobbyism, punding, and compulsive medication use. These disorders have been classified within

overlapping psychiatric categories focusing on phenomenology, particularly among the impulse control disorders (ICDs). In a recent review, Voons and Fox used the term 'repetitive behaviors' to avoid any reference to possible underlying pathophysiological mechanisms. In another comprehensive review on ICDs, Ferrara and Stacy categorized these behaviors among motivational disorders, inversely related to the severity of motor symptoms, and aggravated by dopamine replacement therapy (DRT). They include three categories among dopamine related compulsions (DRCs): (1) reward-seeking behaviors (or ICDs) such as pathological gambling; (2) punding behaviors such as sorting collections; and (3) hedonistic–homeostatic dysregulation syndrome (HHDS), a maladaptive pattern of DRT overuse close to drug addiction.

Punding is a senseless repetitive behavior not described anywhere. The only mention of the disorder in *Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision* (DSM-IV-TR) is 'stereotypical and repetitive behaviors' in amphetamine intoxication. Hence, the classification of repetitive behavior disorders is debated, and the current nosology may be inadequate. Punding shares some similarities with obsessive–compulsive disorder (OCD) as it may be considered a form of compulsion: behaviors are complex, repetitive, and result in isolation from or conflict with other people. In contrast with OCD; however, punding is not driven by anxiety or obsessions (such as religious, checking, symmetry, ordering, counting, or contamination), and is compulsive in the sense that the person could be distracted from the intrusive behavior but would become irritable if prevented from resuming.

Even though there is no study specifically addressing this issue, depression or anxiety was reported in ~10% of cases, a proportion to be expected considering the high prevalence of these disorders among PD patients. Therefore, punding does not correlate with mood or anxiety disorders; punders feel anxious only when they are forced to stop or if prevented from resuming.

Punders frequently present with agitation, disinhibition, irritability, and sleep disturbance, all features of mania. However, disinhibition is neither stereotyped nor universal; moreover, punders do not report typical features of mania like racing thoughts, feeling of grandiosity, or distractibility.

Among PD punders reported so far, one or more ICDs were reported in 13 out of 22 cases (59.1%), a prevalence much higher than reported in other PD series, where 2–8% is the estimated value. Although the role of dopaminergic stimulation in the development of punding is confirmed by several lines of evidence, not all patients taking dopaminergic drugs develop this behavior; moreover, there has been a report of punding following introduction of the atypical neuroleptic quetiapine. On the other hand, most punders improve with neuroleptics, or reduction of dopaminergic stimulation.

Risk Factors and Pathophysiological Considerations

In a recent survey of 141 PD cases it was found that higher impulsivity and younger age of disease onset were independent predictors of higher Punding Scale scores. Others found that, besides younger age, punding was associated with male gender and reduced night time sleep. In PD punders, a history of psychosis is common; this may either reflect a common predisposing condition or the high doses of dopaminergic drugs usually taken by these patients or both. Punding has not been systematically assessed for association with medication subtypes; however, an association with a high LEDD, and overuse of rescue doses (especially during night) have been reported. Even though some punders are on levodopa monotherapy, the majority of punders take a combination of levodopa and dopamine-agonists.

Experimental and clinical evidence suggest that punding is a phenomenon triggered by stimulation of D1 and D2 receptors. Although the pathophysiology of punding is yet to be clarified, its similarity with drug-induced stereotypies in animals, the frequent association with dopamine dysregulation syndrome (DDS) and dyskinesias in PD suggest that it may be related to plastic changes in the ventral and dorsal striatal structures including the nucleus accumbens, and linked to psychomotor stimulation and reward mechanisms.

The role of the frontal corticostriatal circuitry in inhibiting the dopamine (DA)-dependent induction of stereotypic behavior has been established in experimental models. Accordingly, in humans the inability to modulate automatic routines is likely due to impaired frontal lobe function. Large frontal lesions are associated with highly stereotyped behaviors, including forced collectionism ('hoarding'). In addition, homologies of clinical features and epidemiological considerations aside, the role of D1 and D2 receptors, which is already well established for the other conditions, support the view of a common pathophysiologic process shared by addiction, dyskinesias, and stereotypies.

It has been proposed that the basal ganglia store and select specific competing motor programs under the control of frontal cortex and that a dysfunction of this process may underlie conditions involving the abnormal expression of stereotyped motor behaviors such as compulsions. Analogously, punding may be considered a kind of *on* complication like dyskinesias and, accordingly, it has been included among the 'motor complication' of DRT. In favor of this hypothesis, it was recently reported that amantadine can reverse punding.

Management of Punding

Since punding, as well as the other DRCs, presents or increases following the DRT introduction or escalation,

DRT tapering (especially of DA receptor agonists) will be helpful in most patients. Besides DRT reduction, patient and caregiver information and education are important: patient must be discouraged from taking frequent rescue doses, especially during the night. As psychiatric comorbidity is frequent, a psychiatric assessment and follow-up is advisable. If DRT lowering induces worsening of PD symptoms, one strategy (especially when punding coexists with ICDs) is to shift to levodopa monotherapy, as DA agonists seem to be, as a class, more likely to induce ICDs, low dose quetiapine or clozapine can be added. Risperidone should be avoided as it worsens PD symptoms. The role of amantadine and of medications anecdotically reported to help patients with hypersexuality (valproate, lithium, donepezil) need to be assessed. Antidepressants that enhance dopaminergic transmission should be avoided, as they could worsen DRCs. Deep brain stimulation (DBS) in combination with a reduction of DRT has been reported to be effective in controlling DDS. On the other hand, some patients have been reported to develop hypersexuality, mania, and pathological gambling after DBS of subthalamic nucleus.

See also: Obsessive-Compulsive Disorder; Psychosis in Parkinsonism.

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Q

Quinolinic Acid

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Glossary

Excitotoxicity – The biological process whereby neurons undergo cell death upon excess stimulation by glutamate and glutamate-like substances.
GABA (γ-aminobutyric acid) – An inhibitory neurotransmitter found throughout the brain that binds to and inhibits postsynaptic neurons harboring GABA receptors.
Glutamate – An excitatory neurotransmitter found throughout the brain that binds to and excites postsynaptic neurons harboring NMDA receptors.
Huntington's disease (HD) – A genetic, neurodegenerative disease characterized by a mutation in the gene that encodes the protein, huntingtin. Symptoms of HD include a hyperkinetic movement disorder, cognitive decline, and personality changes.
Neurodegeneration – The global phenomenon to describe a loss of neurons in the central and/or peripheral nervous systems.
Striatum – A structure in the forebrain composed of the caudate nucleus and putamen. The striatum receives excitatory input from the cortex and sends inhibitory projections to the globus pallidus and substantia nigra. This brain nucleus is involved in the planning and fine-tuning of motor programs as well as certain cognitive processes.

Description and Mechanism of Pathogenesis

Quinolinic acid (QA) is a 2,3-pyridine dicarboxylic acid ($C_7H_5NO_4$). QA is produced following the metabolic breakdown of the amino acid tryptophan, via the kynurenine pathway. Tryptophan is able to cross the blood–brain barrier (BBB), and upon entering the brain, is taken up by astrocytes, macrophages, microglia, and dendtritic cells and converted into kynurenine. In the presence of the enzyme 3-hydroxyanthranilic acid, kynurenine is converted into QA through a series of enzymatic reactions. QA is normally present in extremely low, nanomolar concentrations in the brain and in cerebrospinal fluid and does not cause damage to the surrounding cells. However, it has been recently demonstrated that increased levels of QA can be produced by activated macrophages and microglia in the brain. Accumulation of endogenous QA has recently been implicated in the etiology of certain neurodegenerative diseases, especially those with a strong inflammatory component, such as Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), Alzheimer's disease (AD), stroke, multiple sclerosis (MS), and epilepsy.

QA exerts its biological effects by binding to and potentiating Mg^{2+}-sensitive *N*-methyl-D-aspartate (NMDA) receptors, which normally bind the neurotransmitter, glutamate. As such, QA acts as a glutamate agonist and can potentiate NMDA receptors to the point of excitotoxicity. Specifically, overstimulating this receptor subtype allows high levels of calcium ions (Ca^{2+}) to enter the cell, activating enzymes such as endonucleases, phospholipases, and proteases. These enzymes can then go on to damage cellular structures such as components of the cytoskeleton, membrane, and DNA and ultimately cause cell death. QA administration induces both apoptotic and necrotic types of neurodegeneration. In addition to a loss of neurons, QA administration also leads to a robust increase in the number of astrocytes (astrocytosis) and reactive microglia (microgliosis) in the region of the lesion.

Animal Models

The exogenous administration of QA to specific areas of the brain harboring NMDA receptors has been associated

with robust cellular dysfunction and cell death. While QA has been used as an excitotoxin to induce neurodegeneration in animal models of various movement disorders such as dystonia (injection into the striatum), stroke (injection into various regions of the cortex or hippocampus), and PD (injections into the substantia nigra pars compacta and/or the striatum), by far, its most widespread application in the past several decades has been in animal models of HD. While HD is strictly a genetic disease caused by a trinucleotide repeat (CAG) in the HD gene on chromosome 4, the most prominent anatomical and behavioral manifestations of the disease (cell loss in the striatum, a movement disorder characterized by hyperkinesia and cognitive decline) can also be seen following injection of QA into animals. Unlike its precursor, tryptophan, QA is incapable of crossing the blood–brain barrier and must be injected directly into the brain region of interest to elicit its neurotoxic effects. In animal models of HD, QA is typically injected into the striatum via stereotaxic injection and has been shown to cause cell death in several species, including mice, rats, and nonhuman primates.

QA Administration in Rodent Models of HD

In both mice and rats, the injection of QA into the striatum leads to a rapid (most cell death occurs within 3 days) and extensive degeneration of medium-sized, spiny, striatal projection neurons that use the neurotransmitter γ-aminobutyric acid (GABA). These cells harbor NMDA receptors and normally receive glutamatergic projections from the cortex and the thalamus, rendering them highly susceptible to QA-induced excitotoxicity. The cell death seen in the striatum following QA administration involves similar degeneration of both enkephalin-positive and substance P-positive GABA-ergic neurons (two subpopulations of striatal projection neurons that are part of the indirect and direct basal ganglia circuits, respectively). QA injection into the rodent striatum also leads to the variable death of cholinergic interneuons (depending on the dose). In rats, a single, 1 μl, unilateral injection of QA into the striatum at a dose of 200 nmol produces almost a complete loss of neurons, as evidenced by immunohistochemical staining of neurons with an anti-NeuN antibody (see photomicrograph, scale bar = 1.2 mm). QA is usually administered unilaterally in rodents, as bilateral injections at doses that induce robust cell death render the animal unable to ambulate and sustain itself with food and water.

Striatal neurons that degenerate following QA administration are an integral component of the basal ganglia and project to the internal and external segments of the globus pallidus, as well as the substantia nigra pars reticulata. Therefore, perturbation of the striatum and the rest of the basal ganglia leads to severe behavioral and cognitive consequences that mimic some of the behavioral manifestations seen in humans with HD. Unilateral QA lesions lead to difficulty in using the contralateral forepaw and digits, as evidenced by the reduced performance of the affected paw in the cylinder and staircase tests. Additionally, unilaterally QA-lesioned rats exhibit apomorphine-induced rotational asymmetry (rotations in the direction ipsilateral to the lesioned hemisphere) and spontaneous dyskinesias at higher doses. Rodents that receive striatal injections of QA also have difficulty performing on certain cognitive tests, and display deficits in the Morris Water Maze and the T-Maze, which examine both long-term and working memory, respectively.

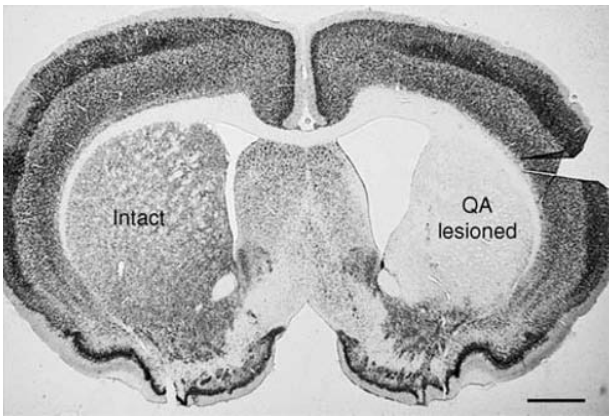

Figure 1 Coronal section of a rat brain stained for the neuronal marker, NeuN. Note the robust loss of NeuN-immunoreactive neurons in the striatum which received a single, 1 μl injection of QA (200 nmol). Scale bar = 1.2 mm.

QA Administration in Primate Models of HD

Injection of QA into the nonhuman primate striatum (composed of the caudate nucleus and putamen) causes a similar type of cell death seen upon administration to rodents a robust loss of medium-sized spiny projection neurons with variable death of cholinergic interneurons. However, because of their much larger brain size and similar anatomical organization of the striatum to humans, primates injected with QA offer the advantage of a much more extensive, measurable behavioral repertoire that more accurately mimics human HD. For example, the cardinal motor deficit seen in HD patients, chorea (involuntary, hyperkinetic movements of the limbs, head, and neck), is not replicated following administration to either the mouse or rat striatum. Conversely, upon bilateral QA injection into the nonhuman primate striatum, animals exhibit an apomorphine-induced choreic phenotype, as well as limb dystonia and orofacial dyskinesias. Monkeys also have a significant difficulty with specific memory tasks, such as the object retrieval-detour task (ORDT), which requires them to coordinate a reaching movement while performing a procedural memory task to retrieve a fruit treat.

This particular test requires intact frontal-striatal circuitry, which is disrupted following QA injections into the caudate and putamen.

See also: Huntington's Disease.

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R

Rabbit Syndrome

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Definition and History

Rabbit syndrome (RS) is an unusual iatrogenic movement disorder named after the characteristic appearance of the movement. It is said to resemble the chewing of a rabbit and consists solely of vertical motion. There is no involvement of the tongue. RS was first described in 1972 by Villeneuve as an iatrogenic movement disorder secondary to exposure to typical antipsychotics. More recently, it has been described after exposure to atypical antipsychotics and other classes of medication.

Pathophysiology

As the majority of cases of RS occur after exposure to antipsychotics, it is presumed that the pathophysiology involves a disturbance in the dopaminergic function of the basal ganglia. One hypothesis is that RS may be due to hypersensitive dopamine D_2 receptors as a result of chronic antipsychotic use. Others have speculated that RS is due to a hypercholinergic state, thus explaining the beneficial results of anticholinergics for treatment. Since RS improves upon withdrawal of the offending agent, it is possible that the syndrome is a direct result of dopamine receptor blockage rather than a result of receptor adaptation to dopaminergic blockade. This last hypothesis is consistent with the idea that RS is a type of drug-induced parkinsonism.

Epidemiology

Most cases of RS are iatrogenic and involve antipsychotic administration. The prevalence of RS after exposure to typical antipsychotics is 1.5–4.4%. It occurs predominantly in middle-aged and elderly populations, and women appear to be at increased risk. Of the reported cases, 66% are women. Prevalence after exposure to atypical antipsychotics is unknown, but the syndrome is documented to occur after exposure to aripiprazole, clozapine, olanzapine, and risperidone. The majority of the case reports (8/11) involve risperidone. RS has also been reported in two patients receiving citalopram or escitalopram. The authors of these cases note that, although rare, selective serotonin reuptake inhibitors are thought to cause other extrapyramidal symptoms (EPS). Additional medications implicated in the development of RS include methylphenidate and imipramine. Isolated case reports of RS citing phenol ingestion, multiple system atrophy, or idiopathic oromandibular tremor as alternative causes of RS exist.

Clinical Features and Differential Diagnosis

RS is a rhythmic movement involving the mouth with a highly recognizable appearance that consists of vertical movements of the mouth and lips, which spare the tongue. The movements are rhythmic with a frequency of ~5 Hz. There can be an associated popping sound produced by the opening and closing of the lips. Not surprisingly, patients may have findings of parkinsonism, including rigidity, bradykinesia, and tremor. In contrast to tardive dyskinesia, the movements of RS continue during stage I sleep. Fatigue and anxiety can worsen the movements of RS. The worsening of the movements can occur during tasks of attention or concentration. Timing of the onset of RS after exposure to antipsychotics is variable, with RS starting in as little as a week after initiation of drug to years after start of therapy.

The most common misdiagnosis of RS is oral tardive dyskinesia. One key to differentiating the syndromes is to examine the tongue. The tongue is uninvolved in RS and displays no abnormal movements. An additional clue to the diagnosis of RS is that unlike oral tardive dyskinesia, the lip movements are restricted to the vertical plane in RS. The speed and rhythmicity of the movements may help to distinguish the two, as RS is faster and more

rhythmic than the movements of oral tardive dyskinesia. Tardive dyskinesia with oral movements resembles chewing and smacking of the lips, whereas RS is a perioral tremor typical of parkinsonism. Unlike oral tardive dyskinesia, RS cannot be suppressed voluntarily. The jaw tremor of Parkinson's disease (which some authors refer to also as RS) and oral stereotypes seen in the elderly and edentulous should be included in the differential diagnosis.

Management and Prognosis

Since RS is secondary to exposure to antipsychotics, treatment involves reducing or replacing the offending agent. RS often responds within days to a reduction in the dose of the antipsychotic drug. If it is not possible to lower the dose of the antipsychotic, then adding an anticholinergic or changing to an atypical antipsychotic are other options. Anticholinergic medications effectively suppress the movements of RS; however, if they are stopped, the movements of RS can reappear. The most commonly used anticholinergics for RS include trihexyphenidyl, procyclidine, and benzatropine. Successful treatment has also been described by switching from a typical antipsychotic to the atypical antipsychotics olanzapine, quetiapine, and clozapine.

Unsuccessful approaches to the treatment of RS include the addition of dopaminergic medications. Dopamine agonists and amantadine have been tried without success, and levodopa was reported to worsen symptoms in one patient. The knowledge of the use of benzodiazepines is limited, but there appears to be no benefit to their use. The antiepileptic phenytoin has also been utilized unsuccessfully.

Conclusion

RS is an unusual iatrogenic movement disorder primarily associated with exposure to antipsychotics. It is readily recognized by the presence of a perioral tremor of the lip and mouth that spares the tongue. It is important to distinguish RS from tardive dyskinesia, as prompt recognition of this unique syndrome will facilitate treatment, which can be effective.

See also: Neuroleptics and Movement Disorders; Parkinson's Disease: Definition, Diagnosis, and Management.

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Ramisectomy

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The word 'ramisectomy' is a combination of words 'ramus' and 'sectioning.' Ramus can refer to a branch and used like 'A nerve ramus such as the dorsal ramus of spinal nerve.' In the management of movement disorders, the term 'ramisectomy' generally means the surgical section of the peripheral branches of the cervical spinal nerves for the treatment of spasmodic torticollis or cervical dystonia (selective peripheral ramisectomy). This surgical procedure is also called 'selective peripheral denervation.'

The spinal nerves have dorsal and ventral rami, and the majority of dorsal rami of the cervical spinal nerves innervate the posterior neck muscles such as the splenius

muscle and the semispinalis muscle. These muscles act to rotate the head horizontally to the ipsilateral direction. By sectioning the dorsal rami from C1 to C6 spinal nerves, the posterior neck muscles are inactivated resulting in symptomatic relief of involuntary horizontal rotation of the neck in patients with spasmodic torticollis or cervical dystonia. This operation is usually combined with sectioning of the contralateral peripheral branches of the accessory nerve that innervate the sternocleidomastoid muscle. A Canadian neurosurgeon, Claude Bertrand (1917), established this procedure in the 1980s. Selective peripheral ramisectomy is called Bertrand's procedure and now accepted as a mode of surgical treatment that can improve symptoms in certain types of cervical dystonia. Clear distinction should be made between Foerster-Dandy intradural rhizotomy and Bertrand's procedure. Foerster-Dandy intradural rhizotomy had been widely performed until the 1980s in which intradural ventral spinal roots are sectioned from C1 to C3 or C4 level. This operation inactivates not only muscles innervated from dorsal rami but also muscles from the ventral rami, which may induce neck instability and swallowing problems. To avoid denervation of the phrenic nerve and nerves to the shoulder and arm, intradural rhizotomy is limited down to C4 on one side and to C3 on the opposite side. This is inadequate to denervate the posterior neck muscles completely. In selective peripheral ramisectomy (Bertrand's procedure), the posterior neck muscles are totally denervated without involvement in the territories of ventral rami of the spinal nerves.

In the original method of selective peripheral ramisectomy of Bertrand, a large hockey-stick-shaped skin incision is made in the posterior neck and occipital area, which results in numbness, sometimes tingling sensation, in the occipital region due to sectioning of the peripheral part of the great occipital nerve. Even if a linear skin incision is used, the sensory component of the C2 is sacrificed at the proximal part of the C2 nerve, because the motor and sensory components are difficult to differentiate during surgery. In order to avoid such a complication, Taira et al. modified Bertrand's ramisectomy by combining both intradural and extradural procedures. In this modified method, the intradural C1 and C2 ventral roots are sectioned after C1 hemilaminectomy, and ramisectomy from C3 to C6 is performed as in Bertrand's procedure.

The sternocleidomastoid muscle (SCM) contralateral to the involved posterior neck muscles is generally active in patients with cervical dystonia with predominant head turn in the horizontal axis, and this muscle is usually denervated simultaneously during the operation. SCM has a nerve supply from the accessory nerve. In the original Bertrand's technique, the peripheral main trunk of XIth nerve is completely exposed by sectioning the SCM with a large skin incision along the direction of XIth nerve. This makes it easier to identify all the motor nerves going to SCM. For cosmetic reasons, a smaller skin incision along the posterior border of SCM may be used. The branch to the trapezius muscle should be preserved, because weakness of this muscle results in marked disabilities such as difficulty in raising the arm and shoulder joint problems.

In some patients with cervical dystonia, the levator scapulae muscle may be responsible for laterocollis symptoms. This muscle is not affected by the traditional selective peripheral denervation, because the levator scapulae muscle is innervated from the anterior rami of the C3/4 peripheral nerves. When this muscle should be denervated, there are two surgical routes: through the posterior cervical triangle and through the same incision as the Bertrand procedure.

When the symptom of CD is retrocollis, and bilateral posterior neck muscles are involved, bilateral peripheral ramisectomy can be carried out. However, bilateral extensive denervation may result in 'head-drop' (inability to raise head), and therefore bilateral denervation should be limited to C1–C5.

After selective peripheral denervation or ramisectomy for cervical dystonia, patients should be well informed of the importance of physiotherapy. It is very important that patients do posture exercises to regain a sense of midline and to improve the range of movement.

Recently, the National Institute of Clinical Excellence of the United Kingdom (http://www.nice.org.uk/) launched a guideline for Selective peripheral denervation (ramisectomy) for cervical dystonia. It mentions as follows.

Current evidence on the safety and efficacy of selective peripheral denervation for cervical dystonia appears adequate to support the use of this procedure provided that the normal arrangements are in place or consent, audit and clinical governance. The procedure should be performed by a multidisciplinary team in a specialist neurosurgical unit. Patient selection for this procedure is important. Patients should be offered the procedure only when their disease has become refractory to best medical treatment.

Standard treatment for cervical dystonia includes physiotherapy, drugs to reduce spasm, injections of botulinum toxin, and brain surgery. Selective peripheral denervation may be an alternative, especially for people who have not responded to other treatments.

Selective peripheral denervation is a surgical procedure that varies according to the muscle groups affected. It is performed under general anaesthetic and involves cutting, through a skin incision, the nerves that supply the affected muscles. Sometimes the muscles themselves may be divided.

The evidence was limited to one systematic review and several case series studies. The review found no controlled studies and no reliable evidence to compare the procedure with other treatments. Two of the larger case series studies found 'very good to excellent' results in 88% (228/260 and 182/207) of patients at follow-up. However, the time to follow-up and how these outcomes were

assessed were not specified in either of these two studies. The largest case series study identified reported the following complications: occasional tic-like pain (1%, 3/260); tonsillar abscess (0.4%, 1/260); transient swelling of the neck in a few patients (number not specified); and pins and needles or sensation of tightness or fullness in a few patients (number not specified). For more details, refer to the Sources of evidence (see right).

The Specialist Advisors have listed potential adverse events as difficulty in swallowing, as well as the usual potential complications of surgery, such as infection and hemorrhage.

Selective peripheral ramisectomy is generally indicated in patients with cervical dystonia who do not achieve adequate response with medical treatment or repeated injections of botulinum toxin. This is a safe procedure with infrequent and minimal side effects. Since this procedure requires a specialized expertise with the understanding of detailed anatomy of cervical peripheral nerves, it is not widely available.

See also: Cervical Dystonia; Rhizotomy.

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Rating Scales in Movement Disorders

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Principles of Measurement

Measurement is an intrinsic attribute of science and forms an indispensable part of neurological diagnosis and severity assessment of impairment and disability. Measurement allows for the sharing of information concerning individuals or groups, aids in therapeutic decisions, and facilitates the evaluation of outcomes of clinical practices, research, and health policy.

In neurology, measures can be either objective (biological assays, functional tests, and physical structure) or subjective (rating scales and questionnaires). Both the modalities are applied to the evaluation of patients with movement disorders (MD). Objective methods are usually complex and expensive, with demanding requirements in terms of staff, equipment, and application conditions. Such methods furnish true measures, in real numbers, though limited in time and site. Subjective methods are

simple and relatively quick. Their application furnishes data susceptible to the influence of individual factors, yet they nevertheless provide global information on the patient's status. Due to these characteristics (simplicity, global information, and low cost), these methods are widely used in clinical research and practice.

To rate something is to estimate its worth or value. In a clinical setting and in operational terms, rating can be defined as 'the assignment to a situation or event of its corresponding quantitative level, according to rules' and is equivalent to measuring (determining the quantity of something by comparison with a given unit). Many attributes or phenomena lack such a unit, belong instead to the conceptual realm, and are thus not directly observable. These abstract concepts or 'constructs' (such as intelligence, pain, or well being) can be indirectly evaluated by means of indicators which are related to them and susceptible to valuation. Such indicators are incorporated as the components (items and domains) of rating scales, which should be tested by using complex methodology to determine the quality of their psychometric attributes.

In MD, severity ratings are applied to assess impairment (objective limitation) or disability (functional loss). Some scales combine both.

In line with the sentiments expressed by the World Health Organization in the International Classification of Functioning, Disability and Health (2001), more comprehensive evaluations that take personal and environmental factors into account, are currently being developed.

The science of rating scale evaluation and development is a dynamic and extensive field, and this discussion will focus on the most widely known scales used to assess MD.

Design and Validation of a Rating Scale

The design of a rating scale should comply with the following principles: (1) inclusion of the most relevant areas for the objective being targeted; (2) integration of relevant components specifically linked to those areas; (3) generation of scores that represent the real situation of the construct being measured; (4) susceptibility of such scores to statistical analysis; and (5) simplicity and brevity.

The steps to be followed when designing a rating scale are, in brief, specifying and/or identifying the (1) objectives (construct and target population); (2) purpose, that is, whether the intention is to obtain a discriminative (for establishing differences among groups), evaluative (for assessing changes) or predictive instrument (for predicting situations or results); (3) format and mode of application (e.g., examination, interview, computer-based, etc.); (4) potential components (items, subscales); (5) type and number of questions and answers; (6) time frame to be considered; (7) score range and definition of each answer option, where applicable (special attention to wording); (8) instructions for application and scoring; as well as, (9) undertaking a pilot study to check the scale's feasibility and identify any ambiguities, redundancies, etc.; and (10) validating the definitive version.

Scale validation entails checking its properties as a measuring tool according to a rigorous methodology based on scientific theories of health measurement, including Classical Test Theory and Item Response Theory. Validation studies are conducted on a representative sample of the target population, with demographic and historical data as well as scores being obtained, not only from the scale being tested, but also from other measures that are applied simultaneously. These data undergo statistical analysis, and the results are then compared against standard values and rules so as to establish the scale's quality. Validation of a scale is a dynamic process because each modification or new application setting means that its properties must be retested.

The fundamental psychometric attributes of a rating scale are:

1. *Acceptability*: This refers to the extent to which the measure is applicable in the envisaged context, and explores the completeness and distribution of the scores in the sample.
2. *Scaling assumptions*: Referring to the correct clustering of items in the scales and the extent to which their direct sum is suitable for generating a total score representative of the construct.
3. *Reliability*: This refers to the extent to which the scale is free of random error, and includes the measure's internal consistency and stability (inter-rater, test–retest).
4. *Validity*: This attribute determines whether or not an instrument really measures what it was designed to measure. Validity assumes various forms, but content and construct validity are the most frequent types. Content validity indicates the extent to which the scale's components are deemed suitable with respect to the construct to be measured. Construct validity refers to the evidence that supports a given interpretation of the scores, based on their theoretical relationship with the construct. It mainly includes: (i) convergent (concurrent) validity, which refers to the correlation with other measures used to evaluate the same or related constructs; (ii) divergent (discriminant) validity, which refers to the relationship with measures that assess different constructs; and, (iii) discriminative (known groups) validity, which indicates the scale's ability to detect differences among groups.
5. *Precision*: The measure's capacity to detect small differences, which in turn depends on the number of distinctions that such a measure is able to make.
6. *Responsiveness*: The instrument's capacity to detect change (across time or after a therapeutic intervention),

explores the association that exists between detected and real change. This property is linked to reliability and precision.
7. *Interpretability*: The assignment of a comprehensible meaning to scores and score changes.
8. *Other aspects of scale validation*: Administrative and respondent burden concern the time, effort, and other demands involved in the instrument's application. When a scale is to be used in a sociocultural context other than that in which it was initially developed and validated (e.g., in a country on another continent), cross-cultural adaptation may be required. This process consists of the following two phases: (i) translation, in order to obtain a version equivalent to the original in conceptual content and linguistic terms and (ii) a check of the psychometric attributes in the new setting.

Rating Scales for Movement Disorders

There now follows a list of the respective MD in alphabetical order. Shown against the corresponding heading are the rating scales for assessment of the specific disorders, including brief comments about the features and psychometric attributes of the most frequently used instruments.

Akathisia

- *Barnes Akathisia Rating Scale* (*BAS, BARS*) 4-item scale assessing the presence and severity of drug-induced akathisia. It includes both objective and subjective items, rated from 0 to 3, leading to a total sum score. Its reliability, validity and sensitivity are adequate. It is the most widely used scale for akathisia.

Ataxia

- *International Cooperative Ataxia Rating Scale* (*ICARS*): Semiquantitative assessment of cerebellar symptoms and impairment. It consists of the following four subscales: posture and gait disturbances (7 items, maximum 34 points), kinetic functions (7 items, 52 points), speech disorders (2 items, 8 points), and oculomotor disorders (3 items, 6 points). Inter-rater and test–retest reliability and internal consistency are satisfactory, but factorial analysis has not confirmed the scale structure, and several items were redundant and overlapping. The scale has been tested in focal cerebellar lesions, Machado–Joseph disease, multiple system atrophy, and Parkinson's disease (PD) patients, with adequate results despite its limitations.
- *Scale for the Assessment and Rating of Ataxia* (*SARA*): It measures the severity of ataxia via 8 items (maximum total score: 40 points). These are gait (scored from 0 to 8), stance (0–6), sitting (0–4), speech disturbance (0–6), finger chase (0–4), nose–finger test (0–4), alternating hand movements (0–4), heel–shin slide (0–4). Scale psychometric properties have been established for both spinocerebellar and nonspinocerebellar ataxia patients, with satisfactory results.
- *Other scales*:
  - *Cerebellar Ataxia Scale.*
  - *Nobile-Orazio Ataxia scale.*

Chorea

Huntington's disease

- *Shoulson and Fahn Functional Disability Scale for Huntington's Disease*: This scale assesses occupation, handling financial affairs, activities of daily living (ADL), managing domestic responsibilities, and required care. The first three items are scored from 0 to 3, the last two from 0 to 2, and they can be converted into a five-stage disease classification. It has still to be formally validated.
- *Huntington's Disease Activities of Daily Living Scale* (*HD-ADL*): 17-item scale for assessment of patient's adaptive functioning, based on an informant's report. Each item is scored from 0 to 3, with 51 points being the maximum possible score. Internal consistency, test–retest reliability, and convergent validity proved satisfactory in the original study.
- *Unified Huntington's Disease Rating Scale* (*UHDRS*): It is a complex scale that assesses clinical and functional manifestations in four domains, namely: motor function (15 items, scored from 0 to 4); cognitive function (including a phonetic verbal fluency test, the Symbol Digit Modalities Test, and the Stroop Interference Test); behavioral abnormalities (rating frequency and severity of symptoms from 0 to 4); and functional capacity (including the Huntington's disease (HD) functional capacity scale, scored on a 0- to 2- or 3-point scale; the Independence scale, scored from 10 to 100; and a checklist of common daily tasks, rated by means of yes/no response options). The UHDRS has shown satisfactory responsiveness in follow-up studies and clinical trials. Although its psychometric properties were adequate, its length and administrative load were criticized, and so a shortened version of the motor section of the UHDRS (15 items) was subsequently developed and validated.
- *Behavior Observation Scale Huntington* (*BOSH*): Description of the manifestations of HD in the final stages. Administered by nursing staff, it contains 32 items in the following three subscales: activities of daily living (ADL), social-cognitive functioning, and mental rigidity and aggression. Inter-rater and internal consistency are adequate and the scale discerns behavioral patterns as the disease progresses.

Sydenham's chorea

- *UFMG Sydenham's Chorea Rating Scale* (*USCRS*): The USCRS comprises 27 items, scored from 0 (no symptom or sign) to 4 (severe disability), and designed to assess ADL, behavioral problems and motor functioning in Sydenham's Chorea patients. Test–retest and inter-rater reliability have proved satisfactory.

Drug-Induced Movement Disorders

- *Extrapyramidal Symptom Rating Scale* (*ESRS*): 12-item instrument assessing four types of drug-induced MD: parkinsonism, akathisia, dystonia, and tardive dystonia. Using a 7-point response option for each item, it rates both frequency and movement amplitude. The ESRS has a 6-factor structure, which has shown satisfactory inter-rater reliability, convergent validity and sensitivity to change.
- *Simpson–Angus Scale* (*SAS*): 10-item scale, with item scores ranging from 1 to 5, designed to assess the presence and severity of rigidity and bradykinesia. It is the most widely used scale for extrapyramidal symptoms in clinical assays. Thanks to its fast and easy mode of administration, it is also suitable for clinical practice. There are 1- and 4-item short versions.
- *Abnormal Involuntary Movement Scale* (*AIMS*): This assesses MD (dyskinesia, akathisia, and chorea) associated with psychotropic medication. The AIMS is made up of 12 items scored from 1 to 5. Widely used in clinical assays as an outcome measure, this instrument registers good inter-rater and test–retest reliability, and convergent validity.

Dystonia

Generalized dystonia

- *Fahn–Marsden Dystonia Rating Scale* (*F–M Scale*): The F–M Scale assesses the severity of generalized dystonia, and consists of two parts, that is, movement (motor examination of nine body regions) and disability (patient's perspective on ADL, rated from 0 to 4). The movement scale includes severity, provocative maneuvers, and weighting factors. The F–M scale is the standard instrument for assessing dystonia, though its psychometric properties were only recently established. Internal consistency, inter-rater (except for some body regions) and test–retest reliability, and convergent validity are satisfactory. Its responsiveness is still to be tested.
- *Barry–Albright Dystonia* (*BAD*) *Scale*: 5-point ordinal severity scale for secondary dystonia in children. Inter-rater and test–retest reliability and responsiveness were found satisfactory. The scale has been used to measure treatment efficacy. Training is recommended before using this scale.
- *Unified Dystonia Rating Scale* (*UDRS*): Developed to overcome the limitations of the F–M Scale, it includes a more detailed rating of body regions and a dystonia duration factor, and eliminates patients' perception and the weighting factor. Severity and duration are scored from 0 to 4. It has a better internal consistency than the F–M scale, and satisfactory inter-rater reliability. The UDRS has been used as a measure of efficacy following surgical interventions but responsiveness has not been tested.
- *Global Dystonia Severity Rating Scale* (*GDS*): It rates dystonia severity in the same regions described for the UDRS, with a scale scored from 0 (no dystonia) to 10 (severe). There are no modifying or weighting factors. Internal consistency, inter-rater reliability, and convergent validity are excellent. It has been found to be easier to administer than the F–M and the UDRS.

Focal dystonia

Blepharospasm

- *Blepharospasm Rating Scale* (Lindeboom et al., 1995): This scale is divided into two sections, namely: a movement scale (including severity of eyelid closure, frequency, location, and influencing factors of involuntary movements) and a disability scale. The disability section has been validated, and has displayed adequate internal consistency, convergent and discriminative validity, and responsiveness. Lindeboom et al. recommend removing two weak or redundant items from the first version (sunglasses and watching movies) to improve the scale's reliability.

Cervical dystonia

- *Spasmodic Torticollis Rating Scale* (Tsui et al., 1986): Specifically designed to measure cervical dystonia severity in clinical trials, this has four subscales, that is, amplitude, duration of movement, shoulder elevation, and tremor. Only inter-rater reliability has been tested, with satisfactory results.
- *Torticollis Rating Scale*: This scale evaluates both movement (direction of muscle pulling, influencing factors, severity of the deformity and pain, and presence of jerking movements, with heterogeneous item scoring) and disability (impact on ADL, scored on a scale from 1 to 2, 3, or 5 points; maximum score, 27). It has not yet been validated.
- *Toronto Western Spasmodic Torticollis Rating Scale* (*TWSTRS*): Despite its complexity, the TWSTRS is the most widely used scale for assessing cervical dystonia in clinical practice and research. It consists of the following three subscales: motor severity (10 items assessing severity, range of motion and duration, scored heterogeneously, maximum score: 35); disability (6 items assessing difficulties in several activities, scored from 0 to 5, maximum score: 30); and pain (severity and duration, and

disability due to pain, maximum score: 20). The total maximum scale score is 85. A teaching video-tape has been developed for the motor section. Inter-rater reliability and convergent validity of the motor subscale are satisfactory. Several studies suggest that the TWSTRS may not be sensitive enough to detect clinically significant changes.

- *Cervical Dystonia Severity Scale* (*CDSS*): Objective measurement of head position in 5-degree intervals, using a wall chart and protractor. The head rotation deviation, laterocollis, and anterocollis/retrocollis scores can be transformed into a severity scale. Good inter-rater and test–retest reliability has been found in the original study, but validity and sensitivity studies are still required.

Limb dystonia

- *Arm Dystonia Disability Scale* (*ADDS*): The ADDS evaluates functional impairment of the dystonic hand, on a 7-item scale, scored from 0 to 3. It has been used as a treatment efficacy measure. Moreover, it shows adequate convergent validity with the Frequency of Abnormal Movements (FAM) Scale.
- *Leg Dystonia Disability Scale*: Assessment of functional impairment caused by the dystonic leg in walking, standing, and other activities. It consists of 7 items, with the final total score expressed as a percentage. It has not been validated to date.
- *Writer's Cramp Rating Scale* (*WCRS*): Objective clinical assessment of writing movement (3 items) and speed (1 item). Item scores range from 0 (no) to 2 (marked/severe). This scale has been mainly used to assess treatment efficacy, with good results. Inter-rater reliability was also satisfactory, though correlation with other writer's cramp measures (ADDS, kinematic patterns analysis) was low, as the latter assess different aspects of motor impairment.
- *Frequency of Abnormal Movements* (*FAM*) *Scale*: It was purpose-developed to assess musician's dystonia. Internal consistency, test–retest and inter-rater reliability, convergent validity, and sensitivity are satisfactory.

Oromandibular dystonia

- *Oromandibular Dystonia Rating Scale*: Includes a severity (severity, frequency, location, and influencing factors) and a disability scale for oromandibular dystonia. It has not been validated.

Hemifacial Spasm

- *Martí and Tolosa Scale*: Assessment of treatment efficacy in hemifacial spasm. It rates: severity, on a scale from 0 (no spasm) to 4 (severe); frequency, from 0 (absent) to 5 (>75% of the time); and functional impairment, with 7 items scored from 0 (no impairment) to 3 (severe). Test–retest and inter-rater reliability have been analyzed, with good results.

Myoclonus

- *Unified Myoclonus Rating Scale* (*UMRS*): The UMRS assesses myoclonus severity, characteristics, and disability. It is made up of 73 items, grouped into 5 sections, namely: patient's questionnaire (12 items, scored from 1 to 5); myoclonus at rest (8 items, scored from 0 to 4, rating frequency and amplitude); stimulus sensitivity (17 items, dichotomous); myoclonus with action (10 items, scored for frequency and amplitude on a 5-point scale); and functional tests (5 items, scored from 0 to 4). There are also 3 items evaluating global disability on a scale from 0 (normal) to 4 (severe disability, invalid), negative myoclonus presence (yes/no) and severity (from 0, not present, to 3, severe). The UMRS displays good internal and inter-rater consistency, as well as adequate sensitivity to change.
- *Other scales:*
  - *Myoclonus Evaluation Scale*: Aimed at quantifying the severity of myoclonus, it consists of two sections that evaluate this MD in upright posture, and dynamic function. Although not validated, it has been used to assess clinical trial outcomes.
  - *Opsoclonus Myoclonus Syndrome Evaluation Scale*: It assesses opsoclonus myoclonus syndrome severity via 12 items rated on a scale from 0 to 3 (normal to severe). A clinical study established inter-rater reliability.

Parkinsonisms

Parkinson's disease (PD)

Multidimensional scales

- *Unified Parkinson's Disease Rating Scale* (*UPDRS*): The UPDRS is made up of 42 items grouped into four subscales: Section I – mentation, behavior and mood; Section II – ADL (scored for 'on' and 'off'); Section III – motor examination; and Section IV – complications. Items from Sections I–III are scored on a 4-point scale. Section IV contains dichotomous items and items scored on a 4-point scale for duration or severity. The UPDRS battery includes also the Hoehn and Yahr, and the Schwab and England scales. Psychometric attributes have been widely analyzed. The scale displays adequate internal consistency. Its factorial structure is stable across studies. Section II displays a higher inter-rater reliability than Section III. Test–retest reliability is also acceptable, except for some Section III items. The UPDRS shows good convergent validity with other PD scales and satisfactory discriminative validity with PD severity levels. Not only is it sensitive to change and the most widely used PD scale, but it is also the reference measure for regulatory agencies (European Medicines Agency, and the US Food and Drug Administration). A revised version (Movement Disorder Society-UPDRS) has been

developed to overcome some problems identified in the previous version. The new scale also is made up of four sections, with a part to be used as a patient's self-assessment. First analyses demonstrate it is a reliable and valid measure.

- *The Short Parkinson's Evaluation Scale* (*SPES*): Inspired by the UPDRS, the SPES is made up of 24 items, scored from 0 to 3, forming four sections and showing adequate sensitivity to change.
- *Scales for Outcomes in Parkinson's Disease – Motor* (*SCOPA–Motor*): This seeks to assess motor signs, functional ability and motor complications in PD. Derived from the Short Parkinson's Evaluation Scale (SPES), it is composed of 21 items grouped in the following three sections: motor examination, ADL, and complications. Each item is scored on a 3-point scale. The three subscales display adequate internal consistency, as well as good test–retest reliability and adequate inter-rater reliability. Convergent validity with PD-related measures is excellent. The SCOPA–Motor shows satisfactory discriminative validity according to PD severity level.
- *Intermediate Scale for Assessment of Parkinson's Disease* (*ISAPD*): This is a short scale for use in clinical practice and in research, composed of a 13-item section that assesses functional aspects, and a 4-item section that assesses dyskinesias and fluctuations, with all items being scored from 0 to 3.

Functional scales

- *Schwab and England Scale*: This measures patients' global functioning and dependency via only 1 item scored on an 11-point scale (0%, completely independent, to 100%, vegetative). The main advantages of this scale are its simplicity and wide use, despite its lack of standardization. It forms part of the UPDRS battery and possesses satisfactory acceptability and construct validity. It displays precision and sensitivity to change comparable to other functional scales (those embedded in the multidimensional scales, for instance).
- *Columbia University Rating Scale* (*CURS*): Made up of 13 items, each scored from 0 to 4, the CURS measures impairment. It was frequently used before the introduction of the UPDRS. Indeed, the UPDRS-Section III (motor examination) was derived from the CURS, as was the Sidney Scale (Hely et al., 1993).

Dyskinesia

- *Parkinson Disease Dyskinesia Scale* (*PDYS-26*): This scale aims at quantifying the impact of dyskinesias on patient functioning, according to the patient's perspective. It comprises 26 items, rated on a 4-point scale, which yield a total score. The scale was developed using Rasch analysis, and then standard psychometric methods were applied. Both methods support the scale's unidimensionality. It displays high internal consistency and good construct validity.
- *Obeso Dyskinesia Scale*: It assesses the intensity and duration of dyskinesia by combining historical and motor examination data. This scale has not yet been validated.
- *Rush Dyskinesia Rating Scale*: An objective evaluation of dyskinesia and its impact on functional state, this scale assesses the three activities of: walking, putting on a coat and buttoning it, and lifting a cup to the lips for drinking. Severity of dyskinesias is scored from 0 to 4. The Rush scale shows good inter- and intra-rater reliability.
- *Clinical Dyskinesia Rating Scale* (*CDRS*): This consists of independent evaluations for hyperkinesia and dystonic posture in seven body parts. Items are scored from 0 to 4, and the maximum possible score is 28 for hyperkinesias as well as for dystonia. This scale does not evaluate disability. It displays good inter- and intra-rater reliability.

Wearing-off

- *Wearing-off Questionnaire*: There are three versions of the wearing-off questionnaire. The original, with 32 items, is referred to as the 32-item Wearing-off Questionnaire (WOQ-32) or as the Patient Questionnaire. Based on the WOQ-32 and validated independently, the 19-item version was developed retrospectively as a more practical tool for clinical practice and research. This 19-item version is referred to as the Wearing-off Questionnaire, the Patient Card Questionnaire, or the Quick Questionnaire. Finally, there is a shorter version, the 9-item Wearing-off Questionnaire (WOQ-9). Both the 9- and 19-item versions are made up of items contained in the WOQ-32. The 19-item version captures wearing-off symptoms more frequently than do other methods, including the original 32-item scale, and a cut-off value of two symptoms results in high specificity and sensitivity. The 9-item version displays high sensitivity and moderate specificity.

Fluctuations and dyskinesia

Home diaries: They are useful tools for obtaining valuable information on PD motor complications. A diversity of diaries exists but, in essence, they capture the patient's situation throughout the day, at scheduled intervals, with regard to the following situations: 'on' and 'off,' with or without dyskinesias, and functional impact of the 'off' period and abnormal movement. Diaries allow to distinguish between good or bad time in 'on with dyskinesia,' an important point for treatment and clinical trials.

Gait evaluation

- *Rating Scale for Gait Evaluation* (*RSGE*), *second version*: This is formed of 21 items, scored from 0 to 3 and grouped

in 4 sections, that is, socioeconomic, functional, examination, and complications. It displays good convergent validity, high internal consistency, and fair inter-rater reliability. The first version of the RSGE was never validated.

- *Clinical Gait and Balance Scale, GABS*: A battery of tests that measures gait-dependent functional activity through historical information and examination. Some items are scored from 0 to 4, and others from 0 to 1, or 0 to 2, with 0 being normal. It displays high intra-rater test–retest reliability and adequate concurrent validity with computerized gait-related measures.
- *Other scales:*
  - *Hoehn and Yahr Staging Scale*: This scale collapses the evolutionary course of PD into five stages. It is mainly used to stratify patients for research purposes and to furnish a global severity assessment. It is reviewed in a separate section of this volume (see Section MS34).
  - *Clinical Impression of Severity Index for Parkinson's Disease* (*CISI-PD*): A 4-item global impression scale that summarizes clinician ratings of motor signs, disability, motor complications and cognitive impairment. Items are scored on a 0- to 6-point rating scale, that then yields a total sum score. It is a fast, valid, and reliable measure.

Multiple system atrophy

- *Unified Multiple System Atrophy Rating Scale* (*UMSARS*): This scale assesses functional deficit, as well as autonomic and urogenital dysfunction. It comprises the following four subscales: historical review, motor examination scale, autonomic examination, and global disability scale. For the UMSARS-I and UMSARS-II, item scores range from 0 to 4, and the maximum possible score for each subscale is 48 and 56, respectively. The UMSARS-III consists of cardiovascular parameters relating to blood pressure and heart rate, and the UMSARS-IV rates overall disability on a 5-point scale. The first two subscales display high internal consistency. Inter-rater reliability of parts I and II is substantial to excellent. The UMSARS also shows adequate internal and discriminative validity. It is used as an outcome measure in therapeutic trials.

Progressive supranuclear palsy

- *Progressive Supranuclear Palsy Rating Scale* (*PSPRS*): The PSPRS is a comprehensive disability rating scale for progressive supranuclear palsy, formed by 28 items grouped into six dimensions, namely, daily activities, behavior, bulbar, ocular motor, limb motor, and gait/midline examinations. Items are rated on a 0–2 or 0–4 scale, thereby providing a total score of 0–100. This scale registers good inter-rater reliability, with a satisfactory independent predictor value of survival.

Psychogenic Movement Disorders

- *Rating Scale for Psychogenic Movement Disorders*: This rates 10 phenomena (rest tremor, action tremor, dystonia, chorea, bradykinesia, myoclonus, tics, athetosis, ballism, and cerebellar ataxia), 2 functions (gait, speech) and 14 body regions. Items are scored for severity (from 0, none, to 4, severe), duration (from 0, none, to 4,>75% of the time) and incapacitation (from 0, none, to 4 severe). A total phenomenology and a total function score are produced, and summed to obtain the total scale score. Inter-rater reliability, construct validity and responsiveness have all been studied, with satisfactory results.

Restless Legs Syndrome (RLS)

- *International Restless Legs Syndrome Study Group* (*IRLS*) *Rating Scale*: This is a 10-item self-administered scale to measure severity and impact of RLS. Items are scored from 0 (none) to 4 (very severe). The scale's psychometric properties have been extensively analyzed, using both classical and item-response methods. Good levels of internal consistency, test–retest and inter-rater reliability, and convergent and criterion validity have been observed. Factor analysis has revealed two factors, namely, symptoms and symptom impact. The IRLS scale has been widely used in clinical trials and epidemiologic studies.
- *Johns Hopkins Restless Legs Syndrome Severity Scale* (*JHRLSS*): The JHRLSS assesses symptom severity based upon the patient's response (from 0, none, to 4, severe) to a single question on the usual time of the day that symptoms start. This scale correlates well with other RLS and sleep measures, and shows good inter-rater reliability. A telephone-based interview has been derived from the JHRLSS (telephone diagnostic interview, TDI), with good psychometric properties.
- *Other scales*:
  - *RLS-6 Severity Scales*
  - *Augmentation Severity Rating Scale* (*ASRS*)

Spasticity

- *Ashworth Scale*: This scale evaluates muscle resistance to passive stretching. It includes 5 grades, ranging from 0 (no increase in tone) to 4 (limb rigid in flexion or extension). The Modified Ashworth Scale (Bohannon, 1987), more frequently used now, increases the sensitivity of low values by adding a grade, 1+, and more descriptive grade information. It displays low inter-rater reliability.

- *Other scales*:
  - *Modified Tardieu Scale*: Based on the Tardieu Scale, it measures passive range of movement at three different velocities.
  - *Resistance to Passive Movement Scale (REPAS)* (Platz et al., 2008): A summary rating scale for REPAS.

Tics and Tourette's disorder

- *Tourette Syndrome Global Scale* (*TSGS*): A multidimensional scale that includes symptoms (4 dimensions, scored for frequency from 0 to 5, and degree of disruption, from 1 to 5) and social functioning (3 dimensions, rated on a continuous scale from 0, no impairment, to 25, severe impairment). These two part scores are transformed into a global score, though they can also be used separately. The TSGS has been used as a primary outcome variable in clinical trials, and has shown good inter-rater reliability. It lacks further validation studies and has been criticized for its underweighting of social dimension (failing to assess tic types) and complexity.
- *Shapiro Tourette Syndrome Severity Scale* (*STSSS*): Composite clinician rating of Tourette syndrome severity, based on the following 5 items: degree to which tics are noticeable to others; whether they elicit comments of curiosity; whether other individuals consider the patient odd or bizarre; whether tics interfere with functioning; and whether the patient is incapacitated, homebound or hospitalized. The sum score affords a global severity index. It has been used to measure treatment results and is simple to use, valid, and highly reliable (inter-rater reliability). It does not include assessment of a wide range of tic characteristics, as it primarily focuses on social disability associated with Tourette syndrome.
- *Yale Global Tic Severity Scale* (*YGTSS*): A semistructured interview for evaluation of motor and phonic symptom severity. The YGTSS includes a tic inventory, as well as items on the number, frequency, intensity, complexity, interference of motor and phonic tics, scored from 0 (none/absent) to 5 (severe/always). It yields total motor and phonic scores, an overall impairment rating, and a global severity score (the sum of motor, phonic, and impairment scores). The scale has been tested primarily in clinical settings, with satisfactory results in terms of internal consistency, stability, and validity, for children and adults alike. It is also suitable for measuring treatment efficacy. The YGTSS is a complex and comprehensive scale, requiring a highly experienced rater, as the final score reflects the clinician's overall impression of the symptoms.
- *Other scales*:
  - *Rush Videotape Rating Scale*
  - *Hopkins Motor and Vocal Tic Scale* (*HMVTS*)
  - *The Tourette's Disorder Scale* (*TODS*)
  - *Tourette Syndrome Symptom List* (*TSSL*)
  - *Tourette Syndrome Questionnaire* (*TSQ*)
  - *Motor tic, Obsessions and compulsions, Vocal tic Evaluation Survey* (*MOVES*)

Tremor

- *Washington Heights-Inwood Genetic Study of Essential Tremor Rating Scale* (*WHIGET*): This aims at assessing the following aspects of essential tremor: intensity, amplitude, oscillation prevalence, and persistence. Rest, kinetic and postural tremor are evaluated separately. The scale is made up of 26 items that assess actions or tasks where essential tremor may occur. Items are scored on a scale from 0 to 3. A revised version adds a score of 4 to the kinetic tremor section, which improves the scale's sensitivity in clinical trials. There is a teaching videotape to improve inter-rated reliability. The scale displays good test–retest and inter-rater reliability, as well as convergent validity with related clinical, functional and computerized measures.
- *Other scales*:
  - *Bain Findley Tremor Scale*: A functional assessment of the effects of tremor on different body parts.
  - *Fahn–Tolosa–Marin Tremor Rating Scale* (*TRS*): A functional evaluation of rest, postural and kinetic tremor.
  - *Essential Tremor Screening Questionnaire*: A shortened version of another screening procedure for essential tremor, consisting of seven yes/no questions and a spiral drawing.

Conclusions

Use of rating scales for assessment of patients with MD is necessary for sharing information, quantifying health status, and outcomes research. A wide variety of scales is available for many MD. Selection of suitable measures should be guided by knowledge of their characteristics, psychometric attributes, and appropriateness for the designated study objectives. Validation of a rating scale is a complex process that follows a rigorous methodology and must precede any clinical or research application.

See also: Fahn–Marsden Rating Scale; Friedreich's Ataxia Rating Scale (FARS); Hoehn and Yahr Staging Scale; International Cooperative Ataxia Rating Scale (ICARS); Scale for the Assessment and Rating of Ataxia (SARA); Schwab and England Activities of Daily Living Scale; Unified Parkinson's Disease Rating Scale (UPDRS) and The Movement-Disorder Society Sponsored-unified Parkinson's Disease Rating Scale (MDS-UPDRS); Yale Global Tic Severity Scale (YGTSS).

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Reaction Time

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Glossary

Choice reaction time – A reaction time that involves multiple stimuli and differing responses for each stimulus.

Reaction time – The time between a stimulus and a response.

Simple reaction time – A reaction time that involves a single stimulus and a single response.

Definition and History

Reaction time may simply be defined as the time between a stimulus and a response. Three basic reaction time paradigms have been described: (1) simple reaction time involves a single stimulus and a single response, (2) recognition reaction time involves the selection of a specific stimulus after the presentation of different multiple stimuli, and (3) choice reaction time involves multiple stimuli and differing responses for each stimulus. Serial reaction time is a combination of recognition and choice reaction time, where the stimulus is a repeating sequence that the subject must learn to predict and then to respond in a prescribed fashion.

Reaction times are usually recorded as a mean of several trials following a practice period (cueing) to minimize practice effects and to reduce variability of the response. Reaction times are very situation specific, and can vary according to choice of device, stimulus, or response. In designing a paradigm for measuring the reaction time, it is important to select the test instrument carefully and to compare trends between studies rather than absolute times if different devices are used. In general, simple reaction times are faster than recognition reaction times and recognition reaction times are faster than choice reaction times. Multiple factors, including age, gender, IQ, handedness, fatigue, sleep deprivation, and medications, may influence the reaction time and it is important for studies to control for these variables. Many reaction time instruments filter results to eliminate responses that are shorter than physiologic (anticipated) or uncharacteristically long (distraction).

Reaction Time in Animal Models of Parkinson's Disease

Reaction time measures can be useful in the study of animal models of disease assuming the animal is able to learn the reaction time task. Rodents subjected to bilateral 6-hydroxydopamine lesions of the nigrostriatal dopamine system perform poorly on a reaction time task while asymmetric lesions have little effect on reaction time performance. High-frequency stimulation of the subthalamic nucleus in hemiparkinsonian rats more dramatically improved basic motor function than choice reaction time.

Reaction Time in Parkinson's Disease

Several studies have investigated reaction time paradigms in Parkinson's disease. The search for specific patterns of impaired reaction time in Parkinson's disease has yielded conflicting results. In general, patients with Parkinson's disease separate from control subjects most dramatically with tasks that have a shorter reaction time. More elaborate tasks require a greater cognitive component and are less specific measure of loss of motor control.

Reaction time in Parkinson's disease tends to correlate with measures of global cognitive capacity and frontal-lobe function, as well as motor disability. Some studies have demonstrated that treatment with dopaminergics had no effect on simple reaction time or choice reaction time, despite clinical benefit on overall motor performance. This suggests that these processes are not substantially dopamine-dependent but may be served by nondopaminergic neurotransmission. Other studies have shown improvement in reaction time measures by either dopaminergics or by deep-brain stimulation. There is also the observation that practice improves reaction times more in normal individuals than in patients with Parkinson's disease. These findings suggest that the frontal lobes are implicated in the slowed response speed in Parkinson's disease. The inability to control for the heterogeneity of frontal and cerebellar deficits seen in individual patients with Parkinson's disease may explain the apparent inconsistent results across studies.

Reaction Time in Other Movement Disorders

Electromyography has been used to devise reaction time tasks for the study of the ability to relax muscles in dystonia. These studies suggest that muscle relaxation is abnormal in patients with focal (multifocal or segmental) dystonia. They demonstrate the difficulty in interpreting the results of reaction time data from a motor-impaired body part. Studies comparing reaction times in patients with Parkinson's disease, Huntington's disease, and cerebellar disorders have been performed. These demonstrated that the patients with Huntington's disease had a significantly longer simple reaction time than those with Parkinson's disease. None of the other group differences in uncued and unwarned simple reaction time and choice reaction time were significant. Generally, the results are similar between the groups suggesting a nonspecific slowness having diverse central mechanisms. In a model examining the speed of wrist flexion in 10 patients with moderate to severe disability from essential tremor, the mean reaction time and movement time of the patients did not differ from the mean values of controls.

Summary

The neurochemical basis of reaction time deficits in Parkinson's disease and other movement disorders remains unclear. Movement disorders, even within a single disease, represent a highly diverse phenotype, and many variables including nonmotor features (depression, cognitive impairment, and sleep disorders), medications, and inherent incongruity of the disease must be considered when designing and interpreting the studies of reaction time in movement disorders.

See also: Akinetic-Rigid Syndrome; Bradykinesia; Huntington's Disease; Intra-Individual Variability in Movement; Movement Time; Parkinson's Disease: Definition, Diagnosis, and Management.

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Recessive Hereditary Methemoglobinemia Type II

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Glossary

Athetosis – Involuntary slow continuous distal writhing movements.
Chorea – Irregular, unpredictable, brief involuntary movements that flow from one part of the body to another in nonstereotyped fashion.
Cytochrome b5 reductase – An enzyme involved in erythrocytic methemoglobin reduction and in fatty acid desaturation; its possible role in neural development and function is unknown.
Dystonia – Movement disorder characterized by involuntary twisting movement or abnormal postures resulting from simultaneous contraction of agonist and antagonist muscles.
Methemoglobin – Oxidized form of hemoglobin that does not carry oxygen and is reduced to hemoglobin by the soluble erythrocytic cytb5r isoform.
Protein isoforms – Different forms of a protein produced by related genes or arising from the same gene by alternative splicing.

Definition and History

Recessive hereditary methemoglobinemia (RHM) is an autosomal recessive metabolic disorder due to NADH-cytochrome b5 reductase (cytb5r) deficiency. The gene that encodes this enzyme is located on chromosome arm 22q13-qter.

This enzyme exists as soluble and membrane-bound isoforms, both of which are ubiquitously expressed. The soluble erythrocytic cytb5r isoenzyme is involved in methemoglobin reduction, while the biological role of the soluble nonerythrocytic cytb5r isoenzyme is unclear (**Figure 1**). The membrane-bound microsomal enzyme plays a role in fatty acid desaturation and in drug metabolism.

Two types of RHM have been delineated. Type I RHM is characterized by cytb5r deficiency restricted to erythrocytes, resulting in benign chronic cyanosis. In 1845, François reported the first patient with long-standing congenital cyanosis despite no obvious cardiac or pulmonary disorders. In 1948, Gibson et al. found that the disease was related to a deficiency in an erythrocytic enzyme that was later identified as soluble cytb5r. Type II RHM is characterized by a profound deficiency of both the soluble and membrane-bound cytb5r isoforms in all tissues. Permanent cyanosis is associated with severe neurological manifestations. The first case was reported in 1948 by Sacerdotti-Favini, and the disease was shown to be due to generalized cb5r deficiency by Leroux et al. in 1975.

Genotype–Phenotype Correlation and Pathophysiology

More than 40 mutations have been identified in the cytb5r gene, some of which are common to both types of RHM.

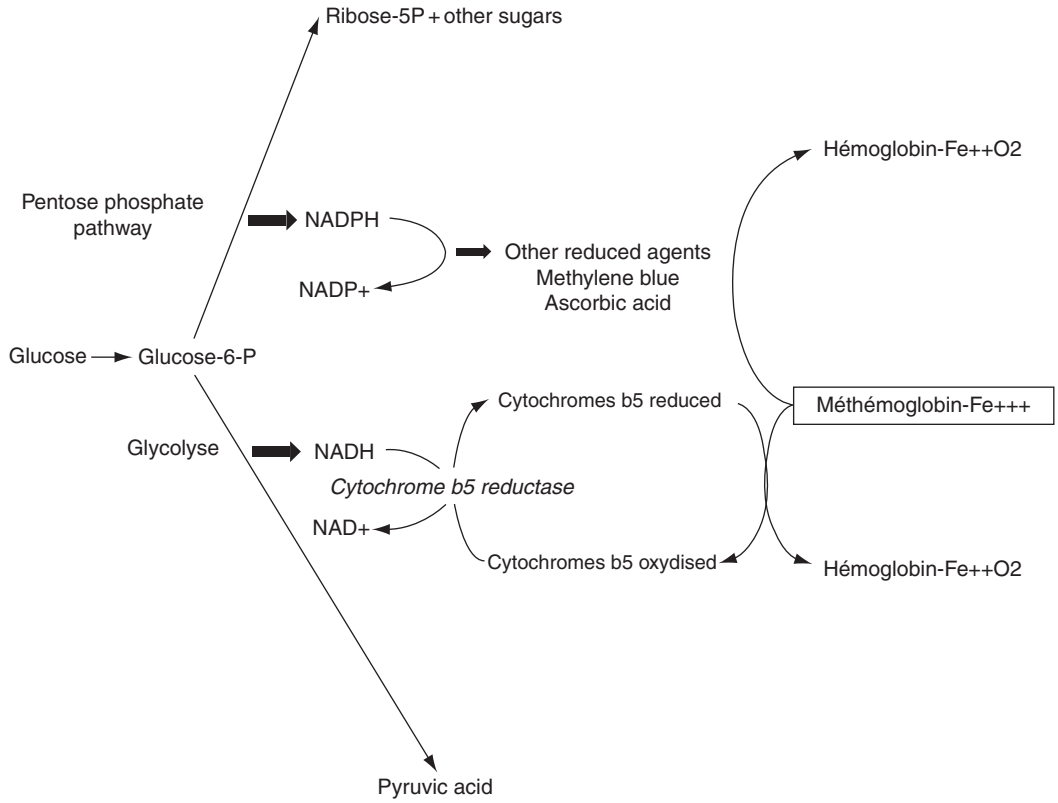

Figure 1 Methemoglobin reduction in erythrocytes. Cytochrome b5 reductase catalyses electron transfer from NADH (produced by the glycolysis pathway) to cytochrome b5. Reduced cytochrome b5 in turn reduces the oxidized ferric ion of hemoglobin. When cytochrome b5 reductase activity is deficient, reduction of methemoglobin uses NADPH from the pentose phosphate pathway, and other electron donors such as methylene blue or ascorbic acid.

Missense mutations are commonly present in type I RHM. They result in amino acid substitutions and diminished enzyme stability. In cells possessing the protein-synthesizing machinery the unstable enzyme is replaced in both its soluble and membrane-bound forms. By contrast, mature erythrocytes cannot synthesize proteins, and the lack of the soluble enzyme results in elevated methemoglobin levels, linked to continuous oxidative stress and nitrite exposure. Mutations associated with type II RHM lead to altered splicing, disruption of the enzyme's active site, or premature truncation of the protein. The enzyme is thus inactive in both its soluble and membrane-bound forms in all cell types.

Although the genotype–phenotype correlation in RHM is becoming clearer, the pathophysiology of the neurological disorder in type II RHM is still completely unknown. Type II RHM is characterized by generalized cytb5 reductase deficiency. The membrane-associated enzyme plays a fundamental role in the microsomal electron transport system and participates in fatty acid elongation and desaturation, as well as in fatty acid synthesis and drug metabolism. In contrast, its role in central nervous system development and function is unknown. Only two autopsy cases have been published. One patient had a hypoplastic brain, a thin cerebral cortex, and delayed myelination. The basal ganglia were normal but the cerebellum showed marked degeneration. The fatty acid composition of tissues (myelin, white matter and gray matter, adipose tissue, liver) was found altered in the second autopsied patient, suggesting that subnormal unsaturated fatty acid production is involved in type II RHM, possibly leading to central nervous system dysmyelination and encephalopathy.

Epidemiology

51 cases of type II RHM have been published since 1948. The disorder seems to occur worldwide but is mainly reported in the Mediterranean basin and Europe. It is probably underdiagnosed, especially in African subjects in whom cyanosis is more difficult to detect.

Clinical Features

During the first 2 months of life, half the patients have normal neurological findings. The full clinical phenotype

emerges at about 9 months of life. The neurological features are fairly uniform. Fixed encephalopathy is always present and extremely severe. Psychomotor skills are always inferior to those of a 1-year-old child. At best, these patients can sit, grip objects in a dystonic palmar manner, react and smile at familiar faces, and utter sounds. All the patients have generalized dystonia that can result in dystonic storms. Dystonia is often associated with axial hypotonia and diffuse choreoathetoid movements. With aging, the axial hypotonia tends to improve, abnormal movements decrease, and the dystonia becomes more fixed. Microcephaly is always present, and progressive growth retardation and converging strabismus are frequent. Refractory epilepsy has been reported in three patients, including a patient with West's syndrome. Behavioral abnormalities, such as screaming and agitation, are reported in the first years of life. The few patients who survive beyond 10 years of age have severe skeletal deformations such as scoliosis, and musculotendinous retractions owing to chronic dystonia.

Cyanosis is the key to diagnosis but may be difficult to detect. The blood has a chocolate-brown color due to the chronically high erythrocytic methemoglobin level. The complexion has been described as pale or 'grayish-blue.' Cyanosis can only be seen on the labial mucosa and nails of dark-skinned patients, and this may explain the lack of reported African cases. Cyanosis is accentuated during stressful events such as infections, but it may remain unnoticed for years. It is the most helpful sign, however, and failure to detect it may delay the diagnosis.

Rare atypical cases in five families (four Japanese and one Cuban) have been reported. These patients appeared to have a milder form of the disease, with prolonged survival and milder psychomotor retardation.

Diagnostic Work-up

MRI shows non specific cortico-subcortical atrophy and delayed myelination. The methemoglobin level is always elevated (over 1%) and usually ranges from 10% to 40% in type II RHM. Methemoglobinemia is suggested by abnormal pulse oxymetry (85–95%), incompatible with normal blood saturation (pO_2 assay). Methemoglobinemia is confirmed by measuring the methemoglobin level in arterial blood by cooximetry.

To confirm the diagnosis, generalized cytb5r deficiency must be established. In type I RHM, the activity of the soluble form of cytb5r is only diminished in erythrocytes. In type II RHM, cytb5r activity is diminished (<30% of normal) in both erythrocytes and leukocytes. Molecular genetic testing can be performed as a basis for reliable genetic counseling and prenatal diagnosis for future pregnancy.

Management and Prenatal Diagnosis

While cyanosis can be treated with methylene blue, riboflavin, or ascorbic acid, there is currently no way of preventing or even slowing the neurological deterioration associated with type II RHM. Patients may benefit from symptomatic treatment of their movement disorders with anticholinergics, benzodiazepines, or tetrabenazine physiotherapy and swallowing rehabilitation are also important part of the management.

Prenatal diagnosis should be proposed to affected families, as each subsequent sibling has about a 25% risk of being affected and there is no effective treatment. Prenatal diagnosis is based on cytb5r assay in fetal amniotic cells, or on the detection of previously identified mutations in trophoblast biopsy specimens.

Prognosis

In the first reports, the life expectancy of patients with typical type II RHM did not exceed 10 years of age. However, a few older patients (up to 24 years) with the typical severe form have now been reported, and they appear to have no particular life-threatening disorders. Survival is likely to depend on swallowing function (risk of respiratory infections and failure to thrive), and overall management, especially prevention of decubitus complications.

See also: Anticholinergics and Movement Disorders; Athetosis; Chorea; Dystonia; Dystonia, Secondary.

Further Reading

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Refsum Disease- a Disorder of Peroxisomal Alpha-oxidation

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Glossary

α-Oxidation – Oxidative metabolism of methyl group at the α position next to the carboxylic acid group of a fatty acid.
β-Oxidation – Oxidative metabolism of fatty acids at the β position after complexing with coenzyme A by removal of two carbon acetyl-CoA units.
ω-Oxidation – Metabolic process with an initial oxidation of the end methyl-group of a fatty acid to produce a double carboxylic fatty acid followed by β-oxidation from either end.
Apheresis – Physical removal of plasma lipoproteins in a process analogous to dialysis.
Peroxisome – Cellular organelle containing enzymes for synthesis of complex long chain fatty acids, first stages of cholesterol as well as enzymes to perform α-oxidation of 3-methyl-fatty acids, and β-oxidation of polyunsaturated or complex fatty acids.
Phytanic acid – (3*R*,*S*, 7*R*, 11*R*, 15-Tetramethylhexadecanoic acid) a bacterial oxidative product of chlorophyll side-chain which accumulates in Refsum's disease.
Plasmalogen – Plasmalogen is an ether lipid where the first position of glycerol binds a vinyl residue (from a vinyl alcohol) with the double bond next to the ether bond, the second carbon is occupied by an ester-linked fatty acid, and the third has a phospholipid group like choline or ethanolamine.
Plasmapheresis – Physical removal of lipoproteins and other plasma proteins in a process analogous to dialysis.

Definition and History

Adult Refsum's disease (ARD) (OMIM 266510), also called *heredopathia atactica polyneuritiformis* and hereditary sensory motor neuropathy type IV, actually first described in 1947, was recognized by Refsum in 1962. Its key features are retinitis pigmentosa and anosmia, but it can present acutely with weakness, ataxia, and sensorimotor neuropathy.

Pathogenesis/Pathophysiology

Clinical Enzymology

Phytanic acid (3*R*,*S*, 7*R*, 11*R*, 15-tetramethylhexadecanoic acid) (PA) is an isoprenoid lipid derived from the phytol side-chain of chlorophyll. PA is preferentially taken up by the liver and may account for up to 50% of the free fatty acid pool in hepatocytes, and can be acutely mobilized secondary to illness or drastic weight loss. Adipose tissue and neurons accumulate PA because of its hydrophobicity. The elimination half-life of total body PA is usually 40 months.

Alpha-Oxidation of PA

Fatty acids are generally metabolized by the β-oxidation pathways in peroxisomes and mitochondria. PA cannot be metabolized by this route because of the presence of a β-methyl group. Instead, PA is metabolized either by α-oxidation to remove the carbonyl group and produce pristanic acid, or by ω-oxidation from the other end of the molecule. Most of the metabolism occurs in the liver, though skin fibroblasts are used for clinical diagnostic purposes. PA enters the peroxisome in association with the sterol carrier protein-2 (SCP2) and is metabolized by a four step α-oxidation pathway. Later cycles of β-oxidation generate the shorter derivatives and release acetyl-CoA or propionyl-coA, which are exported to the mitochondria.

Molecular Genetics

ARD is classically a single peroxisomal enzyme deficiency in contrast to infantile Refsum's disease (IRD) (OMIM 266500) – a mild clinical variant of the peroxisomal biogenesis disorder. The phytanoyl coA-hydroxylase (*PhyH*) gene codes for a 338 amino acid protein, including the N-terminal 30 amino acid 'PTS-2 signal' domain. *PhyH* is imported into peroxisomes by the protein transporter peroxin 7 (*Pex* 7). Deficiency in this transporter is responsible for rhizomelic chondrodysplasia punctata type 1 (RCDP). There seems to be little phenotype–genotype correlation in ARD, though truncation mutations generate a more severe phenotype with leukodystrophy and mental retardation.

A second form of ARD, phenotypically identical to those with PhyH mutations, occurs with some mutations in peroxin-7. These patients also have slight deficiencies of other PTS-2-dependent enzyme functions (plasmalogen

synthesis) consistent with mild variants of RCDP. Though mostly presenting with a sensorimotor neuropathy, α-methylacyl-CoA racemase (AMACR) deficiency (OMIM 604489) can clinically mimic ARD except with gross pristanic acidaemia.

Molecular Toxicology of Refsum's Disease

The exact mechanism of the toxicity of PA to neuronal, cardiac, and bone tissue is gradually being clarified. PA is a direct toxin to mitochondria with a rotenone-like action. This may explain why neuronal or allied retinal pigment tissues rich in mitochondria are the prime tissues affected in ARD.

Clinical Features and Diagnostic Criteria

ARD usually presents in late childhood with progressive deterioration of night vision, the occurrence of progressive retinitis pigmentosa and anosmia (**Figure 1**). Anosmia is a constant feature of ARD. After 10–15 years, cataracts, deafness, ataxia, polyneuropathy, ichthyosis, and cardiac arrhythmias may occur. The severe cases often present with acute weakness allied with ataxia and often deterioration in vision following an episode of illness or starvation. Premature death can occur in acute cases from cardiac arrhythmias.

Osteological abnormalities, including short metacarpals or metatarsals, are found in ~30% of patients. Rare findings include acute psychiatric disturbance and proteinuria. Unlike in RCDP or the peroxisomal biogenesis disorders, no intellectual defects are usually seen and bone abnormalities are mild.

The pathognomic biochemical finding of ARD is a raised plasma PA level ($>200\,\mu mol\,l^{-1}$; normal $<30\,\mu mol\,l^{-1}$), in contrast to other peroxisomal disorders where levels are usually lower. Other metabolic abnormalities of α-oxidation are also present, including decreased levels of pristanic acid and a mild nonspecific elevation in pipecolic acid levels as seen in many peroxisomal disorders. Urine 3-methyl adipic acid levels are raised secondary to induction of ω-oxidation.

Differential Diagnosis

The differential diagnoses of the neuropathic disorders, and relevant signs and investigations are shown in **Table 1**.

Diagnostic Work-up/Tests

The key investigations in the case of neuropathic ARD are the measurement of PA for ARD and pristanic acid for AMACR. These are the diagnostic for these disorders. Other common findings are pipecolic acidaemia and 3-methyl adipic aciduria.

For clinical staging purposes, electroretinograms are often performed, but often show flat responses characteristic of well-established retinitis pigmentosa (RP). Visual fields should be assessed regularly as functional diplopia is a long-term complication of ARD, and slit lamp examination for cataracts is also indicated as these can be treated. Ideally, retinal photography should be performed so that

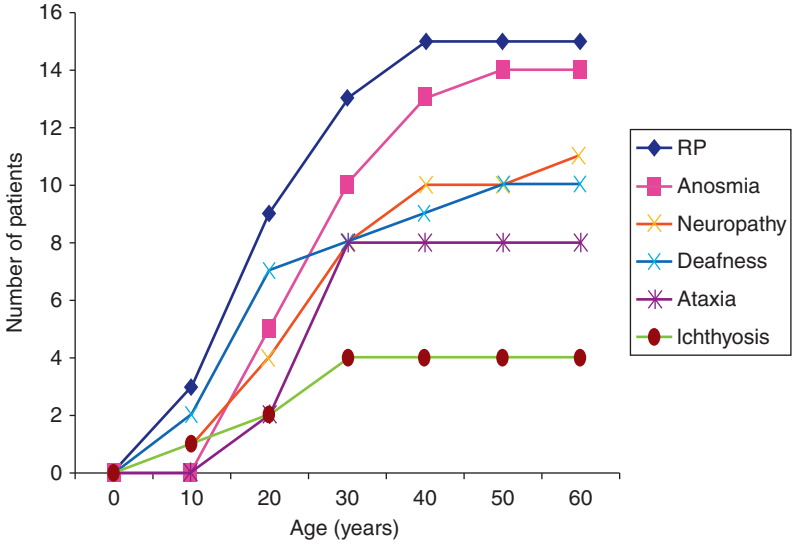

Figure 1 Cumulative incidence of clinical features on presentation of 15 patients with Refsum's disease. RP, retinitis pigmentosa. Reproduced from Wierzbicki AS, et al. (2002) Refsum's disease: A peroxisomal disorder afeecting phytanic acid α-oxidation. *Journal of Neurochemistry* 80(5): 727–735.

Table 1 Differential diagnosis of other adult neuropathies caused by inborn errors of metabolism

Disease	*Age of onset*	*Neuropathy*	*Signs*	*Chemistry*	*Treatment*	*Screening*
Mitochondrial myopathy	15–50	All	Retinitis pigmentosa, epilepsy, ataxia	CSF/plasma lactate	None	Lactate, muscle biopsy
Metachromatic leukodystrophy	15–50	Demyelination sensorimotor	Psychiatry, ataxia	Aryl-sulfatase A	None/bone marrow transplant	Aryl-sulfatase A
Krabbe's disease	15–50	Demyelination sensorimotor	Spastic paraparesis	WBC galacto–cerebrosidase	None/bone marrow transplant	WBC galacto–cerebrosidase
GM_2 gangliosidosis	15–50	All	Psychiatry; ataxia,	Hexosaminidase	None	WBC hexosaminidase
AMACR	10–50	Demyelination sensorimotor	Retinitis pigmentosa, ataxia, anosmia, IQ	Pristanic acid, D/THCA	Low phytanic acid diet (?)	Pristanic acid
Abetalipoproteinaemia	5–20	A,S /S + M	Ataxia, movement disorder, retinitis pigmentosa, acanthocytes	Low cholesterol, low apolipoprotein B, vitamins A and E	Vitamin A and E	Apolipoprotein B
Vitamin E deficiency	10–20	Axonal, demyelination sensorimotor	Ataxia, movement disorder, retinitis pigmentosa, acanthocytes	Vitamin E	Vitamin E	Vitamin E
Homocysteine metabolism (CblC)	15–50	Axonal, motorneurone disease sensorimotor	Psychiatric, stroke, leukoencephalopathy; macrocytosis	Homocysteine; methylmalonic acid	Folate, vitamin B_{12}, B_6, betaine	Homocysteine
X-linked adrenoleukodystrophy	15–50	Axonal, demyelination sensorimotor	Neuropsychiatric leukoencephalopathy; adrenal failure	Very long chain fatty acids	?Lorenzo's oil	Very long chain fatty acids

WBC, White blood cell.

Source: Sedel F et al. (2007) Peripheral neuropathy and inborn errors of metabolism in adults. *Journal of Inherited Metabolic Disease* 30(5): 642–653.

the extent and progression of RP can be monitored. Anosmia is best quantified by the University of Pennsylvania smell identification test (UPSIT), as other tests are neither quantitative nor sufficiently sensitive. Auditory function should be assessed by auditory evoked potentials. Peripheral neuropathy should be investigated using somatosensory potentials, nerve conduction studies, and electromyography. A nonspecific demyelinating pattern is typical of ARD. Osteo- or chondrodysplasia is best identified by a radiological survey of hands and feet for short metatarsals and knee radiology for signs of current or previous chondrodysplasia.

Subtler signs that may accompany these definitive tests include an electrolyte profile showing mild hypokalaemia, and a Fanconi-like amino aciduria can occur in ARD. Liver function tests should be performed, and if bilirubin is raised or AMACR suspected, a detailed bile acid profile should be performed by mass spectrometric methods. As the differential diagnoses include vitamin deficiencies, vitamin A and E levels should be measured to exclude retinol-deficient retinopathy and tocopherol-deficient ataxia. Vitamin B_{12} levels and folate levels are used to exclude cobalamin/folate deficient neuropathy. Though cerebrospinal fluid (CSF) protein is raised in ARD, this investigation is outdated.

To differentiate PhyH from Pex 7 ARD, it is necessary to measure plasma for very long chain fatty acids and plasmalogens. However, often the deficiencies are subtle, and these investigations are superficially normal. For a definitive diagnosis, a skin biopsy should be taken, fibroblasts grown, and detailed enzyme and immunofluorescence profiles examined in a specialist peroxisomal laboratory.

Criteria for Diagnosis

The pathognomic finding of ARD is a plasma PA level ($>200\,\mu mol\,l^{-1}$; normal $<30\,\mu mol\,l^{-1}$), in contrast to other peroxisomal disorders where levels are usually lower. Unlike in RCDP or the peroxisomal biogenesis disorders, no intellectual defects are seen, bone abnormalities are mild (if at all present), and there is no defect in plasmalogen synthesis. In AMACR neuropathy, the pathognomic findings are raised levels of pristanic acid ($>100\,\mu mol\,l^{-1}$) allied with increases in di- and trihydroxy cholestanoic acids (DHCA and THCA). A secondary elevation of PA may be seen, but levels are usually $50–100\,\mu mol\,l^{-1}$.

Management

ARD is one of the few inherited disorders of metabolism with an exogenous precipitating cause. The disease is treated acutely by its removal from plasma using plasmapheresis or apheresis, and chronically by restriction of dietary PA intake. Foods particularly rich in PA include herbivore meat (beef, mutton), dairy products, and top carnivore fish (cod, tuna), while low PA foods include pork and poultry. These regimes reduce plasma PA levels by 50–70%, to values typically $\sim 100–300\,\mu mol\,l^{-1}$ and can eliminate PA completely from fat stores in 35% of patients. Treatment successfully resolves symptoms of ichthyosis, sensory neuropathy, and ataxia in approximately that order.

Prognosis

The prognosis in ARD depends on the degree of reduction of PA achieved. In untreated ARD, presentation is with progressive weakness and neuropathy usually following an acute infective illness, which leads to anorexia and acute hepatic PA release exacerbating the condition. If left untreated, cardiomyopathy and sudden death can occur. If PA levels are reduced by plasmapheresis, adequate parenteral nutrition and then a low-PA diet prognosis is good. If PA levels can be normalized, then ophthalmological changes will be slow. The principal problems in chronic therapy are increasing loss of visual field overlap with subsequent diplopia and progressive cataract formation. Auditory function generally remains good unless PA levels are substantially raised, in which case, cochlear implants are required. Though acute myopathy resolves, patients may suffer from muscle spasms or contractures. Splints and surgical correction of osteopathy may be required. These patients seem to have a normal life expectancy.

Conclusion

The story of PA and α-oxidation started with the discovery of an unusual fatty acid in sheep milk. Only later was this linked to a human neuroophthalmological disease (Refsum's disease), and it took 40 years to clarify the pathways and organelles involved in its metabolism. As an easily identifiable and treatable form of neuroophthalmic disease, ARD should form part of the differential diagnosis of any patient with retinitis pigmentosa and any neurological signs.

See also: Ataxia; DYT3, X-linked Dystonia-parkinsonism (Lubag); GM2 Gangliosidosis; Metachromatic Leukodystrophy; Subthalamic Nucleus; Tocopherol Transfer Protein and Ataxia with Vitamin E Deficiency.

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Relevant Websites

http://www.refsumdisease.org – Adult Refsum's Disease. Information for patients, carers and clinicians.

REM-behavior Disorder

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Glossary

Electroencephalogram (EEG) – The measurement of electrical activity produced by the brain as recorded by electrodes placed over the scalp.
Electromyogram (EMG) – Used during PSG, EMG channels are usually placed on the chin and limbs to assess for the degree of muscle tone and to record muscle movements and during sleep.
Nonrapid eye movement (NREM) sleep – Consists of three stages of sleep, N1–3, which do not include rapid eye movements, are not accompanied by muscle atonia and have parasympathetic dominance.
Polysomnography (PSG) – A test used to study sleep.
Rapid eye movement (REM) sleep – A stage of sleep characterized by REM, muscle atonia, and desynchronized EEG patterns.

Definition/History

Parasomnias are unusual behaviors that occur during sleep and are categorized according to whether they occur during nonrapid eye movement (NREM) or rapid eye movement (REM) sleep. REM sleep behavior disorder (RBD) is a parasomnia characterized by loss of voluntary muscle atonia that normally occurs during REM sleep. Atonia during REM sleep is thought to be a

protective mechanism, enabling relative paralysis against motor activity in response to dreaming. Loss of REM atonia allows for excess motor activity to occur in association with dreaming, leading to potentially significant injuries for both patient and bed partner.

Experimental animal models in the 1960s described brainstem lesions that enabled behaviors during REM sleep to occur. Differentiation between wake and REM events was made by other features of REM sleep that are not seen during wakefulness, such as loss of thermoregulation, blunted response to stimuli, and specific autonomic activity. Subsequently, human behaviors equivalent to animal models were described, associated with dream content, and described as 'stage 1-REM sleep with tonic electromyogram.' RBD was recognized as a distinct sleep disorder in 1986. RBD may occur as an idiopathic disorder or may be associated with neurological diseases such as parkinsonism.

Pathogenesis/Pathophysiology

Polysomnographic criteria of REM sleep consist of three components: REMs, desynchronized electroencephalogram (EEG), and muscle atonia. During REM sleep, the pedunculopontine nucleus and laterodorsal tegmental area within the pons, also termed the perilocus coeruleus, send signals to the thalamus and activate the cortex, causing desynchronized EEG rhythms similar to wake states. The perilocus coeruleus also sends excitatory projections to the medial medulla, which then sends inhibitory signals to motor neurons, resulting in the skeletal muscle atonia characteristic of REM sleep.

Brief muscle twitches commonly observed during REM sleep are thought to be transient interruptions to muscle atonia by excitatory inputs from brainstem to cortex, which generally occur in conjunction with REMs. However, continuous phasic motor activity is actively suppressed by inhibition of muscle tone during REM sleep, perhaps facilitated by descending inhibition to brainstem areas. Activity during REM sleep is thus prevented directly by activating inhibitory mechanisms to spinal motor neurons, and indirectly by inactivating facilitory systems from brainstem to cortex, allowing maintenance of muscle atonia and suppression of prolonged phasic activity.

Structural Pathology of RBD

Prior animal studies demonstrated persistent absence of REM atonia with bilateral lesions at the pontine tegmentum. However, lesions in other brainstem areas also caused RBD, with differing complexity of behaviors depending on specific lesion sites. These studies suggest that RBD can manifest by disrupting specific mechanisms within brainstem centers that establish muscle atonia (i.e., descending from brainstem to spinal neurons) or via interference of phasic suppression of muscle activity (i.e., interrupting inactivation of ascending signals from brainstem to cortex) during REM sleep.

Although RBD in animals generally occurs due to the disruption of brainstem structures, human RBD is not as structurally simplistic. Although RBD manifests with disorders affecting the brainstem including vascular insults, neoplastic diseases, infections, and congenital malformations, RBD is also reported in pathological processes that compromise descending inhibition from higher cortical centers to the brainstem. For example, magnetic resonance imaging (MRI) SPECT studies demonstrate decreased blood flow in frontal, occipital, and pontine regions in some idiopathic RBD cases, with impaired cortical activation as shown by EEG spectral analysis. As such, RBD may not be due to the disruption of one particular structural center but rather by any mechanism that potentially causes imbalance between atonia maintenance and locomotor drive suppression during REM sleep.

Neuropharmacology of RBD

Neuroimaging primarily implicates abnormalities of dopaminergic transmission in RBD. Single photon emission computed tomography (SPECT) studies demonstrate reduction of striatal dopamine transporter binding in some idiopathic RBD cases. Similarly, positron emission tomography (PET) studies show reduction of striatal dopaminergic terminal binding in RBD associated with neurodegenerative disorders. Theories regarding dopaminergic impairment in RBD are further supported by the relationship between RBD and disorders of α-synuclein, such as Parkinson's disease (PD), multiple systems atrophy (MSA), and dementia with Lewy bodies (DLB).

Despite the growing evidence of dopamine's role in RBD, it is unlikely that RBD is caused by dopaminergic dysfunction alone. RBD is also reported in Alzheimer's disease and other neurodegenerative diseases that do not primarily affect dopaminergic pathways. Reports of RBD secondary to antidepressant and cholinergic agents also suggest serotonin and acetylcholine pathway disturbances. Anecdotal reports of RBD induction with beta blockers, monoamine oxidase inhibitors (MAOI), and α-adrenoreceptor antagonists implicate norepinephrine involvement as well. As such, RBD neuropharmacology remains unclear but likely involves an imbalance of several neurotransmitters that influence sleep architecture.

Epidemiology/Risk Factors

RBD has a reported prevalence of 0.38% in the general population and 0.5% in the elderly, the vast majority being older men. However, the prevalence rate of RBD may be higher in neurodegenerative disorders. RBD is clinically present in 25% or more in patients with PD and

in up to 95% of patients with DLB. Up to 90% of MSA patients meet polysomnographic criteria for REM sleep without atonia (RWA), and the presence of RBD may be an early differentiating factor between MSA and pure autonomic failure. Further, RBD may precede motor manifestations of these diseases by 10 years or more.

Racial differences in RBD incidence or prevalence are not reported, and frequency does not vary internationally. Although no deaths have been reported, patients and bed partners experience significant morbidity including minor contusions, assaults to the bed partner, and subdural hematomas. The risk of RBD increases after the sixth decade, although it can occur at any age. Comorbid neurological diseases such as PD, MSA, DLB, narcolepsy, amyotrophic lateral sclerosis, and dementia increase the risk of RBD, although spectral analysis and quantitative evaluation of muscle tone during REM sleep differ across disease states. There are likely genetic factors as well, as demonstrated by familial predisposition in RBD.

Certain medications can cause clinical RBD to manifest in previously asymptomatic cases. Because of suspected dopaminergic dysfunction in both idiopathic and neurodegenerative-associated RBD, dopaminergic agents were initially thought to be potential treatment options. Although some studies do report a therapeutic effect of dopamine agonists and levodopa, others paradoxically report increases in both REM phasic and tonic electromyogram (EMG) activity. This paradoxical effect may be due to the subtle dopamine receptor sensitivities among different patients, particularly those who may have existing neurological diseases. Similar discrepancies have been reported with tricyclic antidepressants (TCAs) and serotonin-specific reuptake inhibitors (SSRIs), with some studies reporting RBD induction while others report RBD suppression. However, the bulk of evidence suggests that SSRIs and TCAs likely induce RBD by increasing EMG tonic activity during REM sleep, particularly in cases with comorbid psychiatric and neurological disorders. Although these discrepancies suggest an imbalance of dopamine and serotonin as the cause for RBD, they do not explain the reports of RBD secondary to other agents such as β blockers and α-adrenoreceptor antagonists that do not primarily affect dopaminergic or serotonergic pathways. Finally, abrupt withdrawal from alcohol and sedatives, treatment with meprobamate, use of pentazocine, and even excess ingestion of caffeine have anecdotally induced RBD, which may be due to REM rebound phenomena after sleep deprivation.

Clinical Features and Diagnostic Criteria

Clinical Features

RBD consists of dream-enacted behaviors that occur more often in the latter half of nocturnal sleep and can range from simple to complex. Simple behaviors include talking, laughing, shouting, and limb jerking. Complex behaviors consist of swearing, gesturing, reaching, grabbing, punching, kicking, sitting up, getting out of bed, and running. While simple movements are not necessarily violent, complex behaviors are generally aggressive and injurious, leading to ecchymoses, lacerations, and fractures to both patient and bed partner. If the patient awakens during an episode, dream content is usually recalled. Aside from dream-related injuries, sleep disruption is generally not reported unless accompanied by sleep disorders such as sleep-related breathing disorders, narcolepsy, and periodic limb movement disorder (PLMD). It is important to note that personality traits do not indicate predisposition to development of RBD, as many studies have found that individuals with RBD tend to be calm and friendly during wake states.

RBD may also occur as a side effect of medications, including MAOIs, cholinergic agents, tricyclic antidepressants (TCAs), and serotonin-specific reuptake inhibitors (SSRIs), implicating dopaminergic nigrostriatal neurons, the locus coeruleus, and cholinergic innervated areas. RBD is also associated with toxic-metabolic states such as alcohol withdrawal, untreated obstructive sleep apnea (OSA), and narcolepsy.

Diagnostic Criteria

Because of the injurious nature of RBD, and the availability of effective treatment, accurate and timely diagnosis is essential. Diagnostic criteria are based on the clinical history and polysomnography (PSG) defined factors, as outlined by the second edition of the International Classification of Sleep Disorders (ICSD): (1) presence of REM sleep without atonia (RWA): the EMG finding of excessive amounts of sustained or intermittent elevation of submental EMG tone or excessive phasic submental or (upper or lower) limb EMG twitching; (2) at least one of the following is present: (2a) sleep related injurious, potentially injurious, or disruptive behaviors by history, (2b) abnormal sleep behaviors documented during polysomnographic monitoring; (3) absence of EEG epileptiform activity during REM sleep unless RBD can be clearly distinguished from any concurrent REM sleep related seizure disorder; (4) the sleep disturbance is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

PSG in RBD shows excess amounts of sustained EMG activity, excessive phasic limb activity, or intermittent loss of REM atonia during PSG. In contrast to disorders of arousal, autonomic hyperactivity is uncommon. Excess periodic limb movements (PLMs) are commonly observed, but normal sleep architecture is otherwise preserved. Time-synchronized video recording is recommended for establishing diagnosis.

Patients who have PSG evidence of RBD without clinical history have 'REM without atonia' (RWA), which is generally considered a subclinical or preclinical state of RBD. At least 25% of cases with RWA eventually display clinical features of RBD.

Differential Diagnosis

Several disorders can manifest as unusual, complex, or injurious behaviors during sleep. Common examples include NREM parasomnias and nocturnal seizures.

Sleepwalking and sleep terrors are NREM parasomnias which primarily affect children and younger adults, although persistence into adulthood is not uncommon. Unlike RBD, NREM parasomnias generally occur within the first 2 h of sleep onset. Arousing the individual during the event is difficult, and dream content is generally absent. NREM parasomnias are associated with autonomic signs of arousal although this is variable from case to case. PSG is the best diagnostic tool, distinguishing whether the events occur during REM sleep or NREM slow wave sleep (SWS). NREM parasomnias typically have normal muscle atonia during REM sleep, but if RWA or RBD is also present, the parasomnia is diagnosed as parasomnia overlap disorder. Like RBD, PSG is also helpful in evaluating nocturnal sleep disorders that may be fragmenting nocturnal sleep, in which case identification and treatment of those disorders help resolve the parasomnia.

Nocturnal seizures can also cause unusual and sometimes violent behaviors. In particular, nocturnal frontal lobe epilepsy is commonly diagnosed in the sleep laboratory, as daytime EEG is often negative for epileptiform activity even when performed during drowsy and sleep states. Nocturnal seizures tend to be stereotypic and are not associated with dream content. Unlike other seizures, altered mental status is not commonly observed after nocturnal events occur. EEG channels on traditional PSG studies may not reveal epileptiform activity, as nocturnal seizures are often deep within the frontal lobe and therefore difficult to detect from standard scalp electrodes. However, atonia during REM sleep is preserved during PSG.

Diagnostic Work-up/Tests

Although the clinical history of dream enactment behaviors is suggestive, PSG is essential in establishing the correct diagnosis of RBD. Clinical evaluation should include a history of sleep deprivation, toxic-metabolic causes, and possible medication effects as exacerbating factors. If underlying structural causes are suspected, MRI of the brain and EEG may be clinically useful. Routine laboratory tests are needed only as indicated from the history and physical examination.

Management

Safety measures such as removal of sharp objects from bedside, placing mattresses on the floor, and separate bedrooms for the bed partner should be discussed with the patient and bed partner. When RBD symptoms are clinically significant, pharmacologic treatment should be considered. Clonazepam is the primary agent prescribed for RBD, although its mechanism of action is not well understood and no controlled studies have been done. Clonazepam may enhance serotonergic pathways that influence RBD events, making it unique amongst benzodiazepine receptor agonists. Clonazepam may be more effective in suppressing phasic motor activity and altering dream content than in restoring REM atonia. Clonazepam is effective for most cases and rarely leads to abuse or tolerance. Initial dose of clonazepam is typically 0.5 mg at bedtime with gradual dose titration up to 1–2 mg if necessary. Although breakthrough simple behaviors may occur during treatment, complex and injurious behaviors tend to be well-controlled. The major side effect of clonazepam is daytime sedation, which tends to be dose-dependent and possibly managed by taking the medication earlier in the evening. Clonazepam may worsen underlying sleep-disordered breathing and contribute to nocturnal confusion, particularly in neurodegenerative disorders. Sudden discontinuation may lead to rebound worsening of RBD.

Melatonin may also be useful in treating RBD. Melatonin is secreted by the pineal gland and helps synchronize the sleep–wake cycle. Its mechanism of action in RBD may involve restoring presumed dysregulation between the underlying circadian rhythm and REM sleep, although this has not been adequately studied. Melatonin seems to partially reestablish REM atonia rather than suppress phasic activity. Melatonin can be discontinued abruptly although RBD events generally recur weeks to months later. Doses between 3 and 12 mg per night are reported to be effective, with response within 1 week. However, there are no placebo-controlled trials evaluating melatonin, and it is not regulated by the Food and Drug Administration. Although a melatonin agonist (ramelteon) is available by prescription, it has not been studied in RBD. Adverse side effects of melatonin can include hallucinations, next-day somnolence, and rare interaction with warfarin.

Pramipexole, a dopamine agonist, is reportedly effective in idiopathic RBD. However, pramipexole is not shown to be effective in controlling RBD in neurodegenerative disorders. It is unknown whether this disparity is due to possible differences in pathophysiology between idiopathic RBD and RBD associated with neurodegenerative disorders.

Medications known to cause or worsen RBD, including antidepressants with serotonergic activity and antihistamines, should be evaluated and changed to an alternative

medication if possible. It is also important to actively treat the underlying medical and sleep disorders that can mimic RBD and cause RWA.

Prognosis

Treatment for RBD is generally effective. RBD may be a harbinger for future neurological disorders. Patients should be regularly evaluated for both neurological and psychiatric disorders. Education about RBD, particularly its association with neurodegenerative disorders, should accompany clinical evaluations. Safety behaviors, avoidance of sleep deprivation and toxic-metabolic conditions, and treatment of comorbid medical and sleep disorders should also be routinely discussed and evaluated.

See also: Parkinson's Disease: Definition, Diagnosis, and Management.

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Rest Tremor

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Glossary

Deep brain stimulation – The surgical implantation of electrodes to specific targets deep within the brain as a treatment for various brain disorders.
MPTP – The chemical 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine.
Positron emission tomography – A computerized radiographic technique used to examine metabolic activity in various tissues.
Psychogenic tremor – Tremor most often resulting from underlying stress that can display variable frequency, amplitude, and direction with distractibility.
Rubral tremor – Irregular low-frequency rest tremor due to lesions in (the vicinity) of the red nucleus.

Definition and History

The Greek physician Galen (AD 129–200) wrote numerous works regarding disorders of motor function and distinguished between different forms of limb shaking based on appearance specifically identifying rest tremor among the aged. The tenth century Muslim physician Avicenna (ibn Sina) studied various motor disturbances and advised bathing in mineral salts and ingesting herbal treatments including rue and scolopendrium to relieve rest tremor.

The term *rest tremor* describes a rhythmic involuntary contraction of alternating agonist and antagonist muscles in an affected body part at rest. Because involved muscles are not actively contracting, they must be supported against gravity such as when the hands rest in the lap or when the entire body is supine on a surface.

Pathophysiology

Most evidence suggests that rest tremor develops from multiple oscillators as a result of abnormal processing of circuits between the thalamus, basal ganglia, and cortex. Synchronization of actively firing neurons within the basal ganglia may also contribute to rest tremor pathophysiology. Experimental models of rest tremor include anatomical lesions within nigrostriatal projections and cerebellar outflow areas mostly in dentatorubrothalamic connections although damage to only one system alone may be insufficient to generate tremor. Some have suggested that subtle variation in tremor frequency can be attributed to spinal reflex or other mechanical mechanisms although the lack of reliable change in rest tremor frequency with weight bearing on an affected limb does not support this theory.

Clinical Features

Stress can increase striatal acetylcholine levels, leading to greater imbalance against striatal dopamine levels and resulting in increased rest tremor amplitude. This relationship explains why anticholinergic medications can improve rest tremor in Parkinson's disease (PD) more so than bradykinesia or rigidity. Walking may also increase rest tremor amplitude in many patients.

Differential Diagnosis

Parkinson's Disease

PD is the most common cause of rest tremor. Low-frequency rest tremor is one of the cardinal features of PD that presents in 80–90% of patients. The typical presentation of distal limb rest tremor involves flexion-extension movements at the elbow, pronation–supination movements of the forearm, and/or pill-rolling movements of the finger and thumb. Various clinical rating scales that quantify PD severity (such as the Unified Parkinson's Disease Rating Scale) consistently demonstrate that rest tremor asymmetrically favors one side of the body. Tremor frequency within a given PD patient often appears to be quite similar in different muscles. Studies of various muscle groups show lack of coherence in rest tremor frequency even on the same side of the body. These findings suggest that rest tremor in PD is generated by not one but multiple oscillatory circuits operating at similar frequencies.

People with tremor-predominant PD tend to have slower progression of disease than those with predominant bradykinesia and rigidity in the absence of tremor. Neuropathologic studies show evidence that retrobulbar area (A8) is more severely affected in tremor-predominant PD. Reemergent tremor in PD is noted in the postural position but develops only after prolonged latency and shares the same average frequency (5.5 Hz) and amplitude of rest tremor suggesting a shared pathophysiology. The same neural mechanisms involved in rest tremor in PD likely remain active with postural change.

In one study of 11 patients with rest tremor, more than 50% reduction in putaminal fluorodopa (^{18}F) levels was noted on positron emission tomography. Unlike rigidity and bradykinesia, rest tremor severity does not correlate with the magnitude of striatal dopaminergic deficit. Performing certain tasks such as counting backwards from 100 or tapping the contralateral foot usually increases rest tremor amplitude within 2–3 min.

Secondary Parkinsonism

Vascular parkinsonism rarely presents with rest tremor unless one or more isolated stroke lesions disrupt key anatomic regions such as the substantia nigra, red nucleus, or other thalamic midbrain connections. Patients with hydrocephalus frequently demonstrate bradykinesia and rigidity but are less likely to display tremor. Although rest tremor is an atypical finding in progressive supranuclear palsy (PSP), 2 of 12 individuals with pathologically confirmed PSP in one study had mild rest tremor. Less than 10% of patients with multiple system atrophy (MSA) have rest tremor.

Drug-Induced Rest Tremor

Rest tremor that develops with acute or subacute use of neuroleptic medications often presents like classic PD although bradykinesia often occurs earlier. Unlike PD, drug-induced parkinsonism may present with bilateral symmetric involvement. Up to 90% of patients with drug-induced rest tremor may develop symptoms within three months of starting the offending drug. Newer atypical neuroleptics may be less likely to result in rest tremor than older drugs although antidepressants can also lead to extrapyramidal syndromes.

Essential Tremor (ET)

Rest tremor of the hands can be seen among some elderly patients with ET although the presence of this symptom is more commonly due to coexistent PD. More commonly, postural tremor involving incompletely relaxed muscles simulates rest tremor but is really postural tremor in ET. The presence of accompanying rest tremor in ET is associated with longer disease duration, higher amplitude postural and kinetic tremor and greater likelihood of head tremor.

Rubral Tremor

Irregular low-frequency rest tremor can be seen in the 'wing-beating' rubral or midbrain tremor (also called

Holmes tremor) in combination with intention and postural tremor. Rubral tremor occurs due to lesion in the red nucleus.

Supratentorial Mass Lesions

Many supratentorial tumors that spare the basal ganglia can disrupt thalamocortical connections resulting in rest tremor that may or may not resolve after tumor debulking or complete surgical excision. These masses include meningiomas, epidermoid cysts, fibrillary astrocytomas, anaplastic oligodendrogliomas, and glioblastomas.

Pineal Gland Mass Lesions

Various pineal gland cysts and tumors have been reported to cause unilateral rest tremor in the absence of other parkinsonian findings. Although the presence of hydrocephalus related to compression of the posterior thalamus and upper midbrain could explain the bradykinesia and rigidity frequently seen in these lesions, another possible theory involves congestion of the deep venous system draining nigrostriatal projections.

Toxic Exposures

Many people exposed to 1-methyl -4-phenyl -1,2,3,6-tetrahydropyridine (MPTP) as a result of illicit drug use can develop acute-onset rest tremor indistinguishable from classic PD. Organophosphate poisoning can frequently present with dystonia, rest tremor and rigidity most likely due to inhibition of striatal acetylcholinesterase (AChE).

Psychogenic Tremor

Rest tremor can be seen in stress-induced or psychogenic tremor along with other types of tremor. The presentation usually involves tremor of variable frequency, amplitude, direction and/or location that is often distractible or entrainable by performing complex volitional movements in the contralateral hand or foot. Rest tremor may also be coupled with classic features of *la belle indifference*, convergence spasm, and/or somatization in the presence of underlying depression or cumulative psychosocial stressors.

Treatment

Pharmacologic Treatments

The primary treatment for drug-induced tremor due to neuroleptic medications such as antipsychotics or metoclopramide is to discontinue the provoking medication after careful consideration of risks and benefits. Whenever possible, the offending drug should be switched to a different class of medication. Anticholinergics are also useful in treating drug-induced tremor.

The standard treatment of rest tremor in PD over the past 40 years is levodopa. Oral dopamine agonists such as pramipexole and ropinirole are also approved for the treatment of PD and are frequently useful in treating rest tremor particularly in the early stages. Monoamine oxidase B (MAO-B) inhibitors, anticholinergics, and amantadine are also used to treat rest tremor.

Deep Brain Stimulation

Deep brain stimulation (DBS) of the subthalamic nucleus (STN), globus pallidus, and thalamus are safe and effective therapies for PD, although rest tremor by itself is rarely disabling enough to warrant surgical intervention. DBS may be more effective than dopaminergic medications alone in reducing rest tremor severity. DBS of the STN is the preferred target for rest tremor as it is generally thought to be more effective in treating accompanying bradykinesia and rigidity in PD whereas DBS of the ventral intermediate nucleus (VIM) usually only improves rest tremor alone. DBS of the globus pallidus interna (GP_i) is less effective in treating rest tremor and is generally not favored for rest tremor. Several reports suggest that midbrain tremor has been successfully treated with DBS although more information is needed to determine long-term outcomes in these patients.

See also: Deep Brain stimulation; Parkinson's Disease: Definition, Diagnosis, and Management; Postural Tremor; Rest Tremor; rTMS; Substantia Nigra; Subthalamic Nucleus; Thalamotomy; Tremor; Tremor, Essential (Syndromes); Tremor, Holmes; Tremor: Drug-induced.

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http://www.pdf.org – Parkinson's Disease Foundation.
http://www.wemove.org – WE MOVE (Worldwide Education & Awareness for Movement Disorders).

Restless Legs Syndrome

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Glossary

A11 region – A cluster of dopamine containing cells located in the diencephalon with projections to the spinal cord.
BTBD9 – The symbol for (Broad-Complex-Tram-Track-Bric-A-Brac Domain 9) and is a gene encoding a BTB (Poz) domain on Chromosome 6p.
DMT1 – The abbreviation for divalent metal transporter 1. DMT 1 removes iron from endosomes and makes iron available to the intracellular labile iron pool.
LBXCOR1 – The code name for ladybird homeobox 1 homolog (*Drosophila*) corepressor 1 and is located near MAP2K5 on chromosome 15q.
MAP2K5 – The symbol for Mitogen-activated protein kinase 5 and is located on Chromosome 15q.
MEIS1 – The symbol for Meis homeobox 1. MEIS1 is linked to embryonic proximal–distal limb formation. MEIS1 is located on chromosome 2p.
MPT1 – The abbreviation for metal transporter 1 (ferroprotein) and is thought to be involved in cellular iron efflux.
Periodic limb movements in sleep (PLMS) – Repetitive stereotypic leg movements that reoccur throughout the night during sleep. Scoring criteria for PLMS include four movements in a row, 0.5–10 s duration, spaced 0.5–90 s apart, and at least 8 μV elevation above the baseline EMG.
Restless legs syndrome (RLS) – It is a sensorimotor disorder with four essential diagnostic criteria: (1) An urge to move the legs usually accompanied or caused by uncomfortable and unpleasant sensations in the legs. (2) The urge to move or the unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting. (3) The urge to move or unpleasant sensations are partially or totally relieved by movement such as walking or stretching, at least as long as the activity continues. (4) The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night.

Definition and History

Restless legs syndrome (RLS) is a neurogical disorder associated with sensory and motor symptoms. Sir Thomas Willis published the original description of RLS in 1672. During the nineteenth century, RLS was considered a form of hysteria or neurasthenia. Theodor Wittmaack,

a German physician, called the condition 'anxietas tibiarum.' RLS was not recognized as a neurological disorder until 1923 when H. Oppenheim described it as a genetic neurological disorder. In 1943, F. Gerard Allison described a phenomenon 'leg jitters' as a common minor ailment characterized by unpleasant, unlocalized restlessness in one or both legs associated with voluntary and involuntary limb jerks and sleep disturbance. Leg jitters, according to Allison, were sometimes relieved by 'getting up and walking.'

In 1944, based on eight cases, Karl-Axel Ekbom, a Swedish neurologist, published a description of a new syndrome, Asthenia Curum Paraethetica (Irritable legs). From 1943 to 1944, Ebkom screened 4259 patients for irritable legs and identified 20 patients with moderate to severe symptoms. Thinking that people with mild symptoms did not seek medical treatment, Ekbom screened 503 patients from an outpatient neurological service and an additional 503 healthy people. Of the 1006 people screened, 65 people had mild RLS symptoms: 39 patients from the outpatient clinic and 26 healthy people.

In addition, Ekbom believed that there was an association between pregnancy and irritable legs. Ekbom questioned 486 postpartum women. Fifty-five of the women described leg paresthenias during pregnancy. In 1945, based on 169 cases and his extensive study, Ekbom published a comprehensive description of the disorder. Ekbom classified symptoms as predominantly sensory or painful and renamed the disorder RLS but noted that symptoms could occur in the arms.

Ekbom and his contemporary, Dr. Nil Brage Nordlander, lectured extensively on RLS. Ekbom described the disease as 'so common that every practicing physician meets it.' We now know that RLS affects 7–15% of the general population and almost 2% of children. The essential symptoms of RLS as described more recently by the International Restless Legs Syndrome Study Group (IRLSSG) are as following:

1. an urge to move the legs usually accompanied or caused by uncomfortable and unpleasant sensations in the legs,
2. the urge to move or the unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting,
3. the urge to move or unpleasant sensations are partially or totally relieved by movement such as walking or stretching, at least as long as the activity continues,
4. the urge to move or unpleasant sensations is worse in the evening or night than during the day or only occur in the evening or night.

Types of RLS

RLS is classified as primary or secondary. Primary RLS is not associated with an underlying medical or neurological abnormality or caused by a drug. Although RLS can be genetic or sporadic, most primary RLS, especially with young onset and a positive family history, are genetic.

Secondary RLS is diagnosed when a precipitating illness, medical condition or causative drug can be identified. Secondary RLS is frequently associated with uremia, diabetes, neuropathy, gastric surgery, and conditions associated with iron deficiency such as pregnancy and frequent blood donations. There is also an association with fibromyalgia, rheumatoid arthritis, and multiple sclerosis. More recently hypertension and heart disease have also been linked to RLS.

Periodic Limb Movements and RLS

Periodic limb movements in sleep (PLMS) are repetitive highly stereotyped movements that occur involuntarily at predictable intervals. Polygraphic recordings done by Coccagna and Lugaresi et al. in 1962 documented that PLMS occurred in patients with RLS. Coccagna called these movements 'nocturnal myoclonus.' Approximately 80% of people with RLS have PLMS. Periodic limb movements also occur in wakefulness in RLS as determined by the Suggested Immobilization Test (SIT). Although the European discovery of the BTBD9 gene was driven by RLS, the simultaneous discovery of the same gene was driven by PLMS in the Icelandic population.

PLMS occur commonly with other sleep disorders such as narcolepsy and REM sleep behavior disorder (RBD) as well as in isolation as an incidental finding on polysomnography.

The current polysomnographic scoring criteria for PLMS include four movements in a row, 0.5–10 s duration, and spaced 5–90 s apart, at least 8 μV elevation above the baseline EMG.

Development of Diagnostic Criteria and Classification

In 1979 and 1990, The Diagnostic Classification Steering Committee of the American Association of Sleep Medicine developed RLS diagnostic criteria, which were published in The International Classification of Sleep Disorders: Diagnostic and Coding Manual (ICSD). In the early 1990s, physicians and scientists dedicated to research on restless legs/periodic limb movements in sleep formed the International Restless Legs Syndrome Study Group (IRLSSG). The IRLSSG felt that the 1990 definition did not include all the essential features of RLS and mistakenly included some nonessential features as well. The IRLSSG currently consists of more than 130 physicians and scientists from 17 countries. In 1995, the IRLSSG published the original consensus definition of RLS. For better clarity, the IRLSSG updated the definition and diagnostic criteria for RLS. The IRLSSG published the updated definition in 2003.

This new definition was incorporated into the new International Classification of Sleep Disorders (ICSD-2) in 2005. This definition now stands as the universal definition of RLS in 2008.

The consensus definition of RLS published by the IRLSSG and the International RLS Severity Scale were instrumental in subsequent RLS research leading to FDA approved medications.

Pathogenesis/Pathophysiology

The pathogenesis of RLS is unknown but appears to involve iron metabolism within the central nervous system, the neurotransmitter dopamine and genetic factors.

Iron is closely linked to secondary forms of RLS. Many of the illnesses that precipitate secondary RLS are characterized by decreased iron levels: renal failure, pregnancy, frequent blood donations. Patients with RLS and low ferritin levels improve with iron therapy. Researchers have found that severity of RLS symptoms increases inversely when serum ferritin levels are decreased below $50\,\mu g\,l^{-1}$.

Ferritin is the major storage protein for iron and has two parts L-ferritin and H-ferritin. Transferrin is the primary iron transport protein. Transferrin is manufactured primarily in the liver and does not cross the blood brain barrier. Cerebral transferrin is manufactured within the brain. When researchers compared the cerebral spinal fluid (CSF) levels and the serum levels of ferritin, iron, and transferrin in RLS patients compared to normal controls, they found that RLS patients with normal or elevated serum iron levels had lower CSF ferritin levels and higher CSF transferrin levels than controls, suggesting a selective reduction of CSF iron. Similarly, histological and immunohistochemical studies have reported reduced brain iron. Likewise, brain magnetic resonance imaging (MRI) studies demonstrate a reduction in iron in the substantia nigra and to a lesser degree the putamen of people with RLS.

Iron is intricately related to dopamine. The D2 dopamine receptor is a protein that contains iron and iron is a cofactor for tyrosine hydroxylase, an enzyme that controls the rate-limiting step in the conversion of tyrosine to levodopa, a precursor to dopamine. Although patients with RLS respond to dopamine, it is possible that dopamine is deficient due to defective acquisition or utilization of iron by brain cells.

The role of dopamine in RLS is substantiated by the remarkable benefit of dopamine drugs for RLS symptoms, and the exacerbation of symptoms associated with dopamine receptor antagonists. Similarly, opioid agents can improve symptoms and opioid antagonists can exacerbate symptoms in RLS patients treated with opioids. Thus both the endogenous dopamine and opioid systems are implicated in the pathogenesis of RLS. Further studies suggest that it is the dopaminergic system that is primarily involved, and that this is modulated by opioids. Some researchers have hypothesized that decreased dopamine-D2 receptor stimulation is responsible for RLS symptoms.

Dopaminergic PET scan studies have shown modest and variable pre and postsynaptic deficits in the nigrostriatal pathways in many studies. However, it does not appear that the predominant abnormality is in the nigrostriatal dopamine pathway, the pathway involved in Parkinson's disease. Rather, it is thought that the dopaminergic neurons in the A11 region of the hypothalamus are involved. The A11 neurons that project to the neocortex and dorsal raphe have local connections within the hypothalamus and descend to the spinal cord as the sole source of spinal dopamine. Diencephalospinal neurons terminate predominately in the dorsal horns of the spinal cord in areas that have sensory afferent input, interneurons, somatic motor neurons and the intermediolateral nucleus (IML).

Preliminary autopsy evidence also suggests that the endogenous opioids Beta endorphin and Met enkephalin are decreased in the thalamus of patients with RLS.

Genetics and RLS

The first chromosome linkage study suggested an autosomal recessive inheritance pattern (RLS1). Subsequent studies of other possible loci suggest an autosomal dominant inheritance pattern (RLS 2, RLS 3, RLS 4, and RLS 5).

Two genome-wide association studies were published based on data from Europe and Iceland. The European researchers studied people with a familial pattern and sporadic forms of RLS. The Icelandic researchers studied people with RLS and periodic limb movements. Both groups identified a common variant in an intron of BTBD9 on chromosome 6p. Additionally, the European researchers identified a MEIS1 gene on chromosome 2p and genes encoding mitogen-activated protein kinase MAP2K5 and the transcription factor LBXCOR1 on chromosome 15q. The MEIS1 gene is thought to be associated with limb development.

Epidemiology/Risk Factors

RLS affects 7–15% of the general adult population and almost 2% of children. Forty to 65% of people with RLS report a positive family history of RLS. A first-degree relative of a person with RLS has a 3–6 times greater risk of developing RLS.

RLS affects both genders and all ethnic groups. Caucasians and women have a higher incidence. Research suggests a lower incidence of RLS among persons from the Indian subcontinent and other Asian countries.

Clinical features and Diagnostic Criteria

Essential Criteria

Restless Legs Syndrome is diagnosed primarily by the patient's description of clinical symptoms. Adults with RLS must have four essential clinical symptoms: (1) An urge to move the legs usually accompanied or caused by uncomfortable and unpleasant sensations in the legs. (2) The urge to move or the unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting. (3) The urge to move or unpleasant sensations are partially or totally relieved by movement such as walking or stretching, at least as long as the activity continues. (4) The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night. Supportive and associated symptoms help confirm the diagnosis. Supportive and associated features are often present but are not essential to the diagnosis. These include a positive family history of RLS, improvement of symptoms with dopaminergic therapy, and the presence periodic limb movements during sleep or wakefulness. RLS almost invariably occurs in the legs but can involve the arms, torso, or face. Symptoms may be unilateral or bilateral.

Children diagnosed with RLS must have the four essential clinical features described above and be able to describe leg sensations in their own words. Alternatively, a child who cannot describe the leg sensations in their own words must meet all four essential clinical features and in addition meet two of the following: (1) sleep disturbance greater than expected for age, (2) a parent or sibling with definite RLS, (3) periodic limb movements that occur during sleep at a frequency greater than five movements per hour.

Differential Diagnosis

RLS must be differentiated from legs cramps, positional discomfort, neuroleptic-induced akathisia, and painful legs and moving toes syndrome.

In children RLS must be differentiated from motor tics, attention deficit hyperactivity disorder, muscle pains, leg cramps, Osgood–Schlatter's disease, arthralgia and akathisia. Growing pains are thought to be the onset of RLS in some cases.

Diagnostic Work-up/tests

The diagnosis of RLS is based on the clinical history. Serum iron, ferritin levels and iron-binding capacity are essential to obtain in order to evaluate whether iron deficiency may play a role. Some researchers recommend checking vitamin B12, folate and magnesium levels, although there is less evidence for these as associated conditions. A polysomnogram is not indicated for diagnosis of RLS, but may be useful if assessment for periodic limb movements or other sleep disorder is suspected. All patients should undergo a physical and neurological examination. If suspected, peripheral neuropathy or radiculopathy can be documented by electromyography (EMG) and nerve conduction studies. Additional testing may be necessary to differentiate primary RLS from secondary RLS. The diagnostic tests recommended depend upon the suspected precipitating condition.

When the diagnosis of RLS is unclear a trial of dopaminergic medication may help confirm the diagnosis. Almost all patients with RLS will respond to dopaminergic agents.

The frequency and severity of symptoms should be documented and the patient classified as having intermittent RLS, daily RLS or refractory RLS.

Management

Nonpharmacologic Therapy

Nonpharmacologic therapies that benefit people with RLS include: (1) mental distraction and mental alerting activities. There are case reports that mental distractions, such as playing the piano, can decrease symptoms. The mechanism is unknown but it is thought that mental distraction activates parts of the brain that block the perception of RLS symptoms. (2) Eliminating dietary triggers such as caffeine, alcohol, and tobacco; (3) hot or cold soaks; (4) massaging the legs; (5) adjusting the bedtime so that the patient goes to bed after symptoms stop; (6) if possible discontinue drugs known to exacerbate RLS symptoms: tricyclic antidepressants, SSRIs, H1 antihistamines, calcium channel blockers and dopamine antagonists; (7) walking or exercising the legs; (8) avoiding excessive exercise.

Pharmacologic Therapy

All medications used to treat RLS should be started at the lowest dose and increased slowly to an effective dose. Because medication half-life is different from peak effect, one recommendation is that medication should be dosed every three hours during the symptomatic period. The number of doses per day depends on the number of symptomatic hours per day.

Replace iron in patients with serum ferritin levels below $50\,\mu g\,l^{-1}$. Recommended dosing is 325 mg of ferrous sulfate three times a day with supplemental vitamin C 500 mg with each dose of ferrous sulfate. Reevaluate the serum ferritin level after 3 months of therapy. There is no indication to treat patients with iron who do not have a low ferritin, and iron overload may occur. Additionally, in patients with iron deficiency, an evaluation for the underlying cause of the deficiency should be undertaken.

In 1982, Akpinar reported that dopamine agonists improved RLS. In 2005 ropinirole, a nonergot dopamine

agonist became the first Federal Drug Administration (FDA) approved medication for RLS. Since 2005 the FDA approved another dopamine agonist, pramipexole. Dopaminergic agonists drugs are regarded as the first line pharmacologic therapy for RLS. There are two types of dopaminergic drugs: ergot preparations and nonergot preparations. Bromocriptine, pergolide, and cabergoline are all ergot dopamine preparations. Prolonged use of ergot preparations is associated with cardiac valvular fibrosis and pulmonary fibrosis. Therefore ergot preparations are used with caution and monitoring for these side effects. Pergolide is no longer available for use in the United States.

Nonergot dopaminergic agents are the only FDA approved medications for RLS in the United States. The two that are approved include pramipexole (Mirapex®) and ropinirole (Requip®). The therapeutic dose of ropinirole ranges from 0.25 to 4 mg day^{-1}. Ropinirole should be started at 0.25 mg given 30 min before the onset of symptoms or 90–120 min before bedtime. The dose is increased by 0.5 mg weekly until alleviation of symptoms. The maximum dose is 4–6 mg day^{-1}.

Pramipexole is available in multiple dosage strengths and should be started at 0.125 mg, the lowest dose available. Medication is increased by 0.125 mg every 4–7 days as needed. The average dose prescribed is 0.5 mg day^{-1}. Some physicians increase pramipexole to a maximum dose of 2 mg day^{-1}.

Levodopa/carbidopa is an older dopaminergic agent with a short half-life. Levodopa/carbidopa is used when symptoms occur intermittently or in preparation for sitting for prolonged times. Because of a tendency to cause more marked augmentation, daily use at higher dosages is not recommended.

Cabergoline is a long acting ergot dopaminergic agonist effective against RLS symptoms but seldom used to treat RLS in the United States due to cost and potential associated side effects.

Side effects of the dopaminergic drugs include nausea, light-headedness, daytime drowsiness, orthostatic hypotension and sleep attacks. Chorea and hallucinations are common side effects of dopamine agonist in Parkinson's disease but are not reported in RLS. Compulsive gambling and compulsive shopping have been reported.

The most troubling side effects of dopaminergic agents in RLS are rebound and augmentation. Rebound occurs when symptoms increase at a time compatible with the half-life of the medication. Augmentation is a more common side effect and is particularly prominent with the use of levodopa. Augmentation is the earlier occurrence of RLS symptoms in the evening, requiring an earlier administration of medication. Furthermore, the symptoms are usually worse and may spread to other body areas besides the legs. The management of RLS augmentation includes avoiding chronic treatment with levodopa, use of longer acting dopamine agonists, earlier doses of the dopamine agonists if mild augmentation occurs, and a reevaluation for iron stores as a low ferritin has been associated with augmentation. For severe or recurrent augmentation, the dose of the dopamine agonist should be lowered or the dopamine agonist discontinued. Alternate therapy can then be chosen.

Other treatment options include the opioids, gabapentin, and benzodiazepines.

For severe RLS, opioids (codeine, propoxyphene, hydrocodone, methadone, oxycodone, or tramadol) are sometimes prescribed. There is little addiction or tolerance to opioids when used to treat RLS. Constipation, dizziness, nausea, and vomiting are side effects associated with opioids. Patients treated with opioids should be monitored for the development or exacerbation of sleep apnea.

Gabapentin (Neurontin) is an anticonvulsant frequently prescribed for painful RLS, daily RLS, and refractory RLS. The starting dose is 100–300 mg. The average dose is 300–1200 mg day^{-1}. The therapeutic range is 300–2700 mg day^{-1}. Side effects associated with gabapentin include ataxia and drowsiness.

Benzodiazepines, clonazepam (Klonopin®), temazepam (Restoril®), and triazolam (Halcion®), may reduce leg discomfort, decrease the urge to move and help patients sleep through periodic limb movements. High doses of benzodiazepines cause carry-over effects such as morning drowsiness and decreased cognition. Benzodiazepines are not recommended in patients with untreated or inadequately treated sleep apnea because benzodiazepines may increase apnea. Addiction and tolerance to benzodiazepines rarely occurs in patients without a previous history of addiction.

Nonbenzodiazepine hypnotics (eszopiclone, zolpidem) are sometimes prescribed to help patients sleep but have not been shown to reduce RLS symptoms or periodic limb movements.

In 2004, the Medical Advisory Board of the RLS Foundation established treatment recommendations for RLS. This approach separates patients into one of three categories: intermittent symptoms, daily symptoms and refractory symptoms. Treatment is based on frequency and severity of symptoms.

Intermittent symptoms are treated with nonpharmacologic therapies alone or in combination with medications. Medications used to treat intermittent RLS include benzodiazepines, levodopa, low potency opioids (tramadol, propoxyphene, codeine), and dopamine agonists.

Dopamine agonists are the drugs of choice for treating daily RLS. Combination therapy is also used. Gabapentin and low potency opioids are also used for daily RLS. Nonpharmacologic therapies may also be helpful.

Refractory RLS is difficult to treat. Treatment may require a change in therapy to gabapentin or another dopamine agonist. Alternatively, refractory RLS can be treated by adding a benzodiazepine, opioids, or gabapentin.

Refractory RLS may require high potency opioids. Combination therapy is also used.

Most medications prescribed to treat RLS are not recommended for pregnant women. Pregnant women should be evaluated for iron deficiency. Iron deficiency should be treated and the use of nonpharmacologic therapies encouraged. There is some evidence that folate, B12 and magnesium are helpful in pregnancy. When pharmacologic therapy is necessary, opioids are used with caution.

Children with RLS should be evaluated for iron deficiency anemia and treated as needed. Children who are not iron deficient or in whom symptoms are not controlled by iron therapy should be first treated with nonpharmacologic therapy. When medication is needed, nonergot dopaminergic agents are recommended. There is anecdotal evidence that gabapentin, benzodiazepines, or clonidine are also helpful.

Prognosis

Primary RLS is an idiopathic or genetic disorder with a familial pattern. When symptoms develop at an early age, progression of symptoms develops slowly and may not occur daily for many years. Although 15% of patients with RLS experience a remission in symptoms for a month or more, primary RLS is considered to be a chronic progressive disorder.

Secondary RLS remits when the precipitating condition resolves. Although some women who develop RLS during pregnancy will continue to have symptoms postpartum, most will be symptom free after pregnancy. There is anecdotal evidence that women who develop RLS during pregnancy have a higher incidence of RLS in later life.

Symptoms of primary and secondary RLS can usually be controlled by medication and nonpharmacologic therapies (**Table 1**).

Table 1 Guide to videotape

Motor restlessness during wakefulness
1. Tossing/turning in bed (patient 1)
2. Foot rubbing (patient 2)
3. Leg flexions (patient 2)
4. Leg stretching (patient 3)
5. Body rocking (patient 3)
6. Marching in place (patient 2) Resting dyskinesias while awake and periodic movements in sleep
7. Periodic myoclonus while awake (patient 1)
8. Clustered myoclonus while awake (patient 3)
9. Periodic movements in sleep involving legs (patient 4)
10. Periodic movements in sleep involving arm and legs (patient 4)

Table 1 and the accompanying video were first published by Walters A, Hening W, and Chokroverty S (1991) Review and videotape recognition of idiopathic restless legs syndrome. *Movement Disorders* 6: 105–110. The table and video are reproduced by permission of the Movement Disorders Society and the *Movement Disorders* journal.

See also: Akathisia; Periodic Limb Movements.

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Relevant Websites

www.neurotalk.org – An online support group for the discussion of brain, neurological, health, and mental health conditions.

www.rls.org – This is an organization of lay people interested in RLS.

www.sleepfoundation.org – Provides comprehensive sleep medicine education and awareness programs for professionals and the general public.

www.wemove.org – A comprehensive internet source for information on movement disorders.

www.irlssg.org – The International Restless Legs Syndrome Study Group (IRLSSG) is an organization of professionals committed to advancing basic and clinical research on Restless Legs Syndrome (RLS).

Rett Syndrome

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Definition and History

Rett syndrome (RS, RTT; MIM 312750) is a neurodevelopmental disorder caused by a mutation in the gene methyl-CpG-binding protein 2 gene (*MECP2*) encoding for methyl-CpG-binding protein2 (MeCP2).

Since the first clinical delineation, substantial progress has been achieved in the clinical understanding of RS, which has been further fortified by the finding of the causative gene.

Its clinical features consist of autistic symptomatology, mental retardation, stereotyped movements mainly involving hands and mouth, dystonia, scoliosis, epilepsy, abnormal respiratory patterns, acquired microcephalus, and female preponderance.

In RS, particular signs and symptoms appear in an age-dependent fashion and this is considered to be due to abnormal synaptogenesis at certain stages of the course of development caused by the *MECP2* mutation. The exploration of the role of *MECP2* in RS is helpful in understanding not only other developmental disorders but also normal brain development.

In 1966, Andreas Rett, a pediatrician in Vienna Austria, described a disorder with the specific symptoms occurring only in females as 'Über ein eigenertiges hirnatrophisches Syndriome bei Hyperammonämie' in German. In 1977, Rett wrote a chapter in the Handbook of Clinical Neurology entitled 'Cerebral Atrophy associated with hyperammonaemia'. Because his initial paper was written in German and his initial English paper was under the misleading heading of hyperammonemia, his original contribution had remained unknown outside of Austria and Germany. The clinical characteristics of the disorder were described as 'hyperammonaemia, hypomimia or amimia, alalia, stereotyped movement patterns in arms and hands, enhanced reflex activity, spastic increase in tone, gait apraxia, tendency to cerebral convulsive attacks, high grade of mental retardation, gynecotrophy (only females), and progressive course'. In 1972, this disorder was first described as 'Rett Syndrom' by Leiber in a syndrome textbook 'Die klinischen Syndrom' known in German-speaking area. In 1978, Ishikawa et al. wrote a short case report with identical symptoms and signs to the cases reported in the article by Rett; however, this report by Ishikawa was not noticed either. In 1983, the paper by Bengt Hagberg et al. in Annals of Neurlogy brought the disorder into medical nosology. We proposed for the first time, in 1984, that this disorder is a developmental disorder involving monoamine systems. In April 8, 1983, Rett organized the first meeting on this disorder in Vienna. It was only then that the international collaboration on the research of the disorder began intensively.

In 1999, the causative gene *MECP2* was identified by Amir et al., and the new era started on the clinical–biological–molecular correlation, and basic research of *MECP2* and its role in the development of brain began.

Pathogenesis/Pathophysiology

RS is associated with characteristic and complex phenotypes. The natural course of RS consists of a unique age-dependent appearance of the specific clinical symptoms and signs. The age-dependent presentation of the features of the disorder is important in considering its pathophysiology, because it reflects the changes taking place along the maturation of the responsible neurons or neuronal systems.

The onset of the disorder is in early infancy, although the initial symptoms and signs are very subtle. The early motor signs of RS are hypotonia with failure of crawling, abnormal pattern of walking, and disturbance in skillful hand manipulation. Clinical evaluation has revealed that the former results from postural hypotonia, with failure in locomotion. Additionally, neurophysiological examination has showed this to be due to hypofunction of the aminergic neurons of the brainstem. The latter signs are considered to indicate dysfunction of the corticospinal tract at higher levels.

Early psychobehavioral characteristics are a poor response to environmental stimulation, a poor formation of circadian rhythm, and more sleep during daytime, which are the earliest features of autistic tendency and can be speculated as being due to hypofunction of braistem serotonergic and noradrenergic systems.

Along with these features, the deceleration of head growth begins to appear in late infancy. This is speculated to be due to the dysfunction of noradrenergic neurons, which is involved in the cerebral cortical synaptogenesis.

The pathognomonic stereotyped hand movements appear in early childhood after the loss of purposeful hand use. These occur on the background of dystonic posturing and fixed position of the hands. With age, rigid hypertonia appears and later, fixed dystonic posture.

The frequency of the repetitive hand movements has been found to be minimally affected by environmental manipulations, suggesting that the movements are driven by automatic reinforcement or neurochemical processes.

The pathophysiology of the stereotyped hand movements with the loss of purposeful hand use and appearance of dystonic posturing are thought to be induced by the dysfunction of the basal ganglia-premotor and supplementary motor area with dopaminergic receptor supersensitivity. Scoliosis, which manifests itself in early childhood and shows progression with time, is also considered to be part of the dystonia.

The psychobehavioral characteristics of the disease include autistic features, and sudden episodes of screaming, laughing, or crying. Abnormal sleep–wake rhythms are present from early infancy.

With regard to the abnormal respiratory patterns and suggested abnormal cardiorespiratory centers in the brainstem, the involvement of the brainstem serotonergic system has been proposed. It is also suggested from experimental observations in mice that decreased substance P and other neuromodulators in the brainstem are the cause of the abnormal respiration.

The cause of sudden death in RS is not fully understood, but alteration of brainstem cardiorespiratory center can be an attributing factor.

Neurochemical studies in the cerebrospinal fluid and brain tissues revealed the involvement of most systems of transmitters, their receptors, and trophic factors, including acetylcholine, dopamine, serotonin, glutamate, substance P, and the nerve growth factor. It is important to note their roles as neurotrophins in brain development and their later role in the normal function of mature brain.

Neuroimaging studies have revealed altered volume of specific areas of the cerebral cortex, such as the prefrontal, posterior frontal, and anterior temporal regions, and relative preservation of posterior temporal and posterior occipital regions.

A neuropathological report by Armstrong showed decreased brain weight to the level of a 1-year-old and decreased pigmentation of the substantia nigra pars compacta. The weight loss does not progress with age, indicating that it is not degeneration. No degenerative, demyelinating, or gross malformative process is recognized. The neuronal size is decreased and increased neuronal packing density is observed in the cortex and subcortical areas. Significant decrease of dendritic territories in the frontal, motor, and subcortical cortices was shown by Golgi technique. In the midbrain and substantia nigra, the large neurons of pars compacta have less melanin and tyrosine hydroxylase staining than controls. Limited studies of the brainstem suggest abnormalities in serotonin receptors and in the substance P content. These neuropathological findings suggest a failure of development. General autopsies show that all organs except the adrenal gland are small for age but not for height.

Studies using receptor autoradiography demonstrate abnormalities in the density of excitatory glutamate and inhibitory gamma-aminobutyric acid (GABA) synaptic receptors in postmortem brain tissue, supporting the hypothesis that RS is a genetic disorder of synapic development, especially that of the synapses that use glutamate and GABA as transmitters.

RS is a genetic disorder affecting mostly girls and is primarily a sporadic disorder with few familial cases.

Mutations in *MECP2*, X-linked gene encoding methyl-CpG-binding protein 2 (MeCP 2), in exons 1 to 4 or DNA deletions, represent the genetic cause of more than 90% of typical cases of RS.

The phenotype–genotype correlation has revealed that MECP2 correlates with clinical severity and characteristics. The *MECP2* mutation is also found in the case of some phenotypes of Angelman syndrome and autism.

The mutation can also be found in normal females or females with mild learning disability. The mutation type, pattern of X chromosome inactivation, or other unknown factors seem to play a role in these phenotypical variations.

The mutation is also found in males, and the phenotypes in males vary from fatal infantile encephalopathy to familial X-linked mental retardation. Classical RS can occur in males with somatic mosaicism or with Kleinfelter syndrome.

MECP2 mediates transcriptional silencing through its methyl-CpG-binding domain (MBD) and transcriptional repression domain (TRD), and modifies gene expression of its target genes. This epigenetic function seems to be significant in the genetic control in brain development.

In normal early embryonic life, MeCP2 is expressed in two developmentally important regions, that is, the medulla and the thalamus. In normal brain development, the neurons of the medulla express monoamines (noradrenaline and serotonin), which act as the critical trophic roles, and send nonspecific afferents to the developing cortex, where they influence migration and organization of neuronal systems. MeCP2 is also a marker of a maturing neuron, being increasingly expressed in neurons as they evolve. The increase in MeCp2 expression in the brain after the prenatal period suggests that MeCP2 might also be required for neuronal maintenance and function.

The abnormalities, observed in the features of clinical symptoms and signs as well as the chemical and anatomical findings, suggest that MeCP2 is essential for neuronal maturation of the specific systems. The signal for the initial expression of MECP2 in a neuronal precursor cell can be regulated by a cell-autonomous mechanism. Its increasing expression in fully matured neurons can then be regulated in part by external factors, such as

synaptic input. Thus, MECP2 appears to be required for both the structural and the functional maturity of the neurons.

The establishment of the *MECP2*-deficient mice displaying phenotypic features mimicking some symptoms of RS as well as the understanding of the function of *MECP2* at the cellular and molecular levels is developing.

Epidemiology/Risk Factors

Cases of RS have been reported worldwide among all ethnic backgrounds. The classical form of RS was reported to have a prevalence of about 1 in 10 000–15 000 girls.

The frequency may increase with the addition of atypical cases, variants, or formes fruste cases. Particularly, the discovery of the causative gene may increase the prevalence by clarifying the genetic bases of atypical, variants, or formes fruste cases. There are some geographical areas where the prevalence is higher.

There are no known risk factors for the occurrence of the disorder.

Clinical Features and Diagnostic Criteria

The clinical presentation of RS is characterized by the specific psychomotor developmental delay, and pathognomonic symptoms and signs, which appear in an age-dependent fashion.

The onset of the disorder was initially late infancy to early childhood after a seemingly normal development. However, placidity and mild muscle hypotonia are present from early infancy, and the onset of RS is believed to be in early infancy. Sleep–wake rhythm is abnormal with increased sleep during the day, starting from early infancy. These earliest clinical features are subtle in most of the cases and are often overlooked.

These clinical features are similar to the ones observed in autism, showing delayed development of the circadian sleep–wake rhythm and poor response to environmental stimulation.

In late infancy, failure to crawl, delayed development of voluntary hand use, and the deceleration of head growth are observed. From late infancy to early childhood, psychomotor regression and social withdrawal appear. This social withdrawal seen in this period and the aforementioned characteristics seen in early infancy comprise the autistic features of RS.

The most striking and pathognomonic symptom of RS is the stereotyped movements of the hands associated with the loss of purposeful hand use appearing at this period. The typical hand stereotypies are characterized by repetitive squeezing, flapping, clapping, wringing, or bizarre hand automatisms. These movements occur mostly in the midline and virtually continue during wakefulness.

Before these stereotypies manifest themselves, habit-like behaviors involving the hands are present, and excessive clapping may be present.

Stereotyped movement of the tongue and mouth and licking and teeth grinding are also characteristics.

These stereotypies are observed during wakefulness, and increase when the child gets excited or becomes anxious.

Age-dependent changes are also observed in the hand stereotypies, evolving from simple to complex and fast, then to slow and simple with age.

In early childhood, dystonic posture appears. Hand stereotypies are obscured by dystonic rigidity. Because of the dystonia, the stereotyped movements of the hands become fixed and this does not change through the rest of the course of the disease.

The pes varus or vulgus, dystonic posture of all extremities progresses after childhood. Kyphosis and scoliosis, which are the postural dystonia involving trunk, progress after childhood to adulthood in some patients.

The deceleration of the growth of the head begins in late infancy, and patients often become microcephalic after early childhood.

The characteristic gait was initially described as apraxic by Rett. However, both failure of crawling and gait dysfunction are due to failure of locomotion.

Epilepsy may be seen, but the severity is variable among individual cases.

Abnormal sleep–wake rhythm and inappropriate laughing or crying during wakefulness or sleep are also seen often.

Breathing abnormalities, such as hyperventilation, breath holding, air swallowing, and bloating are striking features seen in some RS. Heart rate variability, difficulty in swallowing, and constipation suggest autonomic impairment. Cold and small feet are also consistent with dysfunction of the autonomic nervous system.

Height, weight, and hand and foot sizes also decline later. Overweight or emaciation may be seen in some patients.

The age-dependent appearance of the clinical features has led to the proposal of staging the disease.

Because of the difficulty in understanding the complex clinical features, the efforts of constructing the diagnostic criteria were set in 1984 and in 1988. With the increase of reported cases and advances of the understanding of the pathophysiology of the disorder, some components of these diagnostic criteria need to be changed or deleted.

Differential Diagnosis

The diagnosis of RS is not difficult with careful history taking of characteristic symptoms and signs, and noting the age-dependent appearance of these symptoms and signs.

However, there are disorders that need to be differentiated from RS. They include for example autism and Angelman syndrome. Some female cases with autism, particularly the cases with regression during the course, may later prove to be RS. Infantile neuronal ceroid lipofuscinosis may show temporarily similar features to RS. Finally, some neurodevelopmental disorders may present with similar features with RS. Therefore, in these cases, some symptoms or some periods of the course may overlap with the features of RS.

X-linked-cyclin-dependent kinase-like 5 (CDKL5/STK9) has been proposed as another causative gene for RS, particularly early seizure cases with severe mental retardation.

Diagnostic Workup/Tests

The clinical features and their evolution at specific ages are typical of RS. Careful history taking and neurological examination leads to the correct diagnosis in most cases.

There are no pathognomonic laboratory, neurophysiological, or neuroradiological tests.

The finding of mutation of *MECP2* is the best test to clarify the diagnosis; however, it is important to keep in mind that there are cases even with typical clinical features that do not carry the *MECP2* mutation.

Management

Therapeutic approaches are still symptomatic, and unfortunately, no crucial treatments have been established. Rehabilitation, including physical and occupational therapy, and enhancement of communication with music therapy have been tried with limited results. Trials of theoretically attractive treatments in these areas have been reported. Medications directed to possible correction of the underlying pathomechanisms have failed to produce appreciative and sustained effects.

Seizure is one of the common symptoms of RS that appears in early childhood. In such cases, administration of a suitable anticonvulsant(s) is essential. However, there is no antiepileptics specifically recommended for RS, and some cases can be drug resistant.

The effort to control the abnormal respiratory patterns is another challenge. Each abnormal respiratory pattern requires unique and special intervention. Some of the phenotypes can partly respond to pharmacological intervention, but others do not.

When physical therapy and orthopedic management of scoliosis fail, surgical treatments are indicated.

With some patients, management of nutrition becomes necessary, including gastrostomy.

General health care and prompt appropriate management for the undercurrent or acute illnesses is also important. All necessary managements for better quality of life need to be considered.

Prognosis

Initially, RS was thought to be progressive, but the clinical course is basically one of a developmental disorder.

As for the life-expectancy, relatively healthy patients survive into the fourth and fifth decades, although there is an increased incidence of sudden death in adolescent years. Cases surviving into their seventieth have been reported.

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Rhizotomy

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Definition and History

In 1913, Otfrid Foerster, a German neurosurgeon, introduced a technique to relieve severe spasticity mainly due to cerebral palsy by a complete division of the lumbosacral dorsal spinal roots with preservation of the motor roots. As he sectioned almost all the posterior roots, the result was unsatisfactory and this procedure was abandoned. Gros reported modification of Foerster's procedure in 1979 by partially sectioning dorsal spinal roots in an attempt to preserve some sensory function and afferent signals from the muscles. Further refinements to these techniques were made by Fasano and Peacock in the late 1970s. They used electrophysiological evaluation during the operation to determine which roots should be cut. After the introduction of intraoperative neurophysiologic monitoring, the effect of dorsal rhizotomy became satisfactory and complications such as sensory disturbance and too much hypotonicity decreased. In 1980s, selective dorsal rhizotomy (SDR) became a standard neurosurgical procedure for control of harmful spasticity in cerebral palsy children.

SDR (or selective posterior rhizotomy; SPR) is now a well-established treatment for spasticity in children with mainly cerebral palsy when the spasticity has proved unresponsive to less invasive procedures such as oral medications, local drug injections (botox, phenol), or orthopedic surgeries. After a rhizotomy, a patient who had suffered from severe muscle spasticity will be significantly less tight, have more range of motion and more fluidity in motion, and will never have to worry about the same muscles tightening up again as they may have before the procedure.

There have been many reports showing the efficacy of SDR and several reports with evidence-based assessment that showed long-term benefit of SDR. The following issues are scientifically proven:

- decrease of spasticity and improvement of range of motion;
- increase of gait speed;
- improvement of sitting ability;
- improvement of transfer motion;
- improvement of self care and ADL;
- secondary improvement of upper limb function;
- no sensory deficit in children;
- effects probably last longer than 20 years;
- positive effects on higher cognitive function.

General Course After SDR

After the surgery, all patients who were walking independently before surgery regain independent walk within a few weeks. Patients maintain independent walking for the long term; when some have more difficulty in walking independently, they may eventually need an assistive device – however, in nearly all cases spasticity can be eliminated and the quality of independent walking improves. Orthopedic surgery is rarely required after SDR.

In children who are 2–7 years old and walk with a walker or crutches before SDR, independent walking after the procedure is possible. Once they have achieved independent walking, they can maintain it. In children who are older than 7 years and walk with crutches, independent walking is also possible. If they walk with a walker at this age, they will most likely walk with a walker or crutches after the procedure, although it improves the quality of assisted walking and transition movements and alleviates deformities of the legs. Many of these patients will need orthopedic surgeries after SDR.

Indication

Not all patients with spastic cerebral palsy benefit from rhizotomy. SDR should be considered for those younger than 12 years. If a patient is older than 13 years, an intrathecal baclofen pump should be considered, because postoperative dysesthetic pain may become a problem as the age increases. Suitable candidates should fulfill the following conditions:

- at least 2 years of age;
- diagnosis of spastic diplegia, spastic quadriplegia, or spastic hemiplegia;
- some form of independent mobility; for example, crawling or walking with or without an assistive device;
- no severe damage to the basal ganglia on MRI examination;
- potential for improvement in functional skills;
- exclusion of severe dystonia or athetosis;
- motivation to attend intensive physical therapy and perform home exercise program.

Surgical Procedure

The SDR is generally performed by experienced pediatric neurosurgeons. General anesthesia without muscle

relaxant is necessary. With the patient in the prone position, a midline linear skin incision is made in the thoracolumbar region. There are two major approaches in SDR. The traditional and most common approach is through laminectomy from Th12 to S1–2, and all the dorsal roots are exposed at the distal part in the intradural space (Peacock's operation technique). The advantage of this is that the level of spinal roots is easily identified and that the surgeon can easily separate S2 or S3 roots from others to avoid complications regarding bowel and urinary functions. The disadvantage is related to the multilevel wide laminectomy: more invasiveness, postoperative pain, and long-term deformity of the spine. Another approach is through a limited laminotomy of only L1 and L2 (Park's technique). This eliminates the problems of multilevel laminectomy, but differentiation of the level of the roots may become difficult. In both procedures, an operative microscope should be used, although some neurosurgeons still use only magnifying glasses.

Intraoperative electrophysiological assessment is very important to determine which rootlets should be cut. Multichannel evoked electromyography (EMG) is recorded from the muscles in the leg. The dorsal roots are dissected to smaller rootlets, and every rootlet is stimulated with electrical current. If the evoked EMG pattern is "abnormal" with a certain rootlet stimulation, this rootlet should be cut. There are several abnormal patterns: prolonged response, extra-segmental spread, bilateral response, and so on. Some neurosurgeons also use urogenital sensory mapping to avoid urinary and bowel complications. Approximately 50–60% of rootlets from L2 to S1 or S2 have to be cut to achieve satisfactory functional improvement.

Postoperative pain may be severe, a pain related to both the surgical exposure and the nerve root manipulation. Various pain management strategies for children undergoing SDR have been reported. The majority of centers use continuous infusions of opioids, with an intravenous, epidural, or intrathecal approach.

Other Types of 'Rhizotomy'

Foerster-Dandy's rhizotomy had been widely performed for the treatment of spasmodic torticollis or cervical dystonia until the 1980s. In this procedure, intradural ventral spinal roots are sectioned from C1 to C3 or C4 level. This operation inactivates not only muscles innervated from dorsal rami but also muscles from the ventral rami, which may induce neck instability and swallowing problems. To avoid denervation of the phrenic nerve and nerves to the shoulder and arm, intradural rhizotomy is limited down to C4 in one side and to C3 in the opposite side. This is inadequate to denervate the posterior neck muscles completely. Because of such possible complications and the limitations of clinical benefit, this procedure is no longer performed, and it is replaced by selective peripheral ramisectomy (Bertrand's procedure).

Posterior rhizotomy (section of posterior spinal roots) used to be a treatment of choice for the management of intractable pain of malignant origin. However, such kind of procedure is no longer performed for the management of pain, because more effective and less invasive treatment modalities have been introduced.

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Rigidity

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Glossary

Bradykinesia – Slowness of movement.
Dystonic posture – Abnormal posturing of a limb with a torsion component.
Myoclonic jerks – Brief muscle jerks causing displacement of a body segment.
Parkinsonism – Any disorder presenting with the combination of bradykinesia, rigidity, and/or tremor.
Rhizotomy – Surgical sectioning of the nerve roots.

Definition and History

Having been derived from the Latin word 'rigor' meaning stiffness, rigidity refers to the presence of an increased muscle tone detected through passive displacement of a body segment. Hypertonicity or hypertonus is a general denomination for any type of increased muscle tone, including rigidity. Aside from resistance to passive displacement, increased muscle consistency, decreased flexibility, and passivity are additional features usually found in the examination of patients with hypertonicity, irrespective of the nature of the disorder. Paratonia, spasticity, and stiffness (as seen in the Stiff Person syndrome or in any situation where continuous muscular activity is present) are different forms of hypertonia, each having particular clinical features and differing pathophysiology. Rigidity is one of the distinguishing clinical features of the Parkinsonian Syndrome or Parkinsonisms in general (also designated 'akinetic-rigid syndrome'). The term 'rigid' or 'rigidity' is frequently used outside the field of movement disorders, for example, decerebrate rigidity, rigid spine, etc.

In James Parkinson's original monograph, there is no specific mention of rigidity as one of the main features of 'Paralysis Agitans.' It was Charcot, who, in the second half of the nineteenth century, clearly recognized rigidity to be part of the clinical features of this disorder. It was not until the beginning of the twentieth century that the cogwheel phenomenon was first mentioned by Camillo Negro in Italy and Harold N. Moyer in the United States. Apparently, a Spanish neurologist, Robert Novoa Santos, had made the same observation almost simultaneously. A further and significant contribution to the understanding of rigidity was made by another prominent French neurologist, Jules Froment, who extensively studied this motor phenomenon both clinically and with physiological recordings using a myograph. He was the first to discover the presence of 'enhanced resistance to passive movements of a limb about a joint that can be detected specifically when there is a voluntary action of a contralateral body part.' This accentuation of rigidity with voluntary activation of another body part has become known as the 'Froment's maneuver' and is the basis of the activation or facilitation test. Froment also demonstrated that variations in the amount of rigidity depend on changes in posture, increasing during the Romberg test, gaze deviation, and oriented attention. His hypothesis proposed that 'maintenance stabilization' was impaired in PD, whereas 'reactive stabilization' and 'rigidification' were compensatory changes against gravitational forces.

Pathophysiology

The pathophysiological basis of rigidity is not as well understood as that of bradykinesia. Afferent impulses are thought to play a role, as sectioning of the dorsal roots or application of local anaesthetic in the epidural or subarachnoid space decreases rigidity. Several theories have attempted to explain rigidity, through both hyperactivity and hyperxcitability of long-loop reflex pathways or disruption of function of the spinal interneurons due to abnormal afferent input from suprasegmental centers, including the reticular nuclei, via descending tracts. From a biomechanical perspective, these disturbances may cause that the forces generated by lengthening a given muscle during passive movement be offset by activation of the antagonist, that is, 'shortening reaction.' Changes intrinsic to the muscle have also been proposed.

Clinical Features and Diagnostic Criteria

Features that distinguish rigidity from other forms of hypertonicity are the presence of uniform resistance to passive displacement usually referred to as the 'lead pipe phenomenon,' as many perceive this uniform resistance as being similar to what is experienced when bending a soft lead pipe, and the 'cogwheel phenomenon.' Rigidity can occasionally have a ratchety quality, referred to as 'cogwheeling,' whereby the muscle resists and gives way in small, ratchety, step-like movements as if it were being controlled by a cog-wheel. The hypertonicity is regularly interrupted by the cogwheel mechanism at a 6–9-Hz

frequency, which is higher than the frequency of resting tremor (4–5 Hz) and postural tremor (5–6 Hz) frequency. Cogwheeling is not always present or necessary to diagnose rigidity. Cogwheeling appears to be present only when tremor is associated with rigidity. Uniformity of resistance to passive movement is indeed the distinguishing clinical feature of rigidity. The degree of resistance remains fairly constant through the entire range of motion, both flexion and extension, and is not greatly influenced by the stretch velocity or force with which the movement is performed. It persists as long as the stretch is maintained.

Rigidity is one of the cardinal symptoms of the Parkinsonian Syndrome, together with bradykinesia, rest tremor, and postural disturbances. Parkinsonism, and therefore rigidity, is present in a variety of disorders, including primary parkinsonism (Parkinson's disease (PD) both sporadic and genetic), the atypical parkinsonisms (multiple system atrophy, progressive supranuclear palsy, and the corticobasal syndrome), and parkinsonism associated with other heredodegenerative disorders (Juvenile Huntington's disease, Spinocerebellar ataxias, Pantothenate Kinase associated neurodegeneration, Neuroacanthocytosis, Wilson's Disease, etc.). Rigidity also occurs in secondary or symptomatic parkinsonisms (drug-induced, infectious, metabolic, structural, or toxic). The topographic distribution, presentation, and clinical course of rigidity differ from one syndrome to another. In PD, rigidity may be initially restricted to one limb (as often PD starts asymmetrically, involving just the upper or the lower extremity; with progression of the disease, involvement of the contralateral limbs and axial muscles is generally the rule. In progressive supranuclear palsy, the pattern of distribution of rigidity differs from that of PD, preferentially affecting the axial muscles (neck) more than the limbs. The corticobasal syndrome may present initially with rigidity localized to either one of the upper or lower extremities, but it is usually associated with apraxia (and other signs of cortical involvement such as agnosia), myoclonic jerks, and dystonic posturing of the affected limb. In the remaining conditions in which rigidity may be present, the pattern of topographical distribution is not in any way different from that observed in PD, but the presence of other neurological signs that are atypical for PD frequently lead to a correct diagnosis.

The contribution of rigidity to the motor impairment observed in these conditions is controversial, or at least uncertain. It is quite difficult to dissociate rigidity from bradykinesia in most of the cases. However, in clinical experience, it is frequently observed that patients may have very little or no rigidity but nonetheless are significantly impaired by the presence of bradykinesia; or just the opposite: despite the presence of significant rigidity, there is no obvious motor impairment. In the case of PD and other parkinsonisms, it may contribute to the generation of pain in the affected body segment, which is often relieved by the medications that improve rigidity.

Differential Diagnosis

Spasticity, contrary to what is observed in rigidity, exhibits a gradual variation in resistance, depending on the velocity and range of the movement whereby the examiner experiences a phenomenon comparable to the sudden closure of a clasp-knife. Spasticity is also more pronounced in extension than in flexion during clinical examination, contrary to what is usually found in rigidity. However, a recently published biomechanical study has found that, contrary to common belief, rigidity is more readily elicited in the antigravity muscles, although this distinction is not evident in clinical practice. The presence of weakness and additional signs of pyramidal tract involvement (increased deep tendon reflexes, Hoffmann and Babinski signs) helps in differentiating spasticity from rigidity.

Paratonia or gegenhalten, usually observed in cortical or subcortical frontal dysfunction, can also be distinguished from rigidity by the paradoxical and intermittent nature of the response to passive movement, presenting an increase in opposition depending on the degree of force applied. The finding of other signs of frontal involvement (cognitive deterioration of the frontal type, a positive grasp reflex, imitation and utilization behavior, frontal dysequilibrium) also helps in differentiating this type of hypertonia from rigidity.

Stiffness as seen in the 'Stiff-person syndrome' is described as 'board like' increase in muscle tone; it involves preferentially the paraspinal muscles, causing hyperlordosis, and is often accompanied by superimposed muscle spasms. The presence of continuous muscle activity through electromyography helps in confirming the nature of the increased muscle tone in this condition.

Diagnostic Work-up/Tests

In routine clinical practice, rigidity is explored through manual examination of the patient by passively moving the neck and the extremities and estimating subjectively the amount of resistance encountered. Although the evaluation of the consistency of the muscles through palpation, or the passivity with which a body segment is displaced around a joint (e.g., elbow, wrist, knee, ankle) by shaking the affected limb may also give an indication of the presence of rigidity, these are maneuvers that are not routinely used at present. In fact, in the Motor Examination part of the Unified Parkinson's Disease Rating Scale (UPDRS, Part III), which is the standard scale used in the evaluation of the severity of rigidity in PD and other parkinsonisms, only the passive displacement of a body segment around a joint is considered. In the UPDRS, the severity of rigidity is given a score from 0 to 4; 0 means the absence of rigidity; 1 indicates that rigidity

is present only by activation maneuvers (closing and opening the hand repetitively, while the examiner evaluates the presence of rigidity in a given body segment; this is known as the Froment maneuver); score 2 is given when, despite the presence of an increased muscle tone or resistance to passive movement, the whole range of motion can be achieved; a score of 3 is applied when there is limitation in the range of movement; and finally a score of 4 is used whenever there is complete limitation of movement. In the revised version of this scale, the MDS-UPDRS, the most severe level of complete limitation of movement captured in the earlier version is not an option, based on the rare applicability of this score in typical PD.

There have been many attempts at designing objective tests for the evaluation of rigidity by means of mechanical or electrophysiological devices; however, none of these tests has become part of the routine examination of this phenomenon.

Management

There are very few specific measures that can be applied to the treatment or management of rigidity. In PD, levodopa and other dopaminergic medications significantly improve rigidity, almost in parallel with bradykinesia. Some of the other parkinsonisms may also show some degree of response to antiparkinsonian medications, such as Multiple System Atrophy (short lived) and Progressive Supranuclear Palsy (rarely). In the majority of the remaining conditions, there is no significant improvement of rigidity with standard antiparkinsonian drugs. In drug-induced Parkinsonism, the removal of the causative drug, usually an antipsychotic or other dopaminergic receptor antagonist, may lead to progressive improvement of rigidity. In some cases of severe drug-induced parkinsonism, short-term antiparkinsonian medications are reported to accelerate the recovery.

Functional stereotactic surgery is also effective in reducing or improving rigidity. Both the pallidum and the subthalamic nucleus are effective targets for the relief of rigidity either by ablative surgery or by deep brain stimulation. Some of the earliest attempts to relieve rigidity in PD by surgical means involved the sectioning of the dorsal roots (dorsal rhizotomy), which leads to disastrous functional outcomes but provided evidence of the afferent component of this phenomenon.

In severe cases in which rigidity is associated with postural deformity and pain, which is often observed in the Corticobasal syndrome, the use of botulinum toxin may be helpful.

Stretching exercises and passive and active movements in the context of physical therapy may also help in relieving some of the discomfort attributed to rigidity.

Prognosis

Rigidity being a sign among a constellation of other signs and symptoms that are present in the conditions that were discussed in this article, there are no specific considerations to be made regarding prognosis. Rigidity is only one of the contributing factors leading to disability in these disorders. As mentioned previously, it is quite difficult to establish the major contributing factors leading to the progressive functional decline and immobility in such diverse and complex conditions in which rigidity is present.

See also: Akinetic-Rigid Syndrome; Corticobasal Degeneration; Multiple System Atrophy; PARK2, parkin; PARK3; PARK5, UCH-L1; *PARK6, PINK1*; PARK7, DJ1; *PARK8, LRRK2* (Dardarin); Parkinson's Disease: Definition, Diagnosis, and Management; Progressive Supranuclear Palsy.

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RNA Interference

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Glossary

MicroRNA pathway – Posttranscriptional gene silencing process triggered by endogenous miRNAs that bind the target mRNA leading to translational suppression.

Posttranscriptional gene silencing – Process by which expression of a specific gene is suppressed by small, double-stranded RNAs after transcription of the gene into mRNA but before translation of this message into protein.

RISC (RNA-induced silencing complex) – Enzymatic multiprotein complex assembled once the complementary (guide) strand of the dsRNA pairs with the targeted mRNA to mediate the cleavage of the mRNA (siRNA) or to translational repression (miRNA).

RNA interference (RNAi) – Posttranscriptional gene silencing process triggered by exogenous dsRNA in which perfect pairing with the target mRNA leads to its cleavage.

Short hairpin RNA (shRNA) – Short paired strands of RNA joined by a loop to form a hairpin that, after cytoplasmic processing and cleavage of the loop, forms a double-stranded siRNA. shRNAs are usually delivered to cells in the form of a DNA template.

Small interfering RNA (siRNA) – Short, double-stranded RNA formed by two perfectly paired strands of ~21 nucleotides which triggers the assembly of the silencing complex in the RNAi pathway.

Definition and History

The discovery of the process known as RNA interference (RNAi) has been one of the most important advances in biomedical research in recent decades. RNAi is a natural process by which cells use short, double-stranded RNAs (dsRNAs) to recognize messenger RNAs (mRNAs) with exquisite specificity, leading to their enzymatic destruction and preventing their translation into a protein. Therefore, they inhibit gene function. For the exogenous manipulation of this pathway, dsRNA can be introduced into cells in different forms. The two approaches most commonly used to silence a given gene in the laboratory through RNAi are (1) the introduction into cells of in vitro synthesized small interfering RNA (siRNA) or (2) the use of DNA templates known as short hairpin RNA (shRNA) that host cells will use to generate the siRNAs. One way or the other, these techniques allow researchers to block, or silence, expression of a given gene with a wide variety of goals, including therapeutic development.

The Process of RNAi

Scientists are able to use RNAi technology in mammalian cells because they express a highly organized machinery that mediates an endogenous process of posttranscriptional gene silencing, known as the microRNA (miRNA) pathway (**Figure 1**). miRNAs are generated by transcription of noncoding genes in mammalian cells, undergoing enzymatic processing of the transcript in the nucleus before being actively transported to the cytoplasm by exportin 5. In the cytoplasm they undergo additional processing to be converted into mature miRNA. miRNAs recognize their target mRNA, triggering the assembly of RISC (RNA-induced silencing complex) and usually lead to translational repression. The miRNA and RNAi pathways follow a similar process but with some differences. For instance, miRNAs differ structurally from siRNAs, usually pair with untranslated regions of the target

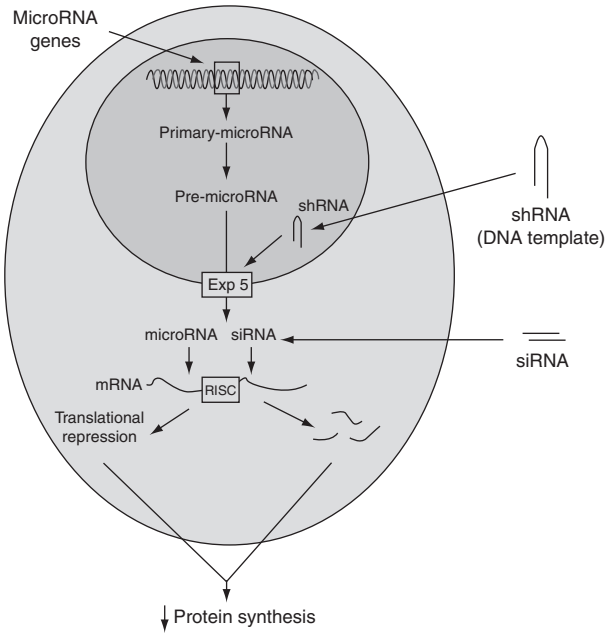

Figure 1 MicroRNA and RNAi pathways.

through imperfect base pairing and do not mediate cleavage of the mRNA. On the other hand, exogenous siRNAs usually pair with coding regions of the target through perfect pairing and direct the enzymatic cleavage of the target. Nevertheless, both ultimately result in the decreased synthesis of a specific protein.

The different constructs used in the laboratory to silence genes through RNAi also exhibit important differences between them. For instance, whereas shRNA incorporate into this pathway as DNA templates in the nucleus to be transcribed, siRNAs enter the cytoplasm ready to identify their targets, thus bypassing nuclear export and cytoplasmic processing (**Figure 1**).

Applications of RNAi

The possibility of manipulating the expression of any given gene through RNAi has facilitated investigations into the cause and treatment of several movement disorders. For instance, RNAi may be used in the laboratory as a molecular tool to understand the pathobiology of these disorders or to generate animal models of diseases caused by loss of gene function. However, the therapeutic use of RNAi is perhaps its most promising application.

The principle of therapeutic RNAi lies in silencing expression of genes that are key to the pathogenic process. In general, diseases considered for the development of therapeutic RNAi are those in which targets amenable to traditional pharmacological approaches are lacking, but our knowledge of disease pathogenesis allows us to identify molecular targets for therapeutic RNAi silencing. In this case, valid targets will be genes that, if eliminated would halt or slow down the pathogenic process without causing significant adverse effects. For instance, many dominantly inherited movement disorders, such as Huntington disease or the spinocerebellar ataxias, are caused by expansion in polyglutamine tracts that, through a toxic gain of function, lead to neuronal dysfunction and death. Although many of the investigational treatments for these diseases act downstream the pathogenic cascade, silencing expression of the mutated gene through RNAi would directly eliminate their cause. In recessive diseases caused by loss of gene function, although silencing the mutated gene would not be helpful, suppressing expression of specific molecular components of the pathogenic cascade could be beneficial. A similar scenario is encountered in the more common sporadic disease, when the molecular etiology remains unknown. For example, there is increasing evidence of a crucial role for α-synuclein in the pathogenesis of Parkinson's disease (PD), whether inherited or sporadic. Consequently, silencing α-synuclein expression in nigral neurons could be a reasonable therapeutic approach for PD. A similar scenario could be found in several diseases in which the aggregation of phosphorylated tau is important in their pathogenesis. In summary, several dominant, recessive, and sporadic diseases may be candidates for the development of therapeutic RNAi.

Once a target gene is identified, the next question is how to deliver the effector complex to the target cells. For the nervous system, most preclinical trials in animal models have used viral delivery of shRNAs, although significant advances in the use of nonviral delivery methods are very promising. If valid animal models are available, preclinical trials can then be performed. Therapeutic trials have been completed, with promising success, in different mouse models of Huntington disease, SOD1-linked amyotrophic lateral sclerosis, spinocerebellar ataxia type 1, Creutzfeldt–Jacob disease, PD, and Alzheimer disease. These trials support the potential of this therapeutic modality, and additional studies are being performed to answer other experimental questions required before planning therapeutic trials in humans.

However, there are potential obstacles faced in the development of therapeutic RNAi. In addition to demonstrating therapeutic efficacy, the completion of animal studies has raised important concerns about the safety of this therapeutic approach. Potential adverse effects include, for instance, the activation of inflammatory responses, sequence-specific silencing of nontargeted genes or the saturation of the endogenous miRNA machinery. In experiments performed by administering shRNA to mice with molecular targets in liver cells, it was found that high expression of these effector complexes saturated the nuclear export pathway, leading to the accumulation of unprocessed endogenous pre-miRNA in the nucleus of hepatocytes, causing cell death and animal demise. Toxicity induced by shRNA was also reported in a mouse model of Huntington disease. However, modifying these shRNAs to mimic endogenous pre-miRNAs, or the use of siRNA, which do not enter the nucleus, prevent the development toxicity. Overall, it seems that manipulation of the RNAi pathway with therapeutic goals may potentially impact neurodegenerative diseases within the next decade.

See also: Ataxia; Huntington's Disease; Parkinson's Disease: Definition, Diagnosis, and Management; Spinocerebellar Ataxias Genetics.

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Rotation, Drug-induced

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Glossary

6-Hydroxydopamine or 6-OHDA – A neurotoxin selective for dopaminergic and noradrenergic neurons.
Hemiparkinsonism – Parkinsonism affecting only one side of the body and often induced by lesion confined to the unilateral substantia nigra or nigrostriatal pathway.
Rotation – A circular locomotor movement.
Substantia nigra – A nucleus in the midbrain containing dopaminergic neurons that degenerate in Parkinson's disease.

Drug-induced rotation was first used by Profs. U. Ungerstedt and Nils-Eric Anden in Sweden more than 40 years ago. It is still a commonly used tool to evaluate the degree of neurodegeneration after lesioning and regeneration after treatment in a rodent model of Parkinson's disease.

Stereotaxic unilateral destruction of nigrostriatal dopaminergic systems in brain is often achieved by the injection of the catecholaminergic neurotoxin 6-hydroxydopamine (6-OHDA). Depending on the site of injection, 6-OHDA can lead to a partial or complete lesion of the mesencephalic dopamine system in one hemisphere. The injection of 6-OHDA into the striatum or substantia nigra of the animal results in a partial lesion of the nigrostriatal dopaminergic system. A near-complete lesion can be achieved by the administration of 6-OHDA to the axonal projection pathway of the nigrostriatal system, also called the medial forebrain bundle lesion. In this model, 6-OHDA is injected in the ascending nigrostriatal bundle and results in a complete destruction of A9 (substantia nigra, SN) dopamine (DA) neurons and their projection in striatum. This loss does not take place immediately and there is a variable time for the loss of phenotype preceeding neuronal death.

The injection of 6-OHDA causes degeneration of dopaminergic neurons in the A9 and their terminals in basal ganglia ipislateral to the injection side, while leaving the contralateral striatum and nigra relatively intact. The destruction of unilateral nigrostriatal dopaminergic pathway also leads to dopamine receptor supersensitivity in the lesioned striatum.

Two classes of chemicals are commonly used to evaluate denervation and receptor supersensitivity after unilateral 6-OHDA lesioning. (1) Amphetamine analogs, such as amphetamine or methamphetamine, cause ipislateral rotations due to differential increase of dopaminergic activity on the intact side, (**Figure 1**). The molecular mechanisms for amphetamines to increase synaptic levels

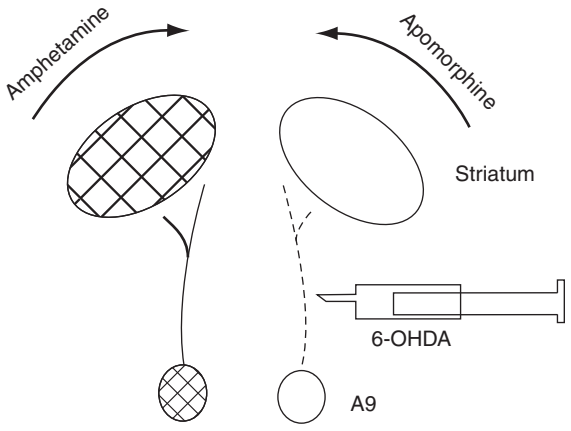

Figure 1 Schematic diagram of drug-induced rotation in unilaterally 6-OHDA lesioned animals. Injection of 6-OHDA to the medial forebrain bundle induces lesioning of DA neurons in A9 and striatum. Administration of amphetamine or apomorphine induces ipislateral or contralateral rotation, respectively.

of dopamine in the intact terminals include redistribution of catecholamines from synaptic vesicles to the cytosol, the reverse transport of neurotransmitter through plasma membrane transporters, blocking the activity of monoamine transporters, and inhibiting the activity of monoamine oxidase. (2) Dopamine receptor agonists in contrast, such as apomorphine, stimulate dopamine receptors directly, preferentially on the supersensitive denervated side and result in contralateral turning (**Figure 1**).

Typical doses that induce rotation are 1–5 mg kg^{-1} for amphetamine, 2.5–5 mg kg^{-1} for methamphetamine, and 0.05–0.2 mg kg^{-1} for apomorphine. These apomorphine doses maximize the differential sensitivity of the denervated DA receptors. Turning behavior can be quantified by various tools, such as infrared systems, mechanical rotomotors, or computerized video systems. Time course for measuring the rotation often lasts from 1 up to 4 h after drug injection.

There is a correlation between the loss of DA in the nigrostriatal system and drug-induced rotation. Significant correlation has been found between amphetamine (5 mg kg^{-1}, s.c.) induced ipislateral rotation or apomorphine (0.05 mg kg^{-1}, s.c.) induced contralateral rotation and the depletion of dopamine in the nigra. Maximal (>90%) lesions of the striatum and substantia nigra are required to generate rotations demonstrable with low-dose (0.05 mg kg^{-1}, s.c.) apomorphine. Partially lesioned (75–90% depleted) rats can still respond to amphetamine. Little correlation has been found between the depletion of dopamine in ventral tegmental area and the rotational behavior induced by apomorphine or amphetamine at these doses.

The number of rotations can also be used to predict the degree of lesioning in the striatum. Animals rotating over 300 turns per hour after 0.05 mg kg^{-1} apomorphine injection have maximal (≥90%) depletion of dopamine content in the striatum. It is less accurate to predict maximal lesioning using D-amphetamine at 5 mg kg^{-1}. It has also been reported that no turning could be elicited in markedly lesioned animals and that nonlesioned rats may rotate extensively on amphetamine. It has also been shown that the early phase of rotation, over the first 5–10 min, may be a behavioral conditioning phenomenon rather than a drug effect.

There are several other precautions for interpreting data, using drug-induced rotation. For example, apomorphine-induced rotation relies on the supersensitivity of dopamine receptors in the lesioned striatum. Further lesions of the denervated striatum can reduce dopamine receptor numbers and can result in the attenuation of apomorphine-induced rotation. Amphetamine can induce sensitization and the repeated administration of amphetamine may thus enhance rotation.

Amphetamine and apomorphine-induced rotation are commonly used to evaluate the protective or regenerative functions in 6-OHDA-lesioned rats after various treatments. For example, administration of glial cell line derived neurotrophic factor (GDNF) protein, transplantation of fetal substantia nigra or mesencephalic progenitor cells, or injection of viral vectors encoding GDNF have been found to reduce apomorphine or amphetamine-induced rotation in hemiparkinsonian rats.

Drug-induced rotation has also been used in nonhuman primates. The administration of apomorphine (0.05–0.5 mg kg^{-1}) or amphetamine (0.5 mg kg^{-1}) increases contralateral or ipislateral rotation in unilaterally 6-OHDA-lesioned marmoset monkeys. At the highest dose of apomorphine, animals vomited and were slow to start rotating.

Drug-induced rotation has sometimes been used in other animal models with unilateral striatal lesions. For example, in a rodent model of Huntington's disease, the administration of high doses of apomorphine (1 mg kg^{-1}, s.c.) induces ipislateral rotation at month 1 after the unilateral intrastriatal injection of quinolinic acid. Similarly, in stroke rats, amphetamine (1 mg kg^{-1}) significantly increases ipislateral rotation, toward the lesion side, at months 1–3 after unilateral middle cerebral artery occlusion (MCAo). However, there is no significant correlation between the rotational behavior and the size of lesion.

See also: 6-OH Dopamine Rat Model; Basal Ganglia; Basal Ganglia, Functional Organization; Parkinson's Disease: Animal Models.

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Roussy–Levy Disease

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Glossary

Amyotrophy – Muscle atrophy.
Charcot–Marie Tooth diseases – Group of hereditary sensorimotor neuropathies characterized by distal atrophy of the legs, deformation of the feet ('pes cavus'), and a predominantly distal motor deficit that is slowly progressive. This group of disease is genetically heterogeneous.
Demyelination – Abnormal process leading to degeneration and ultimately to loss of the myelin sheath of the nerves.
Pes cavus – Deformation of the foot with high plantar arches and clawing of the toes related to a slowly progressive atrophy of the foot muscles.
Schwann cells – Satellite cells of the peripheral nerves associated with myelinated and with unmyelinated axons. In myelinated axons, myelin sheath is formed by the compaction of layers of the Schwann cell surface membrane.
Tomacula – 'Sausage' aspect of myelin fibers seen in teased fiber preparation. This appearance is caused by redundant myelin loops.

Definition and History

In 1926, Gustave Roussy and Gabrielle Levy reported on seven members of a large kindred, who presented with a dominantly inherited disorder over four generations. An unsteady gait of early childhood with pes cavus and generalized areflexia were the prominent features of the disease. The patients eventually developed distal amyotrophy and weakness, clumsiness, postural tremor, and limb ataxia. Sensory modalities were preserved in virtually all cases. Overall, the course of the disease seemed benign. With the report of similar familial cases, the eponym of Roussy–Levy syndrome was subsequently used to designate this pattern of dominantly transmitted hereditary ataxia with tremor.

Roussy–Levy syndrome was considered by some as a forme fruste of Friedreich ataxia, but the absence of pyramidal tract involvement and the autosomal dominant inheritance were not compatible with this diagnosis. Furthermore, reduced nerve conduction velocity and the hypertrophic and demyelinating lesions found in the nerve biopsy of two patients of the original family, and, later on, at autopsy of one case also of the original family led Roussy–Levy syndrome to be considered as a variant of demyelinating Charcot–Marie-Tooth disease (CMT-1).

We have had the opportunity to follow several members of the original family over decades, and were able to perform nerve biopsy and postmortem studies of members of this family and ultimately DNA analysis of one of them. In this review, we will try to summarize our findings, which go together with the progression of our knowledge in clinical, electrophysiological, pathological, and genetic aspects of peripheral nerve disorders.

Clinical Features

As emphasized by Roussy and Levy, the clinical features of the syndrome differed from the classical CMT disease since they had an early onset with prominent ataxia, and they lacked the characteristic distal atrophy and weakness. The main distinctive features of Roussy–Levy Syndrome include: an early onset with pes cavus but with little disability, and delayed milestones. When seen after age 60 years, arched feet with hammer toes were present in all patients.

Kyphoscoliosis, subtle motor deficits with little progression over time, diffuse areflexia, slight or absent sensory impairment, balance problems with difficulty to stand still, and ataxia without cerebellar manifestations were common to all. A postural or kinetic tremor was frequently observed. Although considered a hallmark of the Roussy–Levy syndrome, postural tremor was found in four out of five patients of the original family. Whether postural tremor and the neuropathy represent a combination of two inherited disorders or whether postural tremor is a nonspecific manifestation of minimal weakness and impairment of type 1a afferent fibers, remains unsettled. Nerve conduction velocity was below $20\,m\,s^{-1}$ in the upper limbs, and often nonmeasurable in the lower extremities due to the gradual axon loss that occurs over the years. The progression of symptoms was remarkably slow since four out of five patients survived past the age of 80, and walked independently or with one stick at 70 years of age.

Morphological Findings

From a pathological point of view, the main findings were severe loss of myelinated axons associated with conspicuous irregularity of the myelin sheath. Extensive demyelination, thinly remyelinated internodes, and focal hyperplasia of the myelin sheath were present. Some surviving axons were surrounded by an abnormally thick and hyperfolded myelin sheath, while others were either thinly remyelinated or demyelinated. On teased fiber preparations, all myelinated fibers showed conspicuous abnormalities of the myelin sheath including demyelination, thinly remyelinated short internodes, hyperplastic myelin and accumulation of Schwann cell nuclei dispersed along single fibers. In some places, the thickened myelin sheath had a tomaculous (sausage-like) appearance. These pseudotomacula were so prominent that they mimicked the myelin changes seen in Wallerian degeneration in 20% of the fibers isolated in patient III-1 specimen. On cross sections, these abnormalities of the myelin sheath are comparable to those reported in patients with a mutation located in the extracellular domain of the myelin protein zero (MPZ) and in the MPZ deficient mice. It is worth noting that onion bulb formations were absent in two of the three patients whose nerve was studied morphologically (**Figures 1–3**).

Molecular Genetics

The molecular genetic study performed in four members of the family identified a previously unknown missense mutation in the third exon predicting an Arg131Lys substitution in the extracellular domain of the myelin protein MPZ that segregated with the disease. These findings indicate that the Roussy–Levy family falls into the CMT1b subgroup the group of hereditary demyelinating neuropathies.

Progress in molecular genetics demonstrated the role of the peripheral myelin proteins PMP_{22} and P_0 genes in such neuropathies termed CMT1a and CMT1b. Approximately 70% of the CMT-1 cases carry a segmental duplication of the 17p11.2-12.1 region that encompasses the PMP_{22} gene. Other patients have a point mutation of the PMP_{22} or the P_0 genes. The phenotypes associated with the chromosome 17p11.2-12.1 duplication range from the CMT to the 'Roussy–Levy' pattern. In addition to the historical aspect, the identification of a new MPZ gene mutation in the original Roussy–Levy family illustrates the limits of phenotype–genotype correlations in hereditary neuropathies.

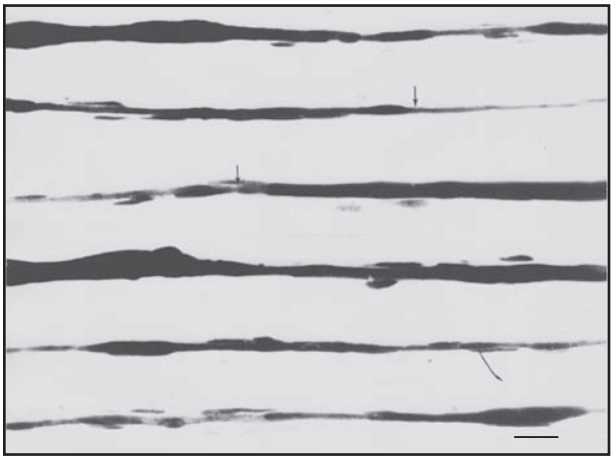

Figure 1 Consecutive segments of a teased fiber after osmication showing conspicuous irregularity of the myelin sheath (arrows) with long segments demyelinated or thinly remyelinated. Myelin sheath changes were so marked that most nodes of Ranvier were impossible to localize. Bar: 10 μm.

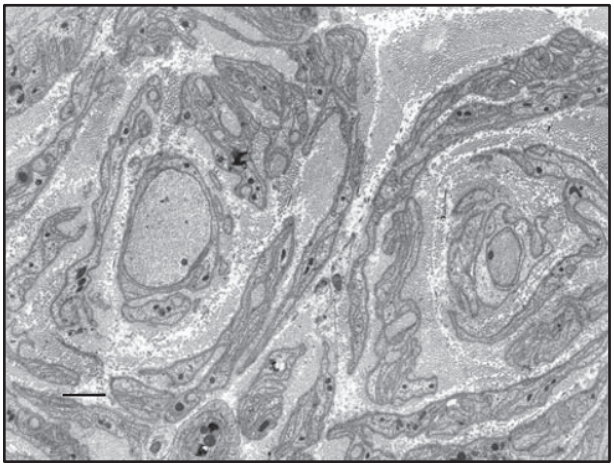

Figure 2 Electron micrograph of the same specimen (III-1) showing conspicuous onion bulb formations due to proliferation of Schwann cells (S) around demyelinated axons (A). Bar: 2 μm.

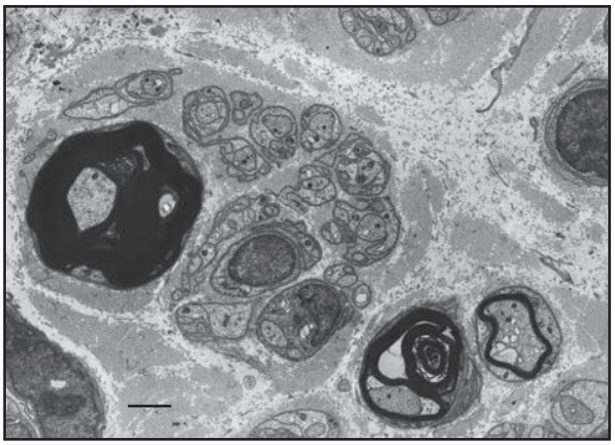

Figure 3 Electron micrograph of a nerve biopsy specimen showing a fiber with an abnormally thick and redundant myelin sheath (A) and preservation of unmyelinated fibers. Bar: 2 μm.

Summary

The Roussy–Levy disease deserves its eponym since it combines original clinical, pathological, and genetic features. Clinically, its early onset with pes cavus and predominant ataxia, tremor associated with very slow nerve conduction are different from the common patterns of CMT syndromes. Pathologically, the irregularity of the myelin sheath with extensive demyelination seems also very peculiar. The identification of a specific missense mutation in the third exon predicting an Arg131Lys substitution in the extracellular domain of the myelin protein MPZ underlines the originality of the disease. The Roussy–Levy kindred, which is clearly individualized morphologically and genetically, illustrates the overlaps between the phenotypes associated with the P_0 and PMP_{22} peripheral myelin protein disorders.

Hence, Roussy–Levy disease represents an original variant of hereditary neuropathy with a combination of characteristic clinical, pathological, and genetic features.

See also: Friedreich's Ataxia and Variants; Postural Tremor.

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rTMS

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Definition and History

Repetitive transcranial magnetic stimulation (rTMS) refers to the application of recurring TMS pulses to a brain region. The first physiological effects of rTMS on speech and counting were reported by Pascual-Leone et al. in 1991. rTMS may work by modulating the cortical excitability. rTMS has been broadly classified as high (>1 Hz) and low (1 Hz or lower) frequency. High frequency stimulation may increase cortical excitability, whereas low frequency rTMS may transiently depress cortical excitability.

rTMS has been studied as a potential noninvasive treatment in several neurological and psychiatric disorders. In movement disorders, rTMS has been evaluated as an adjunctive treatment. Compared to medications, it has the theoretical advantage of modulating specific neural circuits. The neuromodulatory effects depend on the stimulation parameters such as cortical target, frequency, intensity, duration, number of sessions, and patient factors such as disease state, individual symptoms, and state of medication treatment.

Effects of rTMS in Movement Disorders

Parkinson's Disease (PD)

In normal subjects, 10 Hz rTMS of the prefrontal cortex induces dopamine release in the caudate measured by raclopride binding, whereas motor cortex stimulation causes dopamine release in the putamen. In PD, rTMS of the more affected motor cortex caused reduced dopamine release from the putamen compared to the less affected hemisphere.

High frequency rTMS may modulate underactive brain regions in PD patients and produce clinically significant motor improvement. It has been reported that 5 Hz rTMS to the motor cortex improved reaction time and performance in a grooved pegboard test during the stimulation, but a subsequent study did not confirm the results. Some studies also reported improved motor performance after 5 Hz rTMS in PD patients, but other studies reported no effect. The normal increase in motor evoked potential (MEP) size from 5 Hz rTMS was absent in PD patients and was partially restored with dopaminergic medications. High frequency stimulation of the supplementary motor area was found to worsen motor performance in one study. Some of these differences may be due to variations in the stimulus parameters and the brain area being stimulated. More recent studies suggested that repeated sessions of rTMS may lead to improvement in the motor symptoms, and the effects may last for 1 month. Several randomized controlled trials used rTMS to treat the PD motor symptoms. These results are promising, and further studies with larger number of patients and adequate controls are needed to evaluate rTMS as a potential treatment for PD.

Low-frequency rTMS to the motor cortex has also been reported to improve motor symptoms in PD. However, some studies used very low intensity of TMS (20% resting motor threshold) and others used very low frequency of stimulation (0.2 Hz). In these studies, control conditions such as sham stimulation were not performed or may not have been adequate. One study found no effect of 1 Hz stimulation. A relatively large study involving 85 PD patients and a realistic sham control found no significant effect of 0.2 Hz rTMS although there was a significant placebo effect. Thus, low-frequency rTMS appears to have no significant effect on parkinsonian motor signs. However, low-frequency rTMS is a potential treatment for levodopa-induced dyskinesia.

Dystonia

Neuroimaging studies in patients with focal dystonia demonstrated reduced activation of the primary motor cortex and hyperactivity in frontal nonprimary motor areas during writing. Therefore, measures designed to decrease the activities of nonprimary motor areas such as the premotor cortex and the supplementary motor area might improve the dystonic symptoms. In addition, TMS studies have found reduced cortical inhibition in the motor cortex in dystonia. Low-frequency (1 Hz) rTMS over both the premotor and motor cortices was found to reduce motor cortex excitability in normal subjects. Thus, treatment strategies in focal dystonia have involved application of rTMS over the primary motor cortex or the premotor cortex, with the goal of decreasing motor cortex excitability.

In patients with focal dystonia, 1 Hz rTMS for 30 min over the dorsal premotor cortex led to a greater decrease in regional cerebral blood flow (rCBF) in the lateral and medial premotor areas, putamen, and thalamus, and a larger increase in cerebellar rCBF than in controls. These widespread changes in regional synaptic activity of the motor system, observed at rest and during movement, may represent a physiological trait that characterizes patients with focal arm dystonia.

In writer's cramp patients, suprathreshold 1 Hz rTMS over the left primary motor hand area was found to increase the area of rest MEPs, which is different from the effects observed in normal subjects. Subthreshold 1 Hz rTMS also normalized short interval intracortical inhibition and prolonged the silent period, without affecting the stimulus–response curve in writer's cramp patients. In addition, there was temporary improvement in writing with reduced writing pressure.

Tremor

In a double-blind, crossover, placebo-controlled study, low-frequency suprathreshold rTMS of the cerebellum induced short-lasting ($<$1 h) improvement of essential tremor evaluated with both clinical and accelerometric measures. However, some of the effects could be mediated by activation of the peripheral nerve fibers. On the other hand, rTMS of the motor cortex may induce a cerebellar-like and postural tremor during stimulation in normal subjects, possibly by interfering with cerebellar afferent inflow to the motor cortex. The frequency of rTMS-induced tremor is independent of stimulus parameters. Another study showed that rTMS over the premotor

cortex but not to the primary motor cortex led to a decrease in the postural tremor, and 1 Hz rTMS over premotor cortex was reported to improve cortical tremor.

Myoclonus

Low-frequency (~1 Hz) inhibitory rTMS may be able to improve myoclonus by restoring intracortical inhibition. A few reported cases illustrated the potential efficacy of low-frequency rTMS to alleviate myoclonus. Thus, in cortical myoclonus with loss of cortical inhibition, low-frequency rTMS may be a therapeutic option.

Chorea

One study found that MEP size following rTMS trains of 10 stimuli at 5 Hz was unchanged in Huntington's disease (HD), in contrast to increased MEP amplitude in healthy volunteers. The excitability of facilitatory intracortical interneurons may be decreased in HD.

The above studies showed that rTMS can help to understand the pathophysiology of movement disorders and is a promising treatment for some movement disorders. Further investigations are needed to establish its therapeutic efficacy and role in the management of patients with movement disorders.

See also: Chorea; Dystonia; Huntington's Disease; Myoclonus; Paired Pulse TMS; Parkinson's Disease: Definition, Diagnosis, and Management; Single Pulse TMS; Tremor.

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S

Sacsin

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Glossary

aCGH (array-comparative genomic hybridization) – A microarray-based comparative genomic hybridization that detects genomic copy number variations with resolution higher than that of whole chromosomes.
ASO (allele-specific oligonucleotide) – A short molecule of synthetic DNA complementary to the sequence of a variable target DNA, acting as a probe for the presence of the target.
Contiguous gene syndrome – A disorder due to deletion of multiple gene loci that are adjacent to one another; characterized by multiple, apparently unrelated, clinical features caused by deletion of the multiple adjacent genes. Each of the individual genes within a contiguous region, when mutated, gives rise to a specific feature.
EST (expressed sequence tag) – A short piece of transcribed cDNA sequence.
Founder effect – The loss of genetic variation occuring when a new population is established by a reduced number of individuals from a larger population.
Ubiquitin–proteasome system – A cellular quality control system that tags misfolded proteins for refolding or degradation.

Definition and History

Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) was first described in 1978 as an early-onset familial disease with prominent retinal striations. Over 300 patients have been identified, and most of their families originated in the Charlevoix-Saguenay region of northeastern Quebec in Canada. The frequency of several recessive diseases in these Canadian regions increased because of a founder effect caused by the settlement patterns of the late seventeenth to the mid-nineteenth centuries. The gene carrier prevalence was estimated to be 1 out of 22.

Disease presents in early childhood with ataxia and spasticity and progresses in the second and third decades. Retinal striations due to prominent myelinated nerve fibers have been variably reported in the kindreds but in the Quebec families they are always present. Deep tendon reflexes are increased. Distal weakness and atrophy and decreased sensation may occur. Some patients lack spasticity. Patients may become wheelchair-bound by their fifth decade, although this is variable. Sensory nerve conduction potentials are absent, and there is a high incidence of distal axonal neuropathy with slow onset and progression. Brain magnetic resonance imaging (MRI) shows vermian atrophy of the cerebellum as well as extensive cerebral cortical atrophy associated with secondary callosal attrition after the third decade. ARSACS patients show little cognitive impairment; they remain autonomous for all daily living tasks until the very late stages of evolution, despite their motor problems. The principal neuropathological signs are atrophy of the upper vermis and loss of Purkinje cells in the cerebellum.

SACS Locus and Its Evolution

The ARSACS (*SACS*) locus was mapped using Quebec samples to chromosome 13q11 by noting increased homozygosity for locus *D13S787*. Initially, the *SACS* gene was reported as a single, gigantic exon spanning 12.8 kb with an 11.5 kb open reading frame (ORF). Two *SACS* mutations were identified in Charlevoix-Saguenay ARSACS families, both predicted to cause the premature termination of the sacsin protein. An allele-specific oligonucleotide (ASO) based test is now used for ARSACS diagnosis or gene carrier detection for Quebec families at-risk. The human genome assembly revealed 5′ expressed sequence tags

(ESTs) with homology to *SACS*. Now, the gene has 9 exons with an ORF of 13.7 kb. It has a protein coding capacity of 4,759 amino acids, yielding a protein with an estimated molecular weight >520 kDa.

More recently, patients with diseases compatible with ARSACS have been widely recognized outside of Quebec. Although Quebec patients show a homogeneous phenotype, the disease in non-Quebec patients is often more heterogeneous. It is associated with a lower incidence of retinal hypermyelination, a juvenile or early adult onset, and slower disease evolution. A lack of spasticity and an association with intellectual impairment are also seen. To date, over 40 mutations have been found in patients from France, Holland, Belgium, Italy, Japan, Spain, Tunisia, and Turkey. All classes of mutations are represented: in addition to nonsense and missense, splice site mutations and small deletions have also been identified. Generally, the mutations are private (i.e., occurring only in a particular family or small population), but the occurrence of a founder effect for *SACS* mutation, originally useful in mapping and mutation identification in Quebec, is also observed in Dutch patients. The mutation mechanism resulting in ARSACS recently has further expanded. In a Belgian patient, a clinical condition compatible with ARSACS is caused by a heterozygous microdeletion on chromosome 13q12.12 was detected using aCHG. There is a de novo 1.54 Mb deletion encompassing SACS on one allele, while the other carries a novel missense mutation in the giant ninth exon. This microdeletion is thought to have occurred because of nonallelic homologous recombination between segmental duplications at the breakpoint-containing region. Two unrelated Italian patients also have been described with similar microdeletions that include *SACS* combined with private mutations on their other alleles. In addition to the *SACS* region deletion, these three cases also share moderate hearing impairment, the causes of which remain elusive. A recent publication suggests that ARSACS could also be a part of a contiguous gene syndrome, as both ARSACS and limb-girdle muscular dystrophy type 2C were seen in a patient because of a homozygous 584 kb deletion that contains both *SACS* and the immediate upstream gene, γ-sarcoglycan. Thus, worldwide, sacsinopathy is increasingly considered in the differential diagnosis of early-onset cerebellar ataxia with spasticity and peripheral neuropathy combined with other clinical signs.

The Sacsin Protein: Domain Structure and Function

While the initial sequence comparisons, based on the 11.5-kb ORF failed to detect extensive similarity of sacsin to known proteins, a 'DnaJ' motif was detected in the C-terminal. Both human and mouse proteins have three large segments with sequence similarity to each other, of which two show some similarity to the N-terminal domain of the Hsp90 class of heat-shock proteins. It was also noted that sacsin had similarity to the predicted product of an ORF in *Arabidopsis*. The impact of other analyses of the domain structure of sacsin has yet to be fully understood. Sacsin contains a C-terminal HEPN (higher eukaryotes and prokaryotes nucleotide-binding) domain. Although HEPN is present in many bacterial and archeabacterial species, sacsin is currently the only higher vertebrate protein known to contain it. Studies of the crystal structure of the HEPN domain from the bacterium *Thermotoga maritima* show that the domain belongs to a family of kanamycin nucleotidyl transferases. Another publication showed that sacsin has a domain with 35% sequence identity to hHR23 (human homolog of yeast Rad23); hHR23 is an interaction partner of XP-C (xeroderma pigmentosum) group C proteins, involved in global genome repair. Sacsin is the only protein outside the RAd23 family to have domain homology.

Sacsin is an apparent binding partner of a form of LDL receptor related protein (LRP1b), a protein often deleted in tumors. The same study also identified several other protein fragments with chaperone type functions as binding to LRP1B.

Once the final size of the predicted protein became unequivocal, important advances have been achieved in the understanding of sacsin function. A key publication was the elegant demonstration, using yeast two hybrid screens, that the protein is part of an ataxia and Purkinje cell degeneration network and that it shares interaction partners with other ataxia-causing proteins. The most recent and significant advance in understanding sacsin function was a publication that shows sacsin as a functional co-chaperone in the ataxin-1 pathway. When *SACS* mRNA function was inhibited by siRNA in cells that express polyglutamine (polyQ) expanded ataxin-1, this inhibition increased the cellular toxicity of the polyQ ataxin-1, suggesting that normal sacsin function is protective against the toxicity of PolyQ ataxin-1. This publication confirmed that the sacsin protein has a molecular weight of 520 kDa and that its expression is mainly neuronal. In rat brain, it is localized to the cytoplasm of neuronal cell bodies and to dendrites and axons. When the cerebellum was examined, the expression of both *SACS* mRNA and sacsin protein was highest in the Purkinje cells. The bioinformatic analysis of the N-terminal portion showed a ubiquitin-like domain (UbL) that is functional and interacts with components of the 20S proteasomal alpha subunit C8. In fact, the previously described homology to DNA repair protein Rad23 has been attributed to this UbL. Also demonstrated was that the sacsin 'DnaJ' domain can function in an in vitro assay of the Hsp70 chaperone system.

The current hypothesis of sacsin function is that it may act as a molecular scaffold for the assembly of a specific

protein complex and that the regulation of this complex requires the integration of molecular chaperone machinery and the ubiquitin–proteasome system. This hypothesis now opens new avenues of investigation to determine the specific molecular mechanism for each of the clinical signs observed, with the overall aim of developing treatments.

See also: Ataxia; Ataxin; Friedreich's Ataxia and Variants; Proteasome Function in Movement Disorders; SCA1.

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SCA1

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Glossary

Contiguous – Multiple gene loci or nucleotides that are adjacent to one another.
Gain-of-function – A mutation that confers new or enhanced activity on a protein.
Mosaicism – The condition in which an organism has two or more cell populations that differ in genetic makeup.
Polymorphic – Normal variation in a sequence of genetic information.
Transmission – The transfer of genetic information from genes to another generation, or from one location in a cell to another. For example, maternal transmission is inheritance from the mother.

Definition and History

Spinocerebellar ataxia type 1 (SCA1) is a progressive autosomal dominant disorder with cerebellar, pyramidal, and bulbar symptoms caused by a CAG expansion in the *SCA1* gene. In 1974, Yakura reported linkage of a form of autosomal dominant cerebellar ataxia with the Human Leukocyte Antigen (HLA) locus, and Jackson, in 1977, confirmed that the locus was linked to chromosome 6. In 1991, both the Orr and Zoghbi groups determined that the disease was tightly linked to genetic marker D6S89. A unique 20 year collaborative arrangement between the Orr and Zoghbi groups led to the discovery of a repeated CAG trinucleotide on the short arm of chromosome 6. With positional cloning, the *SCA1* gene was mapped, and the groups have gone on to create mouse models and elucidate much of the pathogenesis of this disease.

Pathogenesis/Pathophysiology

SCA1 is caused by a repeat expansion in the *SCA1* gene, which has two coding exons, and is located at 6p23. Normal individuals contain 6–44 CAG repeats, while affected individuals have 39–82 CAG repeats. Expansion of the repeat size depends on transmission, with 63% of paternal transmissions resulting in an increased repeat number and 68% of maternal transmissions resulting in no change or a decrease of repeat number. The CAG repeat is interrupted with a CAT in 98% of normal individuals. When this interruption is missing, the contiguous CAG repeat is more unstable and tends to expand. In the intermediate range, individuals with 39 uninterrupted repeats develop the SCA1 phenotype, but individuals with 39 interrupted repeats do not. Thus, the molecular diagnosis of SCA1 depends not just on repeat size, but on the presence of CAT interruptions as well.

The size of the CAG repeat correlates with age of onset, with the largest allele sizes seen in juvenile cases. Variation in severity and duration of disease also correlate with CAG repeat size. Offspring of an affected father trend toward having a shorter disease course and earlier age of death than offspring of affected mothers. In addition, for the same number of repeats, disease onset is earlier in men than it is in women. Disease penetrance in affected women appears to be incomplete.

The CAG repeat does not exhibit somatic mosaicism like other repeat expansions, such as muscular dystrophy or fragile X syndrome. The *SCA1* gene codes for the ataxin-1 protein. This protein, an RNA binding protein, is predominantly nuclear in neuronal brain cells, but both neuronal and cytoplasmic in Purkinje cells. In the setting of a CAG expansion in the *SCA1* gene, nuclear aggregates containing the polyglutamine protein accumulate in patient neurons, especially in the pons and substantia nigra. Mutant ataxin-1 may disrupt the function of nuclear matrix-associated complexes involved in nuclear RNA metabolism. A dominant toxic gain-of-function model has been proposed for pathogenesis, but it is unclear how the function of ataxin-1 would support this model.

Pathology shows marked loss of Purkinje cells with Bergmann's gliosis and torpedo-like formation of axons. There is severe degeneration in the olivocerebellar and dentatorubral pathways and severe atrophy of cranial nerve III and XII nuclei, with atrophy occurring at the base of the pons and in the middle cerebellar peduncles. Loss of neurons in the dorsal nucleus of raphe and depigmentation of the substantia nigra also occurs. There is extensive loss of motor neurons in the anterior horns and Clarke's nucleus. In addition, there is a loss of dendrites, reduced dendritic arbors, decreased formation of proximal spines, and abnormal accumulation of neurofilaments in affected patients. Despite a lack of parkinsonian features in the disorder, there is a marked reduction of dopamine and tyrosine hydroxylase in autopsied putamen of affected patients, with moderate to severe depopulation of pigmented dopaminergic cell bodies.

Epidemiology/Risk Factors

Unlike many of the other spinocerebellar ataxias, SCA1 has been reported widely around the world in various populations, with varying prevalence rates (**Table 1**).

Clinical Features and Diagnostic Criteria

The mean age of onset of SCA1 is $\sim 34 \pm 9$ years and duration of disease averages 14 ± 7 years. The disorder is characterized by ataxia, bulbar signs, and pyramidal involvement. In the first couple of years of illness, the typical symptoms

Table 1 Selected prevalence studies in SCA1

Population	*Movement disorder*	*Number of patients*	*Prevalence of SCA1*	*Author*
American	ADCA, ARCA, sporadic, unknown	361 families	10/361 (5.6%)	Moseley
Dutch	ADCA families	145 famiies, 391 patients	14/145 (9.6%)	van de Warrenburg
Italian	ADCA	116 families, 248 patients	28/117 (24%)	Filla
British	SCA	146	2/146 (1.4%)	Leggo
Brazilian	SCA	66	0	Jardim
Russian	ADCA	15 families	5/15 (30%)	Illarioshkin
Japanese	ADCA	349	15/155 (9.7%) familial cases	Sasaki
Indian	SCA	57	6/57(11%)	Basu
Chinese	Hereditary SCA	85 ADCA families, 37 sporadic	4/85 (4.7%) ADCA	Tang
South African	SCA	14 families, 22 sporadic	6/14 (43%), 1/22 (4.5%)	Ramesar

ADCA, Autosomal dominant cerebellar ataxia; ARCA, Autosomal recessive cerebellar ataxia; SCA, spinocerebellar ataxia.

include impaired tandem gait, mild limb ataxia, hypotonia, hyperreflexia, paresis of upward or lateral gaze, and nystagmus. In the next 5 years, patients develop worsening limb ataxia, truncal ataxia, dysarthria, and ophthalmoplegia. Amyotrophy (or pes cavus) can be seen in 57%, and dysphagia in 71% at this stage of disease. Ten years and later into the illness, dysphagia and dysphonia become more pronounced. Spasticity with hypertonia and babinski signs is present. Tongue paresis, atrophy with fasciculations, and muscular wasting can occur. Some patients develop intellectual deterioration, with prominent executive dysfunction. Late in the disease, affected patients may have euphoria, emotional lability, crying, irritability, or aggressiveness.

A large affected population with 225 SCA1 ataxic individuals showed that progressive cerebellar deficiency was present in all patients, but that associated signs (dysphagia, tongue atrophy, ophthalmoparesis, and diffuse muscular atrophy) were more likely with higher repeat numbers. Lower motor neuron involvement was seen in 15 of 22 patients with repeat sizes greater than 52. In at risk individuals, symptoms may include occasional unsteadiness, tremor, slight ataxia, or dysarthria. Juvenile onset cases (less than 18 years), that are seen in some kindreds, have larger repeat sizes and manifest typical SCA1 symptoms.

Differential Diagnosis

The two most similar spinocerebellar ataxias to SCA1 are SCA2 and SCA3. However, SCA2 tends to have earlier onset and a prominent sensorimotor neuropathy. SCA3 has many of the cerebellar and bulbar features of SCA1, but in addition, individuals have more oculomotor signs (reduction in the vestibulo-ocular reflex, bulging eyes, etc.) and may have dopamine-responsive dystonia. The other SCAs are less likely, with severe sensory disturbances common in SCA4; SCA5, SCA11, and SCA16 being more pure cerebellar syndromes; SCA10 having an association with epilepsy; and SCA13 and SCA14 having very slow progression. Tremor is seen in SCA8 and is pronounced in SCA12. Nonspinocerebellar ataxia diseases that may mimic some features of SCA1 include Huntington disease and spinal and bulbar muscular atrophy. However, both of these disorders have characteristically fewer cerebellar signs.

Diagnostic Work-up/Tests

EMG can show a mild decrease in motor and sensory nerve conduction velocities, in addition to fibrillation potentials. MRI shows early midline atrophy of the cerebellum. Later in the disease, severe cerebellar atrophy with brainstem involvement is common. Morphometry shows decreased size of the pons, cerebellar hemispheres, middle cerebellar peduncle, and medulla; with an increase in fourth ventricle size Single Photon Emission Computed Tomography (SPECT) shows a profound decrease in the *N*-acetylaspartate/Creatine (NAA/Cr) ratio in clinically affected carriers in the pons and cerebellum, which may reflect loss of neuronal variability in that region.

Management

A potential cure for SCA1 may involve altering the misfolding or nuclear transport of mutant ataxin-1. Recently published, lentivector mediated expression of Collapsin Response Associated GTpase (CRAG), a new guanosine triphosphate, in Purkinje cells of SCA mice cleared polyglutamine aggregates and rescued the mice from ataxia. A study in SCA1 transgenic mice showed that a creatine supplemented diet resulted in maintanence of Purkinje cell numbers, but did not improve or delay the development of ataxia. SCA1 knock-in mice receiving lithium had improved motor coordination, learning and memory, and neuropathologically, lithium treatment attenuated the reduction of dendritic branching in mutant hippocampal pyramidal neurons. Symptomatic treatment for gait ataxia may include medications that modify monoamine transmission, such as amantadine and buspirone, or physical therapy for gait training. Recently, case reports in three patients with ataxia show that varenicline, a partial agonist selective for $\alpha_4\beta_2$ nicotinic acetylcholine receptors and prescribed for tobacco cessation, may be helpful for gait ataxia. Dysphagia is best managed by dietary modifications.

Prognosis

Life expectancy is shortened in SCA1, with average age at death reported to be between 43.2 and 54.1 years. With repeat sizes greater than 52, individuals are more likely to have motor neuron involvement leading to progressive respiratory failure.

See also: Ataxia; Multiple System Atrophy: Animal Models; Trinucleotide Repeat Disorders.

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SCA2

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Glossary

CAG repeat – Genetic mutation characterizing the trinucleotide repeat disorders whereby abnormal numbers of CAG repeats produce the clinical syndrome.
Cerebellar ataxia – Syndrome of cerebellar and often associated brainstem dysfunction with progressive dysarthria, oculomotor abnormalities, and gait and limb ataxia.
Parkinsonism – Syndrome similar to idiopathic Parkinson's disease, characterized by some shared features such as bradykinesia, rigidity, and possibly resting tremor; may or may not respond to antiparkinsonian medications.
SCA2 – Spinocerebellar ataxia type 2; inherited autosomal dominant neurodegenerative movement disorder usually presenting as a progressive cerebellar syndrome with CAG repeat expansion on chromosome 12.

Definition and History

Spinocerebellar ataxia type 2 (SCA2) is an inherited neurodegenerative disorder; patients with this disorder typically demonstrate cerebellar dysfunction. The disorder is characterized by a CAG repeat expansion on chromosome 12, genetically identified in 1996. The spinocerebellar ataxias are a group of autosomal dominant inherited cerebellar ataxias. SCA types 1, 2, 3, 6, 7, and 17 are characterized by a CAG repeat expansion in the coding region of the gene. Prior to the discovery of the genetics, these dominantly inherited ataxias fell under the autosomal dominant cerebellar ataxias (ADCAs) classification, types 1–4; later on, in the absence of a family history, the multiple systems atrophy (MSAc) rubric might have been used. However, as Anita Harding suggested of the ADCAs, it is very difficult to separate these disorders on clinical grounds and the discovery of the genetics of the spinocerebellar ataxias (CAG repeat expansions and other genetic mutations) led to a new clinical classification. It should be noted that there are many other inherited

spinocerebellar ataxias (e.g., SCA12-nonconding CAG expansion; Friedreich's ataxia-GAA repeat expansion), episodic ataxias (e.g., channelopathies), or cerebellar syndromes of other causes (e.g., Marinesco–Sjogren syndrome).

Pathology/Pathophysiology/Genetics

The diagnosis of SCA2 is made by detection of a CAG repeat expansion, greater than 34 repeats, on chromosome 12q24.1. The CAG repeat is unstable, resulting in an earlier age of onset with successive generations (i.e., anticipation). The CAG repeat expansion in the coding region of the gene results in a polyglutamine expansion.

The parkinsonian syndrome associated with SCA2 tends to be characterized by a CAG repeat interrupted by CAA insertions, while the cerebellar syndrome of SCA2 is not associated with CAA interruptions. These CAA/CAG interruptions in the parkinsonian variant of SCA2 are thought to contribute to the relative stability of the repeat over generations, and in general, the parkinsonian variant is associated with a smaller number of repeats than the cerebellar variant. However, anticipation is associated with both variants, suggesting that anticipation may be due to factors other than the expansion of the repeat. The CAG repeat produces a polyglutamine expansion resulting in the expression of the protein ataxin-2.

The pathology of the cerebellar variant of SCA2 shows degeneration of the cerebellum and brainstem, but also the involvement of other areas of the brain, including substantia nigra, striatum, thalamus, and frontal cortex. The degeneration of the cerebellum is reflected in the loss of Purkinje cells in the cerebellar vermis and hemispheres. Ataxin-2 is infrequently detected in neuronal inclusions in comparison to other triplet repeat diseases ataxin-2 is not restricted to cerebellum but is also found in other areas of the brain. The role of ataxin-2 has not been fully defined, but the protein may play a role in RNA metabolism and the plasma membrane.

Epidemiology

In general, the spinocerebellar ataxias are relatively rare neurologic disorders. However, the frequency of each SCA varies with different ethnic populations. SCA2 has a higher prevalence in Caucasian than in Japanese populations; the prevalence of SCA2 is even higher in Cuban and southern Italian populations. In Canada and the United States, the most common (and diagnosable) SCAs are 1, 2, and 3. In the Finnish population, SCA3 is relatively uncommon, while SCA8 is more common. The prevalence of the parkinsonian variant is difficult to estimate, due in part, to underdiagnosis, but probably ranges from 1.5% to 8% of cases of inherited parkinsonism.

Clinical Features and Diagnostic Criteria

The typical cerebellar presentation of SCA2 involves the gradual onset of a cerebellar disorder involving impairment of eye movements, cerebellar dysarthria, limb and gait ataxia, and other neurologic signs mentioned previously. Other neurologic features associated with SCA2 include early slowed saccades, amyotrophy, peripheral neuropathy, dystonia, and myoclonus. A small subgroup of SCA2 patients has a predominantly parkinsonian presentation. The disease has a variable age of onset, dependent on the size of the CAG repeat expansion; the age of onset can range from childhood to late adulthood and is inversely associated with the size of the triplet repeat. The disease is inexorably progressive and results in significant disability, with the affected patient confined to a wheelchair in the later stages of the illness.

Differential Diagnosis and Diagnostic Workup

The diagnosis of SCA2 rests upon the identification of a CAG repeat expansion on chromosome 12. However, there is a differential diagnosis to be considered. A patient presenting with a cerebellar disorder should have a careful history taken regarding the onset and the rate of clinical progression. A rapid rate of progression might suggest a paraneoplastic disorder or prion disease. Family history of balance or gait disturbances as well as a family history of neurologic disorders especially parkinsonism should be reviewed. Documentation of alcohol consumption is often overlooked. The past medical history should also include any inflammatory or autoimmune disorders and a current list of medications. Workup for the ataxias may include neuroimaging (MRI) of the brain and spine, available genetic testing for cerebellar disorders, vitamin E level, testing for celiac disease, and vitamin B12 level; testing for paraneoplastic syndromes should be guided by the rate of clinical progression.

The clinical exam will also further guide the clinician in the diagnostic workup: in addition to cerebellar signs, early slowing of saccades is suggestive of SCA2; systemic signs of neoplasm would point toward a paraneoplastic syndrome; associated rapid cognitive decline may be indicative of a prion disease; and a primary midline ataxia referable to the vermis may point to excessive alcohol consumption.

A patient presenting with levodopa-responsive parkinsonism or parkinsonism with a family history of the same may be tested for SCA2 and SCA3; testing for α-synuclein, parkin, and LRRK2 may be considered, although typically not widely available. Drug-induced parkinsonism should be ruled out.

Management

At present, there are no meaningful pharmacologic treatments for the cerebellar variant of SCA2; treatment of the illness is primarily supportive, involving assessment and treatment of swallowing, balance issues, and bladder issues. Swallowing difficulties, bladder continence issues, and autonomic difficulties are present in later stages of the illness.

Those patients presenting as levodopa-responsive parkinsonism without other signs, or parkinsonism associated with other features, including restless leg syndrome, dystonia, cerebellar signs, or postural tremor. These patients can respond to use of traditional antiparkinsonian medications, including levodopa, dopaminergic agonists, and botulinum toxin. The relatively small numbers of identified parkinsonian SCA2 patients makes a general clinical prognosis difficult. Positron emission tomography in these patients shows a profile identical to that of Parkinson's disease. It has become clear that the clinical profile of SCA2 is much wider than previously thought and that patients with a familial history of parkinsonism should be tested for SCA2.

In patients with an identified SCA2 mutation, genetic counseling and testing should be offered to adult children who are at 50% risk of inheriting the disorder.

See also: Ataxia; Ataxin; Multiple System Atrophy: Animal Models; SCA1; SCA4; SCA6; SCA10; SCA11; SCA12; SCA13, 14, 15, and 16; SCA17; SCA27; Spinocerebellar Ataxia Type 19, 20, 21, 22, 23, 26; Spinocerebellar Ataxias Genetics; Trinucleotide Repeat Disorders.

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SCA3, Machado–Joseph Disease

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Glossary

ADCA – Autosomal dominant cerebellar ataxia is a heterogeneous group of inherited neurodegenerative diseases.
CAG – Cytosine–adenosine–guanosine trinucleotide encoding glutamine at the protein level.
MJD – Machado–Joseph disease designates a clinical and genetic entity of ADCA.
SCA3 – Spinocerebellar ataxia 3 designates the locus on chromosome 14 and the disease, which is also commonly called Machado–Joseph disease.

Definition and History

Autosomal dominant cerebellar ataxias (ADCA) comprise a wide spectrum of diseases with different clinical and neuropathological profiles. Machado–Joseph disease (MJD) or spinocerebellar ataxia 3 (SCA3) is the most frequent form of these diseases worldwide. MJD was initially described in patients of Portuguese-Azorean ancestry variably associating pyramidal, peripheral nerve and extrapyramidal signs, ophthalmoplegia, and dysphagia. Its locus was mapped to chromosome 14q in Japanese families with possible Portuguese origin (MJD locus) and subsequently to the same region in French families with similar clinical

presentation (SCA3 locus). Despite the absence of Portuguese ancestry in the French families and several clinical differences attributed to ethnic background, the mapping results suggested a mutation in the same gene in both clinical entities. This hypothesis was confirmed when the mutation, a CAG repeat expansion in the *MJD1* gene, was found in both groups of families and in large series of patients from various countries.

Pathogenesis/Pathophysiology

Molecular Bases

Because of the nature of the mutations, SCA3/MJD is one of the polyglutamine-coding $(CAG)_n$ repeat expansion diseases that shares common properties: (1) onset mostly in adulthood; (2) progressive, unremitting, and usually fatal disease course; (3) clinical symptoms appearing above a threshold number of CAG repeats (SCA3/MJD: >52 units, normal repeat size: 12–44 repeats, incomplete penetrance for 45–51 repeats); (4) strong inverse correlation between the number of CAG repeats and the age at onset; (5) instability of the repeat sequence that increases in size during transmission resulting in genetic anticipation; (6) ubiquitous expression of the protein; and (7) aggregation of the pathological protein into ubiquitinated neuronal intranuclear inclusions in several affected as well as in nonaffected brain structures.

Pathophysiology

Animal and cellular models have been very useful for exploring the pathophysiology. Directed expression of a human cDNA encoding the *SCA3* gene with expanded CAG repeats causes Purkinje cell degeneration and ataxia in transgenic mice and neuronal degeneration in flies. That expansion alters the conformation of polyglutamine tracts in the product of the gene, ataxin-3, which could explain the formation of insoluble intranuclear aggregates that have also been detected in the brains of patients and models, and appear to constitute a common signature of polyglutamine disorders. However, these aggregates are also present in nonaffected neuronal and nonneuronal tissues in various models, indicating that their presence is not sufficient to cause cell death and/or the phenotype. Despite these unifying features of polyglutamine diseases, clinical symptoms are diverse, suggesting that protein sequences outside the polyglutamine tract contribute to the pathogenesis, and that normal functions of ataxin-3 might be partially involved in the specificity of the degenerative process. It has been suggested that ataxin-3 could be involved in the ubiquitin proteasome system with characteristics of an ubiquitin protease and in transcription regulation as a transcriptional repressor via interaction with the major histone acetyltransferase CREB-binding protein and histone deacetylase 3. Indeed, these functions have been found to be altered in models.

Promising therapeutic avenues that have been successfully applied to SCA3 models include RNA interference and increased autophagy.

Epidemiology/Risk Factors

Although in most countries SCA3/MJD is the major locus for autosomal dominant forms of cerebellar ataxia (~30%), its relative frequency varies widely according to the geographical origin; SCA3/MJD represents 80% of affected families in Portugal (SCA3/MJD prevalence reaches 1 out of 4000 in the Azores Islands) and is also frequent in Germany (49%), Japan (39%), and France (30%), but has only exceptionally been detected in Italy. These differences are the result of regional founder effects and migrations with a major lineage that may have occurred more than 5000 years ago in Asia and were transmitted by Portuguese sailors to Europe and then to the Americas.

De novo mutations from the expansion of large normal alleles are rare in ADCA and have only been reported in SCA7 patients. Even if never observed in SCA3, this is also likely the case since pathological flanking haplotypes are also found associated with large normal alleles of over 33 repeats.

Clinical Features and Differential Diagnosis

Clinical Presentation in Patients

Onset mainly occurs during the fourth and fifth decades but is known to manifest as early as 5 years and also as late as 70 years of age. However, compared to other forms of ADCA, cases with onset before age 20 are exceptional. No single clinical sign is specifically associated with SCA3/MJD compared to other SCAs (see **Table 1**). However, characteristic combinations of several signs in affected family members characterize the phenotype of SCA3/MJD: cerebellar ataxia associated with pyramidal signs, some dystonic postures, and axonal neuropathy. SCA3/MJD patients, such as SCA6 patients, frequently present with cerebellar oculomotor signs such as saccadic smooth pursuit, gaze-evoked nystagmus, and diplopia. Myokymia and bulging eyes are not specific for SCA3/MJD and can be found in SCA1 and 2 in equal frequencies. Interestingly, some patients present with a parkinsonian syndrome responding well to levodopa treatment and showing treatment complications such as fluctuations and dyskinesias, reminiscent of typical Parkinson's disease. This can be associated with orthostatic hypotension as seen in multiple system atrophy.

Table 1 Frequency of neurological signs associated with SCA3/MJD mutations (based on the authors' observations)

Cerebellar syndrome	+++
Cerebellar dysarthria	+++
Extensor plantar reflexes	++
Brisk reflexes	++
Diminished or abolished reflexes	++
Spasticity in lower limbs	++
Wasting	++
Extrapyramidal syndrome/dystonia	+
Myoclonus	±
Gaze evoked nystagmus	+++
Supranuclear ophthalmoplegia	++
Decreased saccade velocity	+
Decreased visual acuity	0
Bulging eyes	+
Myokymia	+
Decreased vibration sense at ankles	+
Dysphagia	++
Sphincter disturbances	++
Cognitive difficulties	+
Tremor	±
Axonal neuropathy	++
Decreased hearing acuity	0

Frequency: 0 = absent; ± = rare; + = 5–24%; ++ = 25–74%; +++ = 75–100%.

Brain Imaging and Neuropathological Lesions

Cerebral magnetic resonance imaging of SCA3/MJD cases is characterized by severe pontine and spinal cord atrophy with moderate cerebellar vermian atrophy.

At autopsy, lesions of the basal ganglia, intermediolateral column, and Clarke's column are severe compared to other SCAs, but the Purkinje cells, inferior olives, and posterior column are spared. This profile varies as a function of CAG repeat size.

Factors Influencing Intrafamilial Clinical Variability

The major factors that influence phenotype are the size of the repeat expansion and disease duration at the time of examination:

1. the frequency of clinical signs such as dysphagia or sphincter disturbances increase with disease duration.
2. CAG repeat size influences the age of onset and clinical profile. There is an inverse correlation between the age of onset and CAG repeat length in SCA3, with a correlation coefficient varying from −0.67 to −0.92. The repeat length only partially explains the variability in age of onset and other factors, including normal allele size and homozygosity, that influence clinical onset. In addition, the frequency of pyramidal signs increases with the size of the expanded repeat, whereas the frequency of altered vibration sense decreases. Late onset SCA3 patients often present with peripheral neuropathy (areflexia and wasting) and have small CAG expansions. Some patients with small SCA3/MJD expansions can present with late onset DOPA-responsive parkinsonism. The presence of mild axonal neuropathy helps to distinguish these patients from patients with idiopathic Parkinson's disease. On the other hand, SCA3 patients with large expansions usually suffer from dystonic postures.

Management

Molecular analysis permits routine diagnostic testing of affected individuals. DNA testing is offered to asymptomatic at-risk individuals in specialized centers with multidisciplinary teams including a geneticist, psychologist, and neurologist. Therapy is symptomatic, mainly targeting the most involved systems: physiotherapy for gait and balance, exercises for cerebellar involvement, levodopa therapy for parkinsonism, botulinum toxin injections for dystonia, and spasticity. Depression is frequent in SCA3/MJD and should be treated, and psychological support should be proposed to the patient and the family. The number of CAG repeats on the expanded allele is a major factor, but given individual variations, age of onset cannot be precisely predicted from the number of CAG repeats.

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See also: Multiple System Atrophy: Animal Models; SCA1; SCA2; SCA4; SCA5; SCA6; SCA7, Spinocerebellar Ataxia with Macular Dystrophy; SCA8; SCA10; SCA11; SCA12; SCA13, 14, 15, and 16; SCA17; SCA27; Spinocerebellar Ataxia Type 19, 20, 21, 22, 23, 26; Spinocerebellar Ataxias Genetics.

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SCA4

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Glossary

Allelic – Allelic of or relating to alleles. An allele is one member of a pair or series of genes that occupy a specific position on a specific chromosome.
Anticipation – The phenotype of the mutant allele increases in severity as it is passed down the generations.
Polyglutamine – CAG, which is a trinucleotide, codes for an amino acid called glutamine. When CAG repeats are expanded pathologically in the human genome, these repeat disorders are collectively known as polyglutamine diseases.

Definition and History

Spinocerebellar ataxia type 4 (SCA4) is an autosomal dominant disorder characterized by a prominent sensory axonal neuropathy, cerebellar, and pyramidal tract signs. A large family with the disorder in Utah and Wyoming led to one of the first major descriptions of SCA4 from the Flanigan group. Subsequent work in SCA4 has also been done in a large affected family from Germany, with multiple studies reported by Hellenbroich. In 1954, Biemond described six patients in a family with severe sensory loss and ataxia, with degeneration of the posterior columns on pathology. He termed the disorder 'ataxie héréditaire des cordons posterieurs.' Two siblings were then reported in 1997 with a similar phenotype, but it is not clear that these cases or the Biemond cases are SCA4 due to the lack of linkage studies in these cases.

Pathogenesis/Pathophysiology

SCA4 has been localized to a 3.69 cM interval on chromosome 16q24. A study investigating 34 candidate genes in this region involved in protein degradation or correlated with neuronal inclusions did not result in detection of the causative mutation for SCA4. Once the original descriptions of the linkage to 16q were reported, a number of Japanese groups reported a pure cerebellar syndrome also linked to this region. The causal mutation was discovered

in 2005 for this Japanese syndrome and was a heterozygous C-to-G single nucleotide substitution in the *puratrophin*-1 gene in the 16q region. Due to the lack of sensory neuropathy in the Japanese ataxia families, it is likely that that the Japanese ataxia and SCA4 are not allelic.

Anticipation can be seen in some individual pedigree branches, but is not universally present. The five generation German family did show some anticipation with the average age of onset of 53.3 ± 6.7 years in the first generation, average age of onset of 37.4 ± 11.7 in the fourth generation, and average age of onset of 25.3 ± 3.3 in the fifth generation. Pathology of one of the affected German SCA4 individuals showed widespread cerebellar and brainstem neurodegeneration. There was marked neuronal loss in the substantia nigra, ventral tegmental area, multiple cranial nuclei, the nucleus raphe interpositus, dorsal column nuclei, and the inferior olive. In addition, there was severe neuronal loss in the Purkinje cell layer of the cerebellum and in the cerebellar fastigial nucleus. Pathology of two Italian patients with possible SCA4 showed similar findings, with abnormalities primarily in the cerebellar Purkinje cell layer, dorsal root ganglia, and posterior columns.

The antipolyglutamine antibody 1C2 failed to detect any polyglutamine-related immunoreactivity in the abnormal central nervous system regions. This may suggest that the disease is not related to a CAG or glutamine expansion or that the expansion is located in a nontranscribed region of the gene.

Epidemiology/Risk Factors

The prevalence for SCA4 has not yet been well determined in ataxia populations as the gene causing the disorder has not been discovered. The disorder is likely to be rare due to its description in only a couple of families to date.

Clinical Features and Diagnostic Criteria

The median disease onset is 39.3 years with a range of 19–59 years. The earliest noted symptom in affected individuals is gait disturbance, but a subclinical neuropathy may be the first true sign of disease. Subsequently, difficulty with fine motor tasks and dysarthria occur and eventually patients develop gait ataxia severe enough to lead to wheelchair dependence. All individuals with SCA4 have sensory findings, with 100% having decreased sensation and vibration and loss of ankle jerks. The majority (95%) of patients also have decreased pinprick, with a smaller percentage having complete areflexia (25%), extensor plantar responses (20%), and distal weakness (20%). Gait ataxia is a characteristic feature in 95%, with the majority of patients having limb dysmetria as well. Oculomotor signs are less frequent, with slight saccadic pursuits occurring in 15%.

In two Italian patients with possible SCA4, decreased pinprick and light touch was seen in the distribution of the trigeminal nerve, with one patient having sensory loss on the anterior chest and abdomen. Vertical gaze evoked rotatory nystagmus was seen in one patient. Detailed descriptions of the five generation German family confirmed previous reports of clinical features with 100% of the affected individuals having ataxia, dysmetria, dysarthria, absent sural sensory nerve action potentials, and cerebellar atrophy on MRI/CT. Less frequently seen were saccadic pursuits in 57%, reduced compound motor action potentials in 38%, and extensor plantar response in 7%.

Differential Diagnosis

Other diseases that may present similarly to SCA4 include Friedreich ataxia (FA) due to the fact that both diseases share areflexia and dorsal column involvement. Ataxia with isolated vitamin E deficiency (AVED) may also present similarly and can be evaluated by serum vitamin E levels. A family history may help to determine inheritance pattern, with an autosomal recessive pattern seen in both FA and AVED. SCA 1–3, 7–8, and dentatorubropallidal luysian atrophy do not typically have severe sensory disturbances. SCA 5–6 and 11 are pure cerebellar disorders, making them less likely. Individuals with SCA12 and the fragile X-associated tremor/ataxia syndrome have kinetic tremor. SCA10 is associated with epilepsy, SCA13 with mental retardation, SCA16 with axial myoclonus, and SCA17 with dementia.

Diagnostic Work-up/Tests

Nerve conduction tests are abnormal in most affected individuals, with most having absent sural sensory nerve action potentials and a smaller percentage lacking radial sensory nerve action potentials. In an Italian man with possible SCA4, median and tibial nerve sensory evoked potentials were not elicitable and sural nerve biopsy showed markedly reduced myelinated axons. MRI shows mild dilatation of the sulci and ventricles and mild atrophy of the cerebellar folia in earlier stages of the disease. Diagnostic testing for SCA4 is not yet available as the causal gene mutation has not yet been identified.

Management

It is unknown whether SCA4 represents a polyglutamine disorder and therapies directed to the pathophysiology are likely to be lacking until the gene is discovered. Symptomatic treatment for gait ataxia may include

medications that modify monoamine transmission, such as amantadine and buspirone. However, studies with these medications have been small, with one being open label. Recently, case reports in three patients with ataxia show that varenicline, a partial agonist selective for $\alpha4\beta2$ nicotinic acetylcholine receptors and prescribed for tobacco cessation, may be helpful for gait ataxia. Despite sensory symptoms in the disorder, most patients do not complain of pain. Dysphagia is best managed by dietary modifications and individuals with nystagmus may respond to a variety of medications reported effective in case reports.

Prognosis

Prognosis for the disorder has not been well described due to the small sample size of affected individuals, but wheelchair dependence later in the disease is common.

See also: Ataxia with Isolated Vitamin E Deficiency; Friedreich's Ataxia and Variants; SCA5.

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SCA5

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Glossary

ADCA – Autosomal dominant cerebellar ataxia is a heterogeneous group of inherited neurodegenerative diseases.

CAG – Cytosine–adenosine–guanosine trinucleotide encoding glutamine at the protein level.

SCA5 – Spinocerebellar ataxia 5 designates the locus on chromosome 11, and the disease.

β-III Spectrin – Protein component of the cellular cytoskeleton, encoded by the spectrin β nonerythrocytic 2 (*SPTBN2*) gene.

Definition and History

Spinocerebellar ataxia type 5 (SCA5) is a rare form of autosomal dominant cerebellar ataxia (ADCA), a clinically and neuropathologically heterogeneous group of diseases for which different genes have been identified. Polyglutamine-coding $(CAG)_n$ repeat expansions have been identified as responsible for the disease in six of the most frequent causative genes, while, more recently, conventional mutations have been reported in six other genes, including *SPTBN2*, responsible for SCA5.

The SCA5 locus was assigned in 1994 to the centromeric region of chromosome 11 in a single large American

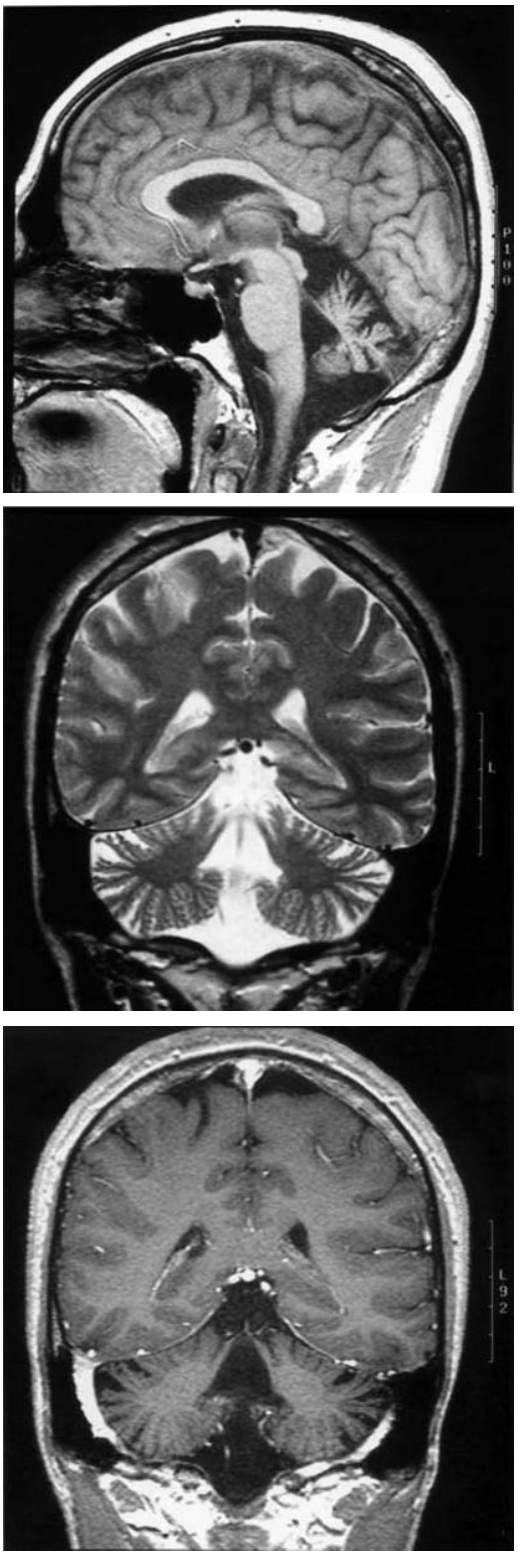

Figure 1 Sagittal T1-(top) and coronal T2- and T1-(middle, bottom, respectively) weighted magnetic resonance scans of a SCA5 patient with 4 years of disease duration showing severe atrophy of the vermis and hemispheres with sparing of the brainstem. Reproduced from Stevanin et al. (1999) Clinical and MRI findings in spinocerebellar ataxia type 5. *Neurology* 53: 1355–1357, with permission from Wolters Klumer Health (http://lww.com).

family descending from the grandparents of President Lincoln, which suggested that his gait and coordination signs were in fact early stages of SCA. Two additional families with European ancestry were subsequently reported in France and Germany, which helped narrow the disease locus to a 5.15 Mb interval in 11q13. Following a decade of positional cloning efforts, three different mutations in the *SPTBN2* gene, encoding β-III spectrin, were identified in these three large families, which highlight the defect of the cellular cytoskeleton as a new mechanism leading to cerebellar degeneration.

Pathogenesis/Pathophysiology

Three different SPTBN2 mutations have been identified in affected members of the three SCA5 families: (1) a 39-bp deletion in exon 12, leading to an in-frame deletion in one of the spectrin repeat domains (p.E532_M544del) in the American kindred, (2) an in-frame 15-bp deletion in exon 14 in the same spectrin repeat, in the French family (p.L629_R634delinsW), and (3) the c.758T > C transition in exon 7, leading to a missense mutation (p.L253P) in the calponin homology domain, in German patients.

The mechanisms linking these mutations to the ataxic phenotype in patients are not fully understood. However, β-III spectrin is highly expressed in Purkinje cells and may be involved in organelle transport and in stabilization of membrane proteins. Indeed, synaptosomal localization and stabilization at the plasma membrane of the excitatory-amino-acid-transporter-4 (EAAT4), a Purkinje cell-specific glutamate transporter, are disrupted compared to the wild-type protein by overexpression of the American mutation in vitro. It should be noted that antisense knockdown of EAAT4 is known to produce a progressive ataxia in rats, and that this gene is downregulated in the SCA1 mouse model. It remains to be determined if the two other SPTBN2 mutations, particularly the different mutation found in the German kindred, similarly affect the function of the β-III spectrin. This is the first spectrin, component of the cytoskeleton, connected to cerebellar ataxia.

Epidemiology/Risk factors

Inherited forms of cerebellar ataxia account for 1–5 out of 100 000 people. SCA5 is likely a rare form of ataxia for three reasons: (1) the three mutations identified were not found in a large series of 310 dominant and sporadic ataxia patients of German ancestry, (2) no new mutations were found by direct sequencing of 22 unrelated German patients, (3) linkage to the SCA5 locus was excluded in seven French kindreds with a similar phenotype. The relative frequency of SCA5, however, is yet to

be determined in large series of patients, using a large-scale mutation screening, but the size of the gene precludes its analysis on a routine basis.

Clinical Features and Differential Diagnosis

The increasing number of genetically defined subtypes of SCAs reported in the past two decades has shown that there is a broad overlap of phenotypes. There are, however, clinical features that point toward some specific SCA types: gaze-evoked nystagmus in SCA3, retinal degeneration in SCA7, slow eye movements in SCA2, and pyramidal signs in SCA1. Pure forms of ADCA, which include SCA5, are defined by the fact that after 10 years of disease duration, there are no additional neurological signs associated with the cerebellar syndrome. Compared to other types, age of onset of SCA5 is usually older and disease progression is relatively slower.

The three SCA5 families reported are Caucasian. Overall, although SCA5 is disabling, the clinical picture is milder than in many other forms of ataxia, in that patients have a very slow disease progression, reminiscent of SCA6.

The mean age of onset and its range are similar in the three families (ranges 10–68, 14–40, and 15–50 years in the American, French, and German patients, respectively) and are discordant with the late onset that was thought to characterize pure cerebellar ataxias. Clinical anticipation affecting the age of onset is also suggested in these families, but although the mutations have been identified, the underlying mechanisms remain unknown.

Patients present with a pure cerebellar syndrome with gaze-evoked nystagmus sometimes occurring prior to the development of other features. Facial myokymia, tremor at rest as well as postural and action tremor, writer's cramp, and decreased vibration sense are also occasionally observed and reflect secondary lesions of structures other than the cerebellum or its pathways. These signs are also observed in other SCAs; however, they do not represent specific features of this genetic subform.

On brain imaging, SCA5 primarily affects, even after short disease duration (**Figure 1**), both the cerebellar vermis and hemispheres, and spares regions of the brainstem and the cerebrum. Cerebellar atrophy is usually global and severe and is strikingly similar to that observed in SCA6 patients.

Management

Confirmatory diagnostic testing and presymptomatic/prenatal diagnosis are possible, with a detection rate close to 100% in the SCA5 families.

There is no specific drug therapy for this neurodegenerative disorder. Therapy remains purely symptomatic (physiotherapy for gait and balance disturbances).

Acknowledgments

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See also: Ataxia; SCA1; SCA2; SCA3, Machado–Joseph Disease; SCA4; SCA6; SCA7, Spinocerebellar Ataxia with Macular Dystrophy; SCA8; SCA10; SCA11; SCA12; SCA13, 14, 15, and 16; SCA17; SCA27; Spinocerebellar Ataxias Genetics.

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SCA6

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Glossary

Ataxia – Impairment of balance and coordination.
Calcium channel – A large class of physiologically important multi-subunit membrane proteins which are voltage-gated, allowing the passage of calcium ions into a cell upon membrane depolarization.
Cerebellum – Structure located behind the brainstem involved in the coordination of movement; cerebellar connections include the primary motor cortex, the spinal cord, the thalamus, and the vestibular nuclei.
Nystagmus – Biphasic involuntary movements of the eye, named for the direction of the fast phase, which may occur spontaneously or be evoked by gaze or positional changes; commonly resulting from damage to the cerebellar and/or vestibular systems.
Spinocerebellar ataxia – An extensive class of hereditary neurodegenerative disorders characterized primarily by degeneration of the cerebellum and its pathways and manifesting clinically as a progressive dysfunction of balance and coordination.

Definition and History

The spinocerebellar ataxias (SCAs) make up a large diverse group of hereditary disorders which can be generally defined as autosomal dominant neurodegenerative conditions involving dysfunction of primarily the cerebellum and its pathways, resulting in progressive impairment of balance and coordination. Many of the disorders grouped under this heading (and discussed in other entries) may also involve additional brain regions and include features such as peripheral neuropathy, pyramidal or extrapyramidal features, cognitive or psychiatric disturbances, or epilepsy. Spinocerebellar ataxia type 6 (SCA6) is often considered a pure cerebellar ataxia with minimal associated features and can be considered as a prototypical spinocerebellar ataxia for illustrative purposes when discussing the class.

In 1997, following the molecular identification of polyglutamine-encoding CAG repeat expansions in a number of neurodegenerative diseases, Zhuchenko et al. examined the role of such repeats in novel genes potentially involved in neurodegeneration. They identified a specific human α_{1A}-calcium channel as a candidate gene due to the presence of polymorphic CAG trinucleotide repeats encoding a C-terminal polyglutamine tract in several isoforms. A screening of patients with late-onset progressive ataxia identified eight unrelated patients whose disease was associated with expansion of these repeats. Four of these patients had similarly affected relatives, and the repeat expansions segregated with the disease in an autosomal dominant manner. This hereditary ataxia was termed spinocerebellar ataxia type 6 (SCA6).

Pathogenesis/Pathophysiology

The human α_{1A}-calcium channel gene associated with SCA6 is now commonly known as the *CACNA1A* gene. This gene, located on chromosome 19p13, encodes the neuronal P/Q-type voltage-gated calcium channel α_1-subunit, $Ca_v2.1$, which forms the voltage-sensitive ion pore. The $Ca_v2.1$ calcium channel is found throughout the human brain, but is particularly concentrated in the cerebellum, including Purkinje cells, granule cells, and cells of the molecular layer, where it is thought to be involved in synaptic transmission. The C-terminus of the protein contains the CAG repeat region expanded in SCA6 (**Figure 1**). Missense and nonsense mutations elsewhere in the *CACNA1A* gene have been reported to disrupt its function and cause other neurological disorders, including familial hemiplegic migraine type 1 (FHM1) and episodic ataxia type 2 (EA2), variably associated with progressive cerebellar ataxia.

The trinucleotide repeat region is located in the C-terminus of the protein and appears to be quite stable with limited intergenerational expansion. The pathological number of repeats is also not marked, with a range that would be considered normal for most of the other SCAs. The normal number of CAG repeats in the *CACNA1A* gene varies from 4 to 18, with 19–20 repeats being intermediate and often nonpathogenic, and repeat numbers of 21 or greater resulting in the SCA6 phenotype. The age of onset appears to inversely correlate with the number of repeats. Of note, extensive alternative splicing generates a variety of *CACNA1A* isoforms where the C-terminus is either coding or noncoding. When part of the coding region, a string of polyglutamine residues is expressed, similarly to most other SCAs.

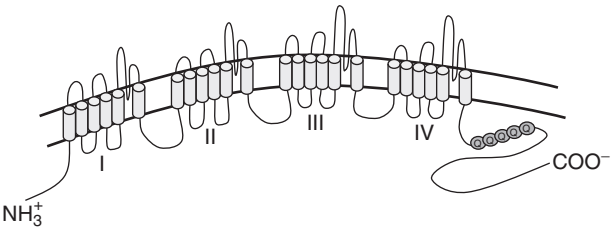

Figure 1 Structure of $Ca_v2.1$, the human P/Q-type α_1-subunit of the neuronal voltage-gated calcium channel associated with SCA6. The protein is depicted within a cell membrane. The four domains which contribute to the formation of the voltage-sensitive ion pore are indicated. The location of the intracellular polyglutamine (Q) repeat region expanded in SCA6 is shown.

The pathogenesis of SCA6 is not yet fully established and may involve contributions both from channel disruption and from polyglutamine toxicity. Studies of channel properties have been inconsistent, showing either gain or loss of function depending on the study and the experimental system utilized. Pathologically there is a loss of Purkinje cell neurons, and cytoplasmic and nuclear polyglutamine aggregates have been detected in cerebellar Purkinje cells. More recent studies have shown that the C-terminus of $Ca_v2.1$ is cleaved and transported to the nucleus both in vivo and in vitro and that the expanded polyglutamine repeats seen in SCA6 are toxic to cultured cells in vitro. This mechanism of action is most consistent with other polyglutamine disorders. This is also consistent with data from a transgenic SCA6 animal model where the murine *Cacna1a* gene was replaced with the human version and no significant differences were detected in the properties of either the normal or expanded CAG repeat mutant channels when expressed in cerebellar Purkinje cells. However, given that symptoms of ataxia are seen with non-CAG mutations in *CACNA1A* and that episodic vertigo and ataxia in some SCA6 patients may be clinically indistinguishable from EA2, impairment of channel function likely contributes to the pathogenesis to some degree. Further study is necessary to determine the precise molecular pathogenesis of SCA6.

Epidemiology

SCA6 is found worldwide but appears to be most prevalent in the countries of Japan and Germany. Interestingly, it is relatively rare in certain populous countries such as China, India, Italy, or Brazil. In the United States, SCA6 is one of the most prevalent SCAs, estimated to account for 15% of adult-onset dominant ataxia, on par with SCA2 (15%) and SCA3 (20%).

Clinical Features and Diagnostic Criteria

SCA6 is clinically characterized primarily as a progressive cerebellar ataxia, leading to it often being referred to as a pure cerebellar ataxia. Patients present with appendicular and gait ataxia, dysarthria, gaze-evoked nystagmus (both horizontal and vertical), cerebellar eye movements, and neurootological dysfunction, including positional vertigo and downbeat positional nystagmus, which can precede progressive ataxia by decades. In some cases, patients may exhibit exacerbation of symptoms with physical or emotional stress. A key physical finding seen in SCA6 is downbeat nystagmus that can be present in primary position or accentuated on horizontal gaze. It is important to note, however, that features such as pyramidal or extrapyramidal signs, peripheral neuropathy, or cognitive impairment may also be observed, albeit less frequently. Average onset is near 50 years of age.

Differential Diagnosis

The evaluation of a patient presenting with a late-onset ataxia can be quite extensive as multiple acquired etiologies cause such symptoms in addition to hereditary and sporadic conditions. The details of such screening is too extensive to be discussed here (see Further Reading) but should include a detailed medical history particularly concerning the family history, magnetic resonance imaging (MRI) of the brain and possibly the spinal cord, as well as additional testing for autoimmune, metabolic, nutritional, infectious, and neoplastic conditions among others. Once acquired causes are excluded, a detailed evaluation of hereditary disorders can be initiated. Based upon historical, clinical, and phenotypic characteristics, genetic testing may then be performed if indicated.

A key historical feature aiding in the diagnosis of SCA6 is that the average age of onset is ~50 years compared to ~30 years for other SCAs. Because the onset is often quite late and the condition can progress slowly, symptoms may be attributed to other medical conditions and patients may not be recognized as having an ataxic syndrome. Therefore, when mild, the disorder can often be overlooked within a family and patients seen in initial evaluation may report negative family histories. Consequently, it is important to rule out SCA6 in all patients presenting with a familial or sporadic ataxia with onset of symptoms after age 40.

Diagnostic Work-up/Tests

There are no common laboratory tests diagnostic or suggestive of SCA6. MRI of the brain will typically show

isolated cerebellar atrophy without brainstem or spinal cord involvement. Neurootologic testing shows abnormal oculomotor findings with impaired suppression of vestibular nystagmus, a poor optokinetic response, and saccadic pursuit with dysmetria despite normal saccade velocity. DNA testing to determine if there is an expansion in the number of CAG repeats present in either allele of the *CACNA1A* gene is the definitive test for SCA6.

Management

Genetic counseling is an important consideration for all patients and their families, particularly since many patients will have children of reproductive age by the time of diagnosis. As this is a progressive illness, it is important for physicians to be cognizant of how their patients are coping with their disease and managing their daily living activities with as much independence and safety as is possible. Physical therapy, especially for gait, balance, and strengthening trunk muscles, can be useful for maintaining functionality. Occupational therapies can assist with the independent performance of activities of daily living and speech therapies can assist with problematic dysarthria and dysphagia. Social work and mental health services may also be appropriate for certain patients.

No effective medical treatment for preventing or arresting the course of disease has been established through clinical trials, and management is therefore exclusively symptomatic. While no pharmacologic agents have been reproducibly shown to benefit SCA6 patients with slowly progressive ataxia, those with transient recurrent vertigo and ataxia have shown a response to acetazolamide (see Further Reading).

Prognosis

Like all other SCA patients, individuals with SCA6 experience progressive decline in cerebellar function and may become wheelchair-dependent and have significant difficultly with typical activities of daily living. However, SCA6 patients tend to have a later onset, milder symptoms, and slower disease progression. As brainstem and autonomic functions remain intact, lifespan does not appear to be significantly altered by the course of this disease.

See also: Ataxia; Ataxia (Familial Cerebellar) with Muscle CoQ_{10} Deficiency; Ataxia with Isolated Vitamin E Deficiency; Ataxia-Telangiectasia; SCA1; SCA2; SCA3, Machado–Joseph Disease; SCA4; SCA5; SCA7, Spinocerebellar Ataxia with Macular Dystrophy; SCA8; SCA10; SCA11; SCA12; SCA13, 14, 15, and 16; SCA17; SCA27; Spinocerebellar Ataxia Type 19, 20, 21, 22, 23, 26; Spinocerebellar Ataxias Genetics.

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SCA7, Spinocerebellar Ataxia with Macular Dystrophy

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Glossary

ADCA – Autosomal dominant cerebellar ataxia is a heterogeneous group of inherited neurodegenerative diseases.
CAG – Cytosine–adenosine–guanosine trinucleotide encoding glutamine at the protein level.
Dyschromatopsia – Loss of ability to perceive colors.
SCA7 – Spinocerebellar ataxia 7 designates the locus on chromosome 3, the gene name and the disease associating cerebellar ataxia with macular degeneration.
STAGA – SPT3/TAF9/GCN5 acetyltransferase complex involved in transcription regulation.
TFTC – Tata binding protein-free TAF-containing complex involved in transcription regulation.

Definition and History

Spinocerebellar ataxia 7 (SCA7) is a rare autosomal dominant neurodegenerative disorder initially described by Professor Jules Froment (Hospices Civils de Lyon, France) in 1937, and later designated olivo-ponto-cerebellar-atrophy type III or autosomal dominant cerebellar ataxia (ADCA) type II. Patients present with cerebellar ataxia and visual impairment because of moderate to severe neuronal loss in the cerebellum and associated structures and degeneration of cone and rod photoreceptors. The responsible locus, SCA7, was mapped to chromosome 3p in the 1990s, and the causative gene was subsequently identified in 1997, thanks to the marked phenomenon of anticipation that oriented researchers toward a trinucleotide CAG repeat expansion as the mutation. SCA7 is indeed caused by an unstable CAG repeat expansion (36–460 units) in the *SCA7* gene, leading to an elongation of a polyglutamine tract in the ataxin-7 protein – a mechanism involved in other disorders also known as polyglutamine diseases.

Pathogenesis

Molecular Bases

The *SCA7* CAG repeat is polymorphic, with sizes ranging from 4 to 35 units in controls, and from 36 to 460 in SCA7 and at-risk carrier chromosomes. Incomplete penetrance is suspected in patients with 36 repeats. Expansions are unstable, particularly during paternal transmissions. The size of the largest expansion and the degree of gonadal instability in SCA7 are greater than those observed in any of other known polyglutamine diseases, and the genomic context has been suspected to play a role in this phenomenon.

Normal Function of Ataxin-7

Ataxin-7 is a ubiquitously expressed protein of 892 amino acids and contains an N-terminal polyglutamine tract, several protein interaction domains, nuclear localization and export signals, and two caspase 7 cleavage sites. It is found in the cytoplasm of all the populations of neurons analyzed in control brains, but a nuclear labeling is observed in some neurons with a frequency and intensity weakly correlated with the topography of lesions in patients. Ataxin-7 is a component of the Tata binding protein (TBP)-free TAF-containing complex (TFTC) and the SPT3/TAF9/GCN5 acetyltransferase complex (STAGA), which is implicated in several steps of transcriptional regulation such as histone acetylation/deubiquitinylation and recruitment of the pre-initiation complex to promoters.

Pathophysiology

As in other polyglutamine diseases, the expansion is expected to confer toxic properties to the mutant protein, which also accumulates aberrantly in neurons in patients and cellular/animal models, leading to the formation of insoluble nuclear inclusions. The relationship between toxicity and aggregation is still a matter of debate. In SCA7, these inclusions were shown to contain cell stress markers in cell cultures and mouse models, but they are not restricted to the affected brain regions, suggesting that their presence is not sufficient to initiate the degenerative process. The inclusions may therefore be simply a pathological hallmark of the diseases and/or a cellular defense mechanism. If they are not responsible for the initiation of the disease, they may be implicated in disease progression and severity. Interestingly, withdrawal of the expression of pathological ataxin-7 in an inducible SCA7 model in Drosophila improved locomotion and longevity as well as disaggregation of inclusions, suggesting that a therapeutic intervention aimed at preventing the nuclear accumulation or increasing the clearance of the mutant proteins might be protective against polyglutamine toxicity. Clearance of the pathological protein was also obtained by increasing the expression of promyelocytic leukaemia protein (PML) that

often colocalizes with inclusions in the brains of SCA7 patient or other polyglutamine disorders, suggesting that PML nuclear bodies play a role in the pathogenesis of SCA7 and might be effective therapeutic targets.

On the other hand, the polyglutamine expansion in ataxin-7 might also impair the activity of TFTC/STAGA complexes independently of aggregate formation; this probably accounts for chromatin remodeling and transcription defects observed in SCA7 models.

Epidemiology/Risk Factors

Although rare, SCA7 is detected in patients of various ethnic and geographical origins. Its relative frequency among ADCA patients (prevalence of 1–5 out of 100 000 people) varies as a result of independent regional founders in each population, but the mean frequencies in many countries are between 2% and 5%.

De novo SCA7 expansions can occur during paternal transmission from intermediate size alleles with 28–35 repeats, which can be considered as at-risk alleles in the healthy population. This observation is important in clinical practice since 'apparently' sporadic patients can then carry pathological mutations in the *SCA7* gene.

Clinical Features and Differential Diagnosis

Symptoms

Clinical manifestations typically begin in the third or fourth decade, with ages of onset ranging from 3 months or less to over 70 years. Analysis of parent–child couples has revealed striking anticipation, greater in paternal than in maternal transmissions.

The SCA7 mutation is almost exclusively associated with the ADCA type II phenotype, which is distinguished by the presence of a retinopathy in most patients, although retinopathy is also sometimes found in other ADCA forms. Cerebellar ataxia is usually the presenting symptom, particularly in adults with onset over thirty, whereas in patients with earlier onset, decreased visual acuity alone or associated with cerebellar ataxia is the initial symptom. Some infantile cases may, however, result in early death without detectable retinal alteration. In some patients with late onset, visual acuity may never decrease.

Cerebellar ataxia is always associated with dysarthria, but patients present variably with a pyramidal syndrome, decreased vibration sense, dysphagia, sphincter disturbances as well as oculomotor abnormalities (supranuclear ophthalmoplegia and/or viscosity of eye movements). Extrapyramidal features (dystonia), myokymia, and mental impairment are rare.

Visual failure is progressive, bilateral and symmetrical, leading to progressive blindness that first affects the central vision, while night vision is not impaired. Interestingly, dyschromatopsia in the blue–yellow axis is found years before visual failure becomes symptomatic. In contrast, fundoscopic abnormalities consisting of a loss of the foveal reflex and progressive mottling of pigment at the macula are often delayed (**Figure 1**). Secondary optic atrophy can often be detected in later stages. Electroretinograms show abnormal scotopic responses, but photopic responses are preserved late.

Neuropathology and Brain Imaging

Brain imaging (**Figure 2**) and neuropathological studies show marked atrophy in the cerebellum, particularly in the superior part of the vermis where Purkinje cells and, to a lesser extent, granule cells degenerate. Extensive neuronal loss is observed in the inferior olive, with marked astrocytic gliosis. Mild cell loss also occurs in the dentate nucleus and in the brainstem, which may be associated with moderate atrophy of the cerebral cortex. Mild cell loss is also observed in the substantia nigra and the basis pontis, whereas the thalamus and the striatum are spared. Ponto-cerebellar pathways are spared, while spinocerebellar, olivocerebellar, and efferent cerebellar tracts are severely affected.

The distinctive neuropathological features of ADCA II are degeneration of the optic pathways and the retina. The pregeniculate visual pathways and the optic nerves are affected, probably as a consequence of retinal degeneration. In juvenile cases presenting with blindness, those systems may not be altered, probably because of the rapid course of the disease. Pathological examination of the retina shows early degeneration of photoreceptors and of bipolar and

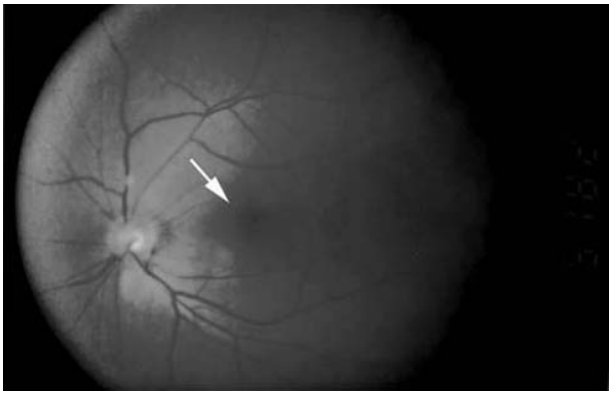

Figure 1 Fundus color picture/fluorescein angiography of the right eye of a SCA7 patient presenting with bilaterally reduced visual acuity (1/10). Note the abnormal aspect of the macula and the presence of a pigmented central core. Reproduced from Stevanin et al. (2000). In: Klockgether T (ed.) *Handbook of Ataxia Disorders*, with permission from Taylor & Francis/Marcel Dekker Inc.

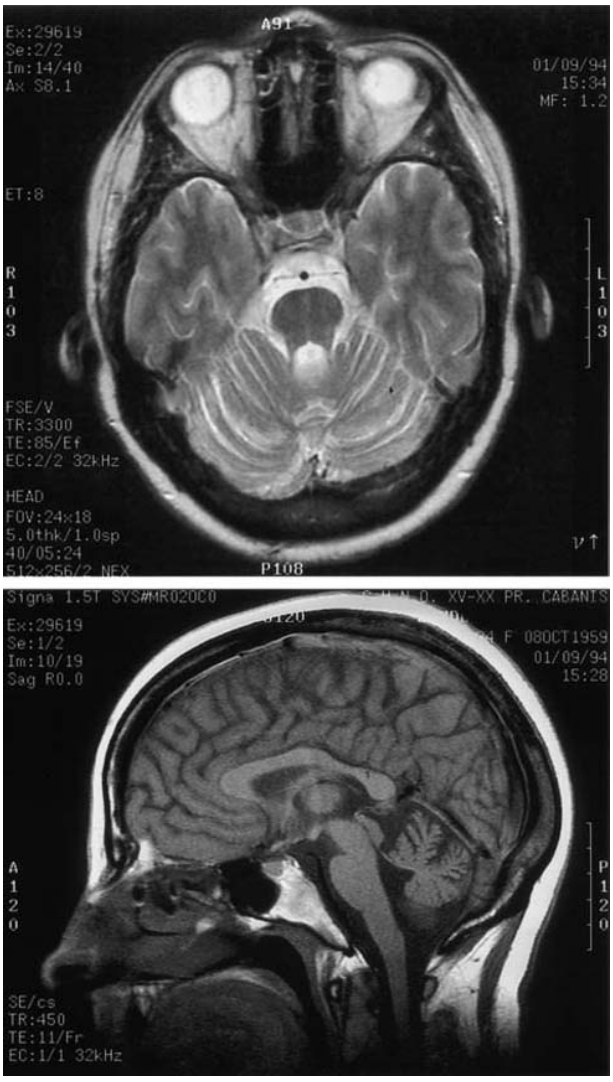

Figure 2 Brain MRI of a SCA7 patient. Top: axial, T2 weighted image (TR = 3300 ms, TE = 85 ms) showing cerebellar cortical atrophy associated with atrophy of the pons. Note the absence of major change in the middle cerebellar peduncle. Bottom: sagittal, T1 weighted sequence (TR = 450 ms, TE = 11 ms) showing obvious atrophy of the cerebellar vermis associated with mild atrophy of the pons. Reproduced from David et al. (1998). In: Wells RD and Warren ST (eds.) *Genetic Instabilities and Hereditary Neurological Diseases*, with permission from Elsevier/ Academic Press.

granular cells, particularly in the foveal and parafoveal regions. Later, patchy loss of epithelial pigment cells and their ectopic migration into the retinal layers are observed.

Phenotype–Genotype Correlations

There is a strong negative correlation between the size of the CAG expansion and age of onset, but other genetic and/or environmental factors likely play a minor role in determining the disease onset. This correlation, together with the increase in expansion size in successive generations, is consistent with the marked anticipation observed in patients. Disease duration until death is also negatively correlated with the number of CAG repeats on the expanded allele and is limited to a few months or years in early onset patients. Anticipation is also associated with increasing severity of symptoms in successive generations. The frequency of decreased visual acuity, ophthalmoplegia, scoliosis, and extensor plantar reflexes significantly increases with the size of the expansion. In some infantile cases with very large repeat expansions, progression is extremely rapid and cardiac involvement may occur.

Management

Confirmatory diagnostic testing and presymptomatic/ prenatal diagnoses are possible with a detection rate close to 100%. In patients with young onset, the largest allele rarely escapes detection; however, additional techniques (southern, long range PCR, etc.) should be used in very early onset patients with homozygous normal alleles.

There is no specific drug therapy for this neurodegenerative disorder. Therapy remains purely symptomatic (physiotherapy for gait and balance disturbances). Appropriate measures during careful neurological follow-up can reduce diplopia, swallowing, or sphincter disturbances. Dementia may be present and needs specific care.

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See also: Multiple System Atrophy: Animal Models; Olivopontocerebellar Atrophy; SCA1; SCA2; SCA3, Machado–Joseph Disease; SCA4; SCA5; SCA6; SCA8; SCA10; SCA11; SCA12; SCA13, 14, 15, and 16; SCA17; SCA27; Spinocerebellar Ataxias Genetics.

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SCA8

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Glossary

Antisense RNA – Single stranded RNA that is complementary to a messenger RNA strand.
Ataxia – Literally (Greek) absence of order. Clinically referred to as a specific motor syndrome with difficulty to stabilize the trunk against gravity, difficulty to stabilize gaze, difficulty in goal-directed limb movements and dysarthria.
CTG repeat disorder – A trinucleotide expansion of a CTG repeat tract found in SCA8 and myotonic dystrophy, different from the polyglutamine repeat disorders with CAG expansions (e.g., SCA 1, 2, 3, HD, among others).

Definition and History

SCA8, or spinocerebellar ataxia type 8, is a dominantly inherited 'pure cerebellar' (ADCA III) ataxia caused by a trinucleotide expansion of a CTG repeat tract. This pathogenic CTG expansion was identified in and isolated from the genomic DNA of an individual with a previously unknown familial form of SCA, which was in turn used to identify a large family in which ataxia was genetically linked to the *SCA8* locus on chromosome 13. SCA8 patients typically have a slowly progressive, predominantly cerebellar disease involving dysarthria, limb and gait ataxia, and impaired smooth pursuit and nystagmus. A broad range of other clinical symptoms has also been reported, including tremor, spasticity, and various kinds of cognitive impairment. Although this clinical picture is not clearly distinguishable from that of other forms of inherited ataxia, the underlying molecular cause of SCA8 appears to be unique among this family of diseases.

Pathogenesis/Pathophysiology

The SCA8 CTG repeat tract is part of the natural antisense RNA of the Kelch-like 1 (*KLHL1*) gene. *KLHL1* antisense transcripts (*KLHL1AS*) are transcribed from a promoter in the first intron of *KLHL1* across the splice donor site, the translation and the transcription start site of *KLHL1*, and are alternatively spliced and polyadenylated. We currently presume that the primary function of this antisense transcript, which is evolutionarily conserved, is to regulate the expression of the *KLHL1* gene. The KLHL1 protein encoded by the sense RNA is located exclusively in the cell bodies and dendrites of Purkinje cells and other neurons. Loss of expression from even a single allele in an SCA8 mouse model causes abnormal gait, progressive loss of motor coordination, and Purkinje cell dendritic deficits. Mice with *Klhl1* specifically deleted in only Purkinje cells have the same phenotype, indicating that Klhl1 is essential for normal motor coordination and for maintaining normal Purkinje cell functions. We hypothesize that pathogenic SCA8 CTG expansions cause ataxia in humans through a

mechanism involving the loss of KLHL1 activity in Purkinje cells and that loss of proper expression from even a single *KLHL1* allele would be sufficient to cause disease.

Ataxia patients analyzed with either magnetic resonance imaging or computed tomography typically have marked atrophy of the cerebellar vermis and hemispheres and relative preservation of the brainstem and other parts of the brain. The MRI findings from SCA8 patients were compared with those from SCA6 patients, who are also considered to have a pure cerebellar ataxia, and no statistically significant differences were found between these two patient groups on MRI. The slowly progressive nature of SCA8 was documented by MRI analysis in one study. MRI scans of an SCA8 patient taken 9 and 18 years after the disease onset were compared and showed little, if any, progression of the prominent cerebellar atrophy during those years. Published reports also indicate that atrophy found in MRI scans can be present during the preclinical stage of the disease and even in asymptomatic SCA8 carriers. A neuroradiological finding of cerebellar atrophy may therefore be the first or only sign of SCA8 neuropathology in some patients.

Clinical Features

A consistent clinical picture of SCA8 has emerged as researchers in various parts of the world have identified ataxia families with SCA8 expansions and published their findings The clinical features of SCA8 are similar to those of the other SCAs and include limb and truncal ataxia, ataxic dysarthria, and horizontal nystagmus, either gait ataxia or dysarthria being the initial clinical symptom. Many patients also had increased deep tendon reflexes, limb spasticity, and reduced vibratory sense. The most distinguishing clinical feature of SCA8 is that the disease progression is typically very slow.

Cognitive impairments have been observed in many of the reported SCA8 patients, and this may represent a significant but variable clinical feature of this disease. In the original SCA8 family, three of the 13 affected family members and two of the 22 carriers of SCA8 expansion without ataxia had been treated for depression and one affected family member was being treated for a psychotic disorder. Other published reports describe SCA8 patients with similar cognitive impairments. A recent case report indicates that these additional impairments may be associated with white matter hyperintense lesions on cranial MRI.

Diagnostic Test

Unlike many of the other spinocerebellar ataxias, there is little direct relationship between expansion size and disease severity, and some individuals with large SCA8 CTG alleles never develop ataxia. For these reasons, it is not currently possible to predict either the onset or the severity of the disease.

The size of the *SCA8* CTG tracts in a patient's genomic DNA can be determined by generating and electrophoretically sizing PCR products from both of the patient's *SCA8* alleles, using an oligonucleotide primer pair that flanks this repeat tract. The number of trinucleotide repeats present at this locus is extremely heterogeneous in the general population, and as a result, the genomic DNA from the vast majority of individuals will generate PCR products with two distinct sizes. In those instances where only a single size is detected, Southern analysis of the genomic DNA sample should be performed to differentiate between individuals with two SCA8 alleles of the same size and those who have one expanded allele that is too large to amplify by PCR (typically $\geq \sim 200$ CTG repeats).

Interpretation of the SCA8 CTG DNA test is not straight forward. Individuals who do not have CTG expansions at the SCA8 locus do not have and will not develop this form of ataxia, and this test is useful for providing this information. On the other hand, detection of a large SCA8 CTG repeat and determination of its size cannot be used to directly predict either the severity or the onset of ataxia. We feel that the underlying problem with using the size of the SCA8 CTG repeat in a predictive manner is that the CTG expansion in the genomic DNA that is analyzed in a DNA test is not in itself the direct molecular cause of the SCA8 neuropathology. Rather, we currently believe that the cerebellar neurotoxicity of this expansion mutation is mediated through the transcription of this repeat into RNA. Since direct analysis of patient cerebellar RNA is not a practical option, definitive predictive testing for SCA8 will probably not be possible until the precise molecular mechanism that leads to the neuropathology and the modifiers of this pathology are more fully understood.

Prognosis

Since SCA8 is predominantly a cerebellar disease, SCA8 patients can be expected to lose cerebellar function gradually over a number of decades while largely avoiding the brain stem involvement found in many other types of SCA. There is currently no known method for effectively treating SCA8 patients.

See also: Ataxia; Cayman Ataxia; SCA1; SCA2; SCA3, Machado–Joseph Disease; SCA4; SCA5; SCA6; SCA7, Spinocerebellar Ataxia with Macular Dystrophy; SCA10; SCA11; SCA12; SCA13, 14, 15, and 16; SCA17; SCA27; Scale for the Assessment and Rating of Ataxia (SARA); Spinocerebellar Ataxia Type 19, 20, 21, 22, 23, 26; Spinocerebellar Ataxias Genetics.

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SCA10

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Glossary

Anticipation – The tendency for the severity of a condition to increase in successive generations.
Autosomal – Any trait determined by a gene localized in chromosomes other than the sex-chromosomes, X and Y, and therefore, transmitted with equal probability through the mother or father.
Dominant – In human genetics, any trait that is expressed in a heterozygote.
Dynamic mutation – An unstable expanded repeat that changes size between parent and child.
Founder effect – Refers to the presence in a population of many individuals all with the same chromosome or chromosomal region derived from a single ancestor.
G-protein signaling – A widespread intracellular signaling system. G proteins are guanine nucleotide-binding proteins residing in the plasma membrane. They form inert trimeric complexes when bound by GDP. When GDP is replaced by GTP, the trimeric molecule is broken-down into subunits, one of which then activates or represses a target protein.
Microsatellite – Small stretch of usually less than 0.1 kb of tandem repeats of a very simple DNA sequence, usually 1–6 bp in length. They are often polymorphic.
Microsatellite repeat instability – A phenomenon where during DNA replication the repeat copy number of microsatellites is subject to changes. It is the underlying cause of more than 20 hereditary diseases, and often seen in cancerous cells.
Toxic gain-of-function – Protein expressed by the mutated gene has, in addition to all its normal cellular functions, some additional function that makes it toxic to the cell.

Definition and History

Spinocerebellar ataxia type 10 (SCA10; MIM 603516) is an autosomal dominant disorder characterized by progressive cerebellar dysfunction often associated with seizures.

The disease was initially described in two families of Mexican origin, and genome-wide linkage analysis localized it to a region on chromosome 22q13. In 2000, Matsuura et al. identified an expanded pentanucleotide ATTCT repeat in intron 9 of the *E46L* gene (later renamed *ATXN10*) that cosegregated with the disease in all affected members of five Mexican families. The ATTCT

repeat is polymorphic, ranging from 10 to 29 repeats in normal individuals and from 800 to 4500 repeats in patients. Anecdotal reports suggest that alleles with 280–800 repeats have reduced penetrance, although further evidence is needed to clarify this issue.

Pathogenesis

The *ATXN10* gene consists of 12 exons spanning 173 kb of genomic DNA, with an open reading frame of 1428 bp encoding a 475 amino acid protein. The polymorphic ATTCT pentanucleotide repeat is located in intron 9, ranging in normal individuals from 10 to 29 repeats. Eighty percent of normal individuals are compound heterozygotes for alleles in this range and 20% are homozygous. The normal repeat tract is usually a pure ATTCT stretch in small normal alleles (11–16 repeats), but more than half of normal alleles with $\geq$17 repeats have ATTGT–TTTCT or TTTCT interruptions confined to the penultimate repeating unit.

Only three affected SCA10 families have been analyzed for the purity of the repeat. In one of them, the mutant tract was apparently uninterrupted while the other two had interruptions. These families show differences in disease penetrance, severity and repeat instability, which may be influenced by the differences in their sequence configuration.

The causal role of the expanded *ATXN10* alleles in SCA10 is supported by the fact that these alleles cosegregate with the SCA10 phenotype in all affected families and were absent in more than 1000 normal chromosomes analyzed as controls. *ATXN10* is highly expressed in the cerebellum, which is the tissue primarily involved in disease pathology.

ATXN10 is an evolutionarily conserved cytoplasmic protein of unknown function; however, the discovery of some potential interacting proteins suggests that ATXN10 may promote G-protein signaling and increased neurite formation. A decrease in ATXN10 transcript in cultured neurons induced apoptosis, with cerebellar neurons being significantly more sensitive than cortical neurons. The significance of this finding in the context of SCA10 is unclear since it has been shown that the expanded ATTCT repeat does not interfere with either transcription or posttranscriptional processing of mutant *ATXN10*, and that the level of processed mRNA is unaltered in SCA10. More recent data point toward a toxic RNA gain-of-function by the expanded ATXN10 transcript.

Epidemiology

SCA10 has so far only been described in Latin-American populations, mainly in Mexican and Brazilian families, where it represents a common cause of autosomal dominant ataxia, second only to SCA2 in Mexico, and SCA3/MJD in Brazil. One family from Argentina has also been identified. Haplotype analyses flanking the *ATXN10* gene support the notion of a common ancestor.

Clinical Features

The common phenotype of SCA10 is that of a progressive pure cerebellar ataxia (ADCA type III) of adult onset. The initial manifestation is most commonly unstable gait and stance with limb ataxia, which is later followed by dysarthria. Neurological exam shows wide-based ataxic gait, difficulty in tandem-walking, dysmetria, dysdiadokinesia, intention tremor, and ocular dyskinesia. More variable findings are pyramidal signs and mild lower limb sensory loss. Age of onset ranges from 12 to 48 years.

As more families with SCA10 have been identified, it is possible to subdivide them into three subphenotypes: (1) pure cerebellar ataxia of slow progression, often accompanied by mild cognitive deficit; (2) cerebellar ataxia plus seizures; and rarely (3) cerebellar ataxia plus nonneurological symptoms.

The initial clinical description of SCA10 was that of cerebellar ataxia with epilepsy, with 25–80% of the Mexican patients experiencing seizures. Interestingly, only one patient of Brazilian origin has had seizures, and therefore, the epilepsy phenotype may be considered a 'Mexican' variant of SCA10.

Patients affected with epilepsy present with generalized motor seizures and/or complex partial seizures which may precede or follow the onset of overt ataxia, and can be severe enough to cause status epilepticus.

Genotype–Phenotype Correlation

A weak inverse correlation between repeat size and age of onset has been noted in SCA10 patients, with a correlation coefficient (r^2) of 0.34, which means that only about one-third of the variation in the age of onset is determined by the size of the repeat.

Anticipation has been described in SCA10, mainly via paternal transmission, and is associated with increased repeat instability in the male germline. In contrast, instability of expanded alleles is not seen during maternal transmission. Paradoxically, in some cases, clinical anticipation has also been seen despite a decrease in the size of the repeat. Whereas, the phenotypic significance of the repeat length per se needs further clarification; it has recently been suggested that the presence of non-ATTCT sequence interruptions may also act as modifiers of disease severity.

Diagnosis

The diagnosis of SCA10 should be considered in Mexican or Brazilian patients presenting with adult onset autosomal dominant cerebellar ataxia of slow progression, with or without seizures.

The brain imaging shows progressive pan-cerebellar atrophy with relative preservation of cerebrum and brain stem. They may have electroencephalographic evidence of diffuse cortical dysfunction, with or without cortical irritability or slow activity, and electrophysiologic abnormalities compatible with peripheral neuropathy.

The diagnosis is confirmed by molecular genetic testing to identify abnormally expanded ATTCT repeats in the *ATXN10* gene. Affected individuals have alleles that range from 800 to 4500 repeats. Reduced penetrance alleles may exist, as suggested by one asymptomatic woman carrying the same 280 ATTCT-repeat allele as her clinically affected daughter, and two alleles of 360 and 370 repeats reported in two asymptomatic Brazilian individuals.

Management

The main objective of treatment in SCA10 is the appropriate control of epilepsy, which if left untreated can lead to life-threatening status epilepticus. Otherwise, treatment is focused on symptomatic support and physical therapy. Appropriate genetic counseling should be provided to SCA10 families. SCA10 is transmitted as an autosomal dominant trait, therefore, offspring of an affected individual has a 50% chance of inheriting the mutation. Once the diagnosis is confirmed by molecular testing in the proband, prenatal diagnosis may be offered for future offspring, and predictive testing is also an option for at-risk family members.

See also: Ataxia; Juvenile Myoclonic Epilepsy; Multiple System Atrophy: Animal Models; SCA1; SCA2; SCA3, Machado–Joseph Disease; SCA4; SCA5; SCA7, Spinocerebellar Ataxia with Macular Dystrophy; SCA8; SCA11; SCA12; SCA13, 14, 15, and 16; SCA17; SCA27; Spinocerebellar Ataxia Type 19, 20, 21, 22, 23, 26; Spinocerebellar Ataxias Genetics.

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SCA11

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Glossary

Ataxia – Impaired coordination leading to problems of balance, finger and hand movements, and speech.
Cerebellum – Part of the brain that receives afferent fibres from the cortex, brainstem and spinal cord and sends efferent fibres via the cerebellar deep nuclei towards the thalamus and cortex. The cerebellum has an essential role in coordinating movements.
Linkage analysis – Genetic method that allows to map disease causing gene mutations on chromosomes.
Tau tubulin kinase-2 (*TTBK2*) – TTBK2 is a member of the casein kinase group of protein kinases. TTBK2 has the ability to phosphorylate tau and tubulin.

Spinocerebellar ataxia type 11 (SCA11) was first identified by Worth et al. in a large British family with ataxia ascertained in seven generations. Disease onset was 25 ± 8 years with no evidence of anticipation. Life expectancy was almost normal with mean age at death of 71 ± 14 years. All affected family members had gait ataxia, impaired smooth pursuit eye movements, gaze-evoked nystagmus, ataxic speech, and hyperreflexia. Most affected patients had also limb ataxia, while vertical nystagmus and diplopia were less frequent. Ataxia was mild; after a disease duration of 24 ± 13 years, no affected subject was wheelchair-bound.

Apart from a mild reduction of sensory nerve action potentials in one subject, nerve conduction studies were normal. MRI scans revealed isolated cerebellar atrophy. A neuropathological examination of one affected brain showed almost complete loss of cerebellar Purkinje cells and marked loss of cerebellar granule cells. Neurofibrillary tangles were found in several areas of the brainstem, midbrain, basal ganglia, and neocortex.

A genome-wide linkage study mapped the disease to a 7.6-cM region on the proximal long arm of chromosome 15 (15q14–21.3). Sequencing of the gene encoding tau tubulin kinase-2 (*TTBK2*), one of more than 50 candidate genes in the critical region, led to the identification of a one-base insertion in exon 13 at nucleotide 1329 that created a premature stop and truncated the normal protein of 1244 to 450 amino acids. In a second family of Pakistani origin, a frameshift deletion of two bases in exon 13, also leading to a premature stop, was found. Both mutations segregated with the disease and were not found in normal chromosomes. Semiquantitative polymerized chain reaction (PCR) of lymphoblast RNA from both families showed an ~50% reduction of *TTBK2* mRNA. *TTBK2* is expressed in all brain regions with a particularly high expression in the cerebellar cortex, hippocampus, midbrain, and substantia nigra. Whether the neurofibrillary tangles observed in one SCA11 brain are a consequence of the *TTBK2* mutation or rather an expression of normal ageing remains to be clarified.

See also: Ataxia; Ataxia with Isolated Vitamin E Deficiency; SCA1; SCA2; SCA3, Machado–Joseph Disease; SCA4; SCA5; SCA6; SCA7, Spinocerebellar Ataxia with Macular Dystrophy; SCA8; SCA10; SCA12; SCA13, 14, 15, and 16; SCA17; SCA27; Spinocerebellar Ataxia Type 19, 20, 21, 22, 23, 26; Spinocerebellar Ataxias Genetics.

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SCA12

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Glossary

Endogamy – The practice of marrying within a social group.
Haplotype – The determination of markers close to and on the same chromosome as the mutation of interest.
Heterozygosity – Describes the condition where different alleles occupy the gene's position in each of the homologous chromosomes. In other words, it describes an individual who has two different alleles for a trait.
Penetrance – An index of the proportion of individuals with an allele who have manifestations of it.
Transmission – The transfer of genetic information from genes to another generation, or from one location in a cell to another. For example, maternal transmission is inheritance from the mother.

Definition and History

Spinocerebellar ataxia type 12 is an autosomal dominant ataxia caused by a CAG expansion that results in kinetic tremor, ataxia, hyperreflexia, and subtle parkinsonism. The first description of SCA12 came from the Holmes, O'Hearn group, and Margolis in 1999, in a large American family of German descent. A second family, of Indian descent, was discovered by Fujigasaki in 2000. Nineteen other families have now been reported in the Indian population, due to a founder effect. Subsequently, several groups have conducted screening studies for SCA12 repeat expansions and determined that the SCA12 mutation is a rare cause of ataxia in most populations.

Pathogenesis/Pathophysiology

SCA12 is caused by a CAG repeat expansion at 5q31–33 in the 5′ untranslated region of *PPP2R2B* gene. The repeat expansion is 133 nucleotides upstream from the transcription site of the gene, which codes for a brain-specific regulatory subunit of serine/threonine protein phosphatase PP2A. Normal CAG repeats at this locus are 7–32, most members of the general population having 10 repeats. Heterozygosity at the locus is 61–71%. Pathological repeats at this locus range from 55 to 78 CAG repeats; however, the exact cutoff is still uncertain. Ataxic individuals with 40–49 repeats have been reported, in addition to normal individuals in the same range. Evidence of polyglutamine expansions has not been seen with Western blots of protein in the one SCA12 brain examined, which is consistent with the location of this expansion in a nontranscribed region of the gene. There is a mild instability of the repeat size on transmission (±1–4 CAG) from parent to offspring, usually with paternal transmission. It is uncertain whether the penetrance is incomplete or age-dependent as some asymptomatic individuals with repeat expansions have been reported but may be too young to manifest symptoms. There is no correlation between the repeat size and the age of onset. Protein phosphatase (PP2A) is a highly conserved protein that is involved in the regulation of cellular processes, including tau regulation. It is widely expressed in the Purkinje cells of the cerebellum. The Bβ subunit (PPP2R2B), or regulatory unit, is the portion that is affected by the CAG repeat expansion. Preliminary evidence suggests that the SCA12 repeat expansion may alter the level of expression of the protein. The most likley mechanisms of pathogenesis include: toxicity at the level of the BB protein or its RNA (similar to the fragile X-associated tremor ataxia syndrome or myotonic dystrophy); alteration of splicing patterns; or direct inhibition of transcription with a secondary effect on associated proteins. Pathological findings in SCA12 show diffuse atrophy, most marked in the cerebral and cerebellar cortex, with loss of cerebellar Purkinje cells.

Epidemiology/Risk Factors

Multiple screening studies have been conducted to determine the prevalence and distribution of the SCA12 repeat expansion in various populations (**Table 1**). With the exception of the original American family of German descent, most families with the disorder have been Indian. Single patients from Singapore and China with SCA12 have been reported. The high prevalence of the disorder in India is due to a common founder. Ninety percent of the Indian SCA12 pedigrees (20 individuals in total) share a single haplotype associated with the majority of expanded chromosomes, as against the 4% of ethnically matched unrelated normal individuals. These Indian SCA12 families belong to the state of Haryana, which has a strictly

Table 1 Prevalence Studies in SCA12

Author	*Movement disorder*	*No. of patients*	*No. of Controls*	*Population*	*Prevalence of SCA12*	*Expanded Repeat Size (CAG)*
Srivastava	ADCA	293 (77 families)	135	Indian	6/293 (2%)	55–69
Fujigasaki	ADCA, ARCA, sporadic	247 families	257	French, Indian	1/145 ADCA family (0.6%)	55–61
Zhao	Ataxia	204	0	Chinese, Indian, Malay	1/204 (1.7%)	66
Worth	Cerebellar ataxia	392	0	British	0	na
Cholfin	ADCA, ARCA, sporadic, unknown	211 (180 families)	0	Chinese, Japanese, Southeast Asian, East Indian, Middle Eastern, Hispanic, African American, European	0	na
Holmes	Neurological diseases	1099	394	European	0	na
Nicoletti	Essential tremor	30	58	Italian	0	na
Cho	Parkinson disease, MSA	1076	100	Korean	0	na

ADCA, Autosomal dominant cerebellar ataxia; ARCA, Autosomal recessive cerebellar ataxia; na, not applicable; MSA, multiple system atrophy.

endogamous population. The SCA12 family of German descent does not share this haplotype, suggesting that that the Indian mutation arose from a different founder. Other studies in the Indian population show that there is a statistically significant difference in the number of normal controls with CAG repeat sizes over 12 in the Indian compared with the French controls.

Clinical Features and Diagnostic Criteria

The age of onset of disease is 8–55 years, with a mean age of onset of 34 years. The duration of disease in patients examined has varied from 3 to 13 years. In many of the patients, tremor is the first neurological sign, with many patients diagnosed initially with essential tremor. The tremor is kinetic or postural, intention tremor being frequent. A tremor frequency of 3 Hz was described in one patient. The tremor is usually in the upper extremities, but can also be seen in the mandible, voice, or with tongue protrusion. Head tremor, which is of large amplitude and low frequency, is also a feature. Cerebellar features tend to be milder than other forms of ataxia and include gait ataxia, limb dysmetria, dysdiadochokinesia, and dysarthia. Abnormal eye movements can be seen, with nystagmus on lateral gaze, slowed saccades, and broken pursuit – all reported. Parkinsonism is common in the American SCA12 kindred, with bradykinesia and rigidity most frequently seen, but has not been reported in Indian SCA12 patients. Focal dystonia, anteroflexion, and retropulsion have been reported. Hyperreflexia with extensor plantar responses is present in the majority of cases and a subclinical peripheral neuropathy was discovered on NCV in the majority of the affected Indian individuals in the Fujigasaki study. A subclinical peripheral neuropathy has also been observed in some members of the American SCA12 kindred. Facial myokymia, axial dystonia, laterocollis, and cognitive abnormalities are present in some patients, with cognitive decline seen most commonly in the older patients. Anxiety and depression are seen in a proportion of affected individuals.

Differential Diagnosis

Kinetic tremor may also be seen in SCA 2, 3, 6, and dentatorubropallidal luysian atrophy (DRPLA) and these disorders should be considered in the differential. Ethnicity of the patient and associated features may better refine testing. The fragile X-associated tremor/ataxia syndrome (FXTAS) should also be considered. This disorder is caused by a CGG repeat expansion in an untranslated portion of the *fragile X mental retardation 1* gene on the X chromosome. FXTAS manifests itself in kinetic tremor and gait ataxia, with varying degrees of parkinsonism, peripheral neuropathy, and executive dysfunction. However, individuals with FXTAS tend to be males over the age of 60 and will have an X-linked transmission pattern on family history, rather than an autosomal dominant pattern. Parkinsonism is also seen in SCA 2, 3, 6, and DRPLA. Hyperreflexia and extensor plantar responses can be seen in SCA 1–8, making this sign less helpful in diagnosis.

Diagnostic Work-up/Tests

Subclinical peripheral neuropathy may be seen on nerve conduction studies. Nerve conductions have shown sensory neuropathy and axonal sensorimotor neuropathy. Magnetic

resonance imaging and computed tomography show cortical and cerebellar atrophy in most individuals. SCA12 genetic screening may be considered in those individuals who have neurological signs in addition to cerebellar features, especially kinetic tremor. Ethnicity may be helpful, individuals of Indian descent being potentially more likely to have the mutation and an appropriate family history. Polymerase chain reaction testing using primers flanking the CAG repeat expansion in the *PPP2R2B* gene is diagnostic and can be ordered at several laboratories.

Management

Kinetic tremor in SCA12 has been reported to respond to primidone or beta-blockers in some patients. Alcohol was reported to help in one patient as well. This suggests that affected individuals with kinetic tremor should have trials of medications typically prescribed for essential tremor. Symptomatic treatment for gait ataxia may include medications that modify monoamine transmission, such as amantadine and buspirone, or physical therapy for gait training. Recently, case reports in three patients with ataxia show that varenicline, a partial agonist selective for $\alpha 4\beta 2$-nicotinic acetylcholine receptors and prescribed for tobacco cessation, may be helpful for gait ataxia. However, this medication may exacerbate tremor, and therefore, patients should be monitored closely. Dopaminergic therapy for parkinsonism and therapy for anxiety of depression should be considered, if appropriate.

Prognosis

Although disease progression is reported to be slow, there have not been studies reporting the prognosis or life expectancy of patients with SCA12.

See also: Ataxia; Multiple System Atrophy; Multiple System Atrophy: Animal Models; SCA1; SCA2; SCA3, Machado–Joseph Disease; SCA4; SCA5; SCA6; SCA7, Spinocerebellar Ataxia with Macular Dystrophy; SCA8; SCA10; SCA11; SCA12; SCA13, 14, 15, and 16; SCA17; SCA27.

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SCA13, 14, 15, and 16

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Glossary

Deletion – A part of a gene or chromosome is missing.
Gene mutation – Change in a gene that leads to an altered or abnormal gene product.
Haploinsufficiency – The presence of a dominant mutation on one allele leads to only a single functional copy of the gene on the other allele, which is insufficient to maintain a normal function of the gene product.
Linkage study – The search for the chromosomal location of a disease gene, by identifying a specific set of selected genetic markers that are inherited jointly and segregate with disease transmission.
Missense mutation – Type of point mutation where a single nucleotide is changed, resulting in a different amino acid.
Myokymia – Spontaneous, small contractions of muscle fascicles.
Penetrance – The rate at which the presence of a genetic mutation actually leads to the development of the corresponding disease.
Purkinje cell – Large neurons in the cerebellar cortex with an extensive dendritic arbor.

Spinocerebellar Ataxia 13

Clinical Features

The phenotype of the original French SCA13 family consisted of a slowly progressive spinocerebellar ataxia with early childhood onset. Delayed motor milestones and mild mental retardation were observed in most affected family members. Occasional features included seizures, short stature, facial dysmorphia, and cervical dystonia. A second family, of Filipino descent, manifested a more isolated cerebellar syndrome with onset ages ranging from 22 to 48 years. No extracerebellar features were reported, except for brisk tendon reflexes.

Genetics and Pathophysiology

The SCA13 locus on chromosome 19q13.3–13.4 was found in 2000, and refined in 2005. The combined effort of the two research groups that were involved in the linkage studies led to the identification of two different missense mutations in exon 2 of the *KCNC3* gene in 2006. *KCNC3* encodes Kv3.3, a voltage-gated potassium channel that is expressed in the various cerebellar neuronal populations. Functional studies have indicated that both the Filipino R420H mutation and the French F448L mutation alter channel function, which presumably changes the activity of fast-spiking cerebellar neurons.

Epidemiology and Relevance

So far, only two SCA13 families have been published. However, as the gene identification was quite recent, large-scale screening for *KCNC3* mutations in ataxia cohorts are necessary to establish its actual relevance.

Spinocerebellar Ataxia Type 14

Clinical Features

To date, numerous SCA14 families have been reported. There is a markedly variable age of onset, ranging from early childhood to 60 years. Clinically, SCA14 patients mostly display a very slowly progressive, isolated cerebellar or spinocerebellar ataxia. However, some relevant noncerebellar features have been documented, of which extrapyramidal signs are the most important. In some early-onset cases, axial myoclonus and focal hand dystonia were the presenting features. Action myoclonus can be a predominant feature, leading to a Ramsay–Hunt phenotype, and extrapyramidal rigidity and chorea have occasionally been observed. In addition, some SCA14 patients manifested facial myokymia, depression, cognitive impairment, vertical gaze palsy, and rippling muscles. Incomplete penetrance has been suggested in some papers, but this has not been confirmed by others. Neuroimaging mostly reveals cerebellar atrophy.

Genetics and Pathophysiology

Linkage to the SCA14 locus on chromosome 19q13.4-qter was first described in a Japanese family in 2000, with a second American family of English–Dutch ethnicity showing linkage to an overlapping region 2 years later. The causative gene was identified in 2003 by Chen et al., who discovered exon 4 missense mutation in the *PRKCG* (protein kinase C, gamma) gene. Many mutations, mostly missense mutations, but also small deletions and possibly splice site mutations have been described. Mutations are

located in exons 1, 2, 3, 4, 5, 10, and 18, but exon 4 harbors most of the mutations reported so far, and thus, appears to be a mutational hotspot. *PRKCG* codes for the gamma isoform of protein kinase C (PKCγ), which belongs to the serine/threonine kinase family and is involved in second messenger signaling systems, and has been shown to play an important role in Purkinje cell morphology and function. The exact disease mechanism is yet unknown, but available studies suggest that most PKCγ mutations lead to an increased kinase activity and an increased redistribution of the protein to the plasma membrane accompanied by a reduced ability to phosphorylate target substrates. One consequence of this might be an increased cellular influx of calcium, which subsequently disturbs Purkinje cell signaling. However, further work is needed.

Epidemiology and Relevance

Some studies have assessed the relative contribution of *PRKCG* mutations in dominant ataxia cohorts of various ethnic origins. In the Netherlands, SCA14 represents ~4% of the total SCA population. In France, this percentage is 1.5. Contrary to this, SCA14 is quite rare in Japan, as only two mutation carriers were identified among 882 ataxia patients – although the authors only screened exon 4. In the United States, 2.6% of SCA patients who tested negative for the more common subtypes (SCA1, 2, 3, 6, and 7) were found to carry *PRKCG* mutations.

Spinocerebellar Ataxia 15

Clinical Features

The first SCA15 family, Australian but of Anglo-Celtic origin, was characterized by a slowly progressive, relatively pure cerebellar ataxia with a mean age of onset being 26 years (range 10–50). Hyperreflexia was noted in some. Subsequently, two Japanese SCA15 families were reported; the clinical picture was that of a progressive cerebellar ataxia, starting between 12 and 47 years, but with postural and action tremor of hands and trunk, pyramidal signs, and peripheral neuropathy.

Genetics and Pathophysiology

The SCA15 locus on chromosome 3p24.2–3pter was reported in 2003. The two Japanese families showed linkage to 3p26.1–25.3, thus partly overlapping the SCA15 locus. Missense mutations in an obvious candidate gene, *ITPR1* (inositol 1,4,5-triphosphate receptor type 1), were initially excluded as being causative. Later, deletions of a large part of *ITPR1*, as well as a part of the neighboring *SUMF1* (sulfatase-modifying factor 1) gene, were identified in the Australian SCA15 family, a finding that was reproduced in two British families (the clinical details of which have not been published in detail, but appeared to be an uncomplicated cerebellar ataxia). Findings were corroborated in the two Japanese SCA15 families, but the results in one of the two Japanese families, carrying a p.P1059L missense mutation in *ITPR1* rather than an *ITPR1–SUMF1* deletion, strongly suggest that *ITPR1* is indeed the culprit. *ITPR1* is predominantly expressed in Purkinje cells, and involved in an intracellular second messenger pathway. The exact pathophysiology is currently unknown, but probably involves haploinsufficiency resulting in disturbed intracellular calcium homeostasis.

Epidemiology and Relevance

It recently became evident that SCA16 is also due to partial deletions of the *ITPR1* gene (see below). Therefore, at present, six families with *ITPR1* mutations have been reported. Hara et al. did not observe mutations of this gene in 54 unrelated Japanese dominant ataxia families with unknown genotypes. Further screening efforts are awaited to assess the relative frequency of *ITPR1* mutations in dominant spinocerebellar ataxias.

Spinocerebellar Ataxia Type 16 (now also referred to as Type 15)

Clinical Features

In the single Japanese SCA16 family, onset of disease ranged from 20 to 66 years. In addition to the slowly progressive cerebellar features, mild cognitive impairment and a head tremor were noted in some affected members.

Genetics and Pathophysiology

Initially, SCA16 was mapped to chromosome 8q22.1–24.1, but was later reassigned to 3p26.2-pter, partly overlapping the SCA15 locus. A 'point mutation' (4.256C→T) in the 3′-UTR of the *CNTN4* gene, coding for contactin-4, was found to cosegregate with disease. After the finding of *ITPR1* mutations in SCA15, Iwaki et al. also tested for this gene given the overlap between the SCA16 and SCA15 loci. They identified a deletion of exons 1–48 of the *ITPR1* gene. The previously observed *CNTN4* variant is probably a rare polymorphism in linkage disequilibrium with the *ITPR1* mutation.

Epidemiology and Relevance

The single SCA16 family turned out to have an *ITPR1*/SCA15 mutation, and one could thus argue that the designation SCA16 is now invalid or perhaps vacant.

See also: SCA1; SCA2; SCA3, Machado–Joseph Disease; SCA4; SCA5; SCA6; SCA7, Spinocerebellar Ataxia with Macular Dystrophy; SCA10; SCA11; SCA12; SCA17; SCA27; Spinocerebellar Ataxia Type 19, 20, 21, 22, 23, 26.

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SCA17

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Definition

Spinocerebellar ataxia type 17 (SCA17) is an autosomal dominant neurodegenerative disorder caused by expansion of a CAG/CAA repeat coding for a polyglutamine stretch of the TATA-binding protein (TBP) gene. Expansions of polyglutamine stretches have been identified in at least nine hereditary neurodegenerative diseases including spinal and bulbar muscular atrophy (SBMA), Huntington's disease (HD), SCA1, 2, 6, 7, and 17, Machado–Joseph disease (also called SCA3), and dentatorubral-pallidoluysian atrophy (DRPLA). SCA17 is the latest member among these polyglutamine diseases.

Clinical Features and Diagnostic Criteria

The clinical features of SCA17 are characterized by ataxia, psychiatric symptoms including personality changes, cognitive impairment, and extrapyramidal symptoms including chorea, dystonia, and parkinsonism. The mean age of onset is about 30 years ranging from 3 to 55 years. The initial symptoms at onset are ataxic gait in many cases, but other symptoms including psychiatric symptoms, cognitive impairment, and extrapyramidal symptoms may appear first. Furthermore, it should be noted that the clinical presentations of SCA17 are highly heterogeneous and that some patients exhibit clinical presentations indistinguishable from those of HD, emphasizing the broad spectrum of the clinical presentations of SCA17.

Normal alleles range from 25 to 42 repeat units. Although affected individuals carry expanded alleles ranging from 43 to 63, alleles of 43–48 are not fully penetrant. The configuration of the expanded alleles is heterogeneous with interrupting CAA elements. As observed in other polyglutamine diseases, there is an inverse correlation between the size of expanded CAG repeats and the age of onset. Patients carrying expansions of CAG/CAA repeats in both alleles tend to exhibit earlier ages of onset, severer clinical presentations, and a more rapid disease progression compared with those carrying a single allele of expanded allele.

Expansion of the CAG repeat of TBP gene was first described by Koide et al. in a 14-year-old Japanese patient with a de novo partial duplication of the CAG/CAA repeat in the TBP gene. The patient had an expanded CAG/CAA repeat gene coding for 63 glutamines. The initial symptoms at the age of 6 years were ataxic gait and intellectual deterioration. The patient showed a severely impaired intellectual performance, cerebellar ataxia of the limbs and the trunk, dysarthria, dysphagia, and hyperreflexia with extensor plantar responses.

Subsequently, familial cases with expansion of the CAG repeats of the TBP gene have been reported. Nakamura et al. identified four Japanese pedigrees. The CAG/CAA repeats of the TBP gene were expanded to 47–55 repeat units. The mode of inheritance was an

autosomal dominant one with incomplete penetrance. The age of onset ranged from 19 to 48 years with the mean age of onset of 33.2 years. Including the case with de novo expansion of the CAG/CAA repeat, a strong inverse correlation between the age of onset and the size of expanded CAG/CAA repeats was observed. The clinical presentations included gait ataxia, dementia, hyerreflexia, and parkinsonism. Dystonia, chorea, and epilepsy were present in some patients. Stevanin et al. screened a group of patients with Huntingon's disease-like phenotype and identified two patients with expansions of CAG repeats (44 and 46 repeat units) in the TBP gene. The patient with 46 repeat units showed behavioral changes, chorea, ataxic gait, dysarthria, increased tendon reflexes, and parkinsonism. The other patient had gait instability, behavioral abnormality, dementia, and increased tendon reflexes with extensor plantar responses. Oda et al. conducted a large scale screening for CAG/CAA repeat expansions of the TBP gene. By screening 734 patients with SCA, 216 with Parkinson disease and 195 with Alzheimer disease, they identified eight SCA patients with alleles exceeding 43 CAG/CAA repeat units. Alleles with 43–45 repeats were seen in three of the normal subjects and in two patients with Parkinson disease. They further identified a 34-year-old patient carrying 47 and 44 repeats, who had developed progressive cerebellar ataxia and myoclonus at the age of 25 and exhibited dementia and pyramidal signs, while his father and mother were asymptomatic but carried 44 and 47 repeats, respectively, as a heterozygous state, strongly supporting a gene dosage effect of expanded alleles.

Differential Diagnosis

Given the highly heterogeneous heterogeneities of the clinical presentations, the possibility of SCA17 should be considered for patients with the family history compatible with autosomal dominant inheritance and with clinical presentations including ataxia, cognitive impairment, and psychiatric symptoms such as personality changes, chorea, dystonia, or parkinsonism. Differential diagnosis should include various forms of autosomal dominant SCAs, HD, and HD-like phenotypes and neuroferritinopathy. It should be noted that there are reports of sporadic cases of SCA17. The diagnosis is confirmed by molecular testing of the CAG/CAA repeats of TBP gene. There are no specific treatments for SCA17 available, and the treatment largely remains to be symptomatic treatment.

Pathogenesis/Pathophysiology

Among the nine polyglutamine diseases, the physiological functions of the gene products have been known only for SCA6, SBMA, and SCA17. Thus, SCA17 is a good target for investigating the pathophysiologic mechanisms of neurodegeneration. TBP is an important general transcription initiation factor and is the DNA-binding subunit of RNA polymerase II transcription factor D (TFIID), the multisubunit complex crucial for the expression of most genes. Intranuclear accumulation of mutant proteins carrying expanded polyglutamine stretches and subsequent nuclear dysfunction through association of mutant proteins with various transcriptional factors have been considered to play essential roles in the pathogenesis of polyglutamine diseases. Intranuclear inclusions identified in autopsied brains of SCA17 cases support this hypothesis. In contrast to the 'gain-of-toxic function' hypothesis, interference with the physiological functions of TBP may also be involved in the pathophysiologic mechanisms.

Recent studies have demonstrated that expansion of polyglutamine stretches causes abnormal interaction of TBP with the general TFIIB and induces neurodegeneration in transgenic SCA17 mice. Furthermore, it has been shown that mutant TBP with expanded polyglutamine stretches with a deletion spanning part of the DNA-binding domain does not bind DNA in vitro but forms nuclear aggregates and inhibits TATA-dependent transcription activity in cultured cells. These findings suggest that the polyglutamine stretches affect the binding of TBP to promoter DNA and that mutant TBP with expanded polyglutamine stretches can induce neuronal toxicity independently of its interaction with DNA.

See also: Ataxia; Huntington's Disease; Spinocerebellar Ataxias Genetics.

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SCA27

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Glossary

Anticipation – When symptoms of a genetic disorder become apparent at an earlier age from one generation to the next.
Ataxia – A lack of coordination of movement.
Dyskinesias – Repetitive involuntary movements, similar to a tic or chorea. Can occur at any part of the body.
Dystonia – Sustained muscle contractions cause twisting and repetitive movements, or abnormal posture of a body segment.
Growth factor – Refers to a naturally occurring substance capable of stimulating cellular growth, proliferation, and differentiation.
Homeostatic factors – Factors regulating the internal environment to maintain a system stable.
Nav channel – Voltage-gated sodium channel.
Orthologous – Refers to any similarity between characteristics that is due to their shared ancestry.
Penetrance – A term used in genetics to describe the proportion of individuals carrying a particular variation of a gene (an allele or genotype) and expressing an associated trait (the phenotype).
Promoter – A region of DNA facilitating the transcription of a particular gene.
Proteoglycans – Glycoproteins heavily glycosylated.
Splice variants – Is the RNA splicing variation mechanism in which the exons of the primary gene transcript, the pre-mRNA, are separated and reconnected to produce alternative ribonucleotide arrangements.
Tremor – Rhythmic movement involving to-and-fro movements (oscillations) of one or several body parts.
Tyrosine kinase receptors – Are high-affinity cell surface receptors for many polypeptide growth factors, cytokines, and hormones.
Voltage-gated sodium channels – Membrane proteins forming ion channels, conducting sodium ions (Na^+) through the plasma membrane. They are activated at depolarized membrane potentials.

Definition and History

For autosomal dominantly inherited cerebellar ataxias (ADCA), about 25 genetic loci have been identified by linkage analysis, and mutations in $\geq$12 of the corresponding genes have been reported. Molecular analysis of these genes reveals expansions of tri- or penta-nucleotide repeat causing 10 spinocerebellar ataxias (SCAs). Trinucleotide repeats occurr in SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, SCA12, SCA17, and DRPLA, while the pentanucleotide repeat expansion is found in SCA10.

Recently, a missense point mutation in the gene encoding for the fibroblast growth factor 14 (FGF14) on chromosome 13q34, FGF14*phe145ser* ($FGF14^{F145S}$), was identified in a Dutch family presenting with multiple neurological deficits including impaired cognitive abilities and spinocerebellar ataxia. The disorder is now classified as spinocerebellar ataxia 27 [OMIM (Online Mendelian Inheritance in Man) number 609307, SCA27].

SCA27 is characterized by the absence of anticipation and a complete penetrance.

The Family of Fibroblast Growth Factors (FGFs)

Fibroblast growth factors (FGFs) make up a large family of polypeptide growth factors found in organisms ranging from nematodes to humans. In vertebrates, the 22 members of the FGF family range in molecular mass from 17 to 34 kDa and share 13–71% amino-acid identity. Between vertebrate species, FGFs are highly conserved in both gene structure and amino-acid sequence. FGFs have a high affinity for heparan sulfate proteoglycans. They require heparan sulfate to activate one of four cell surface FGF receptors. During embryonic development, FGFs have diverse roles in regulating cell proliferation, migration, and differentiation. In the adult organism, FGFs are homeostatic factors and participate in tissue repair and response to injury. When inappropriately expressed, some FGFs can contribute to the pathogenesis of cancer. A subset of the FGF family, expressed in adult tissues, is important for neuronal signal transduction in the central and peripheral nervous systems.

Genetics of FGFs

The FGF gene expression has been hypothesized to be coincident with a phase of global gene duplications taking place during the period leading to the emergence of vertebrates (Coulier et al., 2000).

Most FGFs are found scattered throughout the genome. In mice, there are at least 22 FGF genes (Gene bank; Mouse Genome Informatics), and the locations of 16 of them have been identified. In humans, 22 FGF genes have been identified and the chromosomal locations (except for FGF16) are known (GenBank; HUGO Gene Nomenclature Database).

The prototypical FGF genes contain three exons. Exon 1 contains the initiation methionine, but several FGF genes (for instance FGF2 and FGF3) have additional 5′ transcribed sequence initiating from upstream CUG codons. The size of the coding portion of FGF genes ranges from under 5 kb (in FGF3 and FGF4) to over 100 kb (in FGF12). Some subfamilies of FGFs (such as FGF11–14) have alternative amino termini, due to the use of alternative 5′ exons. It is still unknown whether a common 5′ untranslated exon splices to these exons or whether an alternative promoter and regulatory sequences are used.

Across species, most orthologous FGF proteins are highly conserved and share more than 90% amino-acid sequence identity. To date, FGF 2, 4, 8, 12, 14, 18, and 19 have been identified in chicken (Gene Bank), whereas others have been identified in zebrafish and *Xenopus*. Most FGF share an internal core region of similarity, with 28 highly conserved and six identical amino-acid residues. Ten of these highly conserved interact with the FGF receptor (FGFR). FGF 11–14 lack signal sequences and are thought to remain intracellular.

The 22 members of the mammalian FGF family are differentially expressed in many tissues, but the patterns and timing of expression vary. Each FGF appears to have unique sites of expression. Some FGFs are expressed exclusively during embryonic development (FGF3, 4, 8, 15, 17, 19), whereas others are expressed in embryonic and adult tissue (FGF1, 2, 5–7, 9–14, 16, 18, and 20–23). The expression pattern of FGFs suggests that they play important roles in development. FGFs often signal directionally and reciprocally across epithelial–mesenchymal boundaries. The integrity of these signaling pathways requires an extremely tight regulation of FGF activity and receptor specificity.

Fibroblast Growth Factor 14 (FGF14)

The fibroblast growth factor 14 (FGF14) gene is located at chromosome 14q34 (**Table 1**). FGF14 belongs to the intracellular FGF homologous factor family (iFGFs), a set of neuronally expressed FGFs (iFGF11–14) that are not secreted and do not activate tyrosine kinase receptors.

Human FGF 14 (FHF 4) is a 245 amino-acid polypeptide containing no signal sequence and possessing a bipartite NLS with a secondary signal motif. The gene is composed of five exons. There are three splice variants: a 245 amino-acid (FGF 14A), a 252 amino-acid (FGF 14B), and a 163 amino-acid (mouse only, FGF 14C) isoform. Splice forms A and B are N-terminal extensions of the common to all 163 amino-acids of the C-terminal sequence of FGF 14.

FGF14 is highly expressed in the brain, in particular, in the cerebellum (the highest levels are in granule cells), the hippocampus, and the nondopaminergic cells in the striatum. The neurological phenotype developed by SCA27 individuals suggests that FGF14 is important for the normal function of several areas of the central and peripheral nervous system.

Protein structure studies suggest that substitution of the *phenylalanine* with a *serine* in position 145 strongly reduces the stability of FGF14, resulting in a loss of function of the protein (**Figure 1**).

The iFGFs interact directly with the pore forming (alpha) subunits of neuronal and cardiac voltage-gated Nav channels. Heterologous coexpression of FGF12, FGF13, or FGF14 with Nav α subunits affects Nav current densities and the voltage dependences of Nav channel activation and inactivation. $FGF14^{F145S}$ expression directly disrupts neuronal excitability by interfering with the functioning of Nav channels. Indeed, expression

Table 1 Chromosomal localization of FGF14 in human and mouse

Human		*Mouse*		*References*	*Accession numbers*	
Gene	Location	Gene	Location		Human	Mouse
FGF14 (FHF4)	13q34	Fgf14	14	Smallwood et al.	U66200	U66204

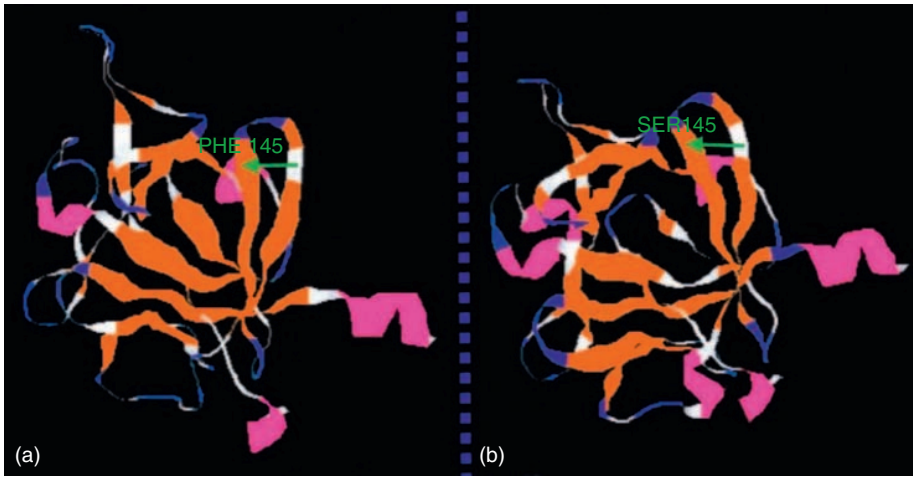

Figure 1 Molecular models of the structure of the normal (a) and mutant (b) FGF14 protein. The pink and orange zones correspond to the α-helix and β-sheet structures, respectively. Green arrows indicate the wild-type PHE145 residue (a) and the mutated SER145 residue (b).

of $FGF14^{F145S}$ attenuates peak Nav current densities in hippocampal neurons. More specifically, $FGF14^{F145S}$ disrupts the interaction between FGF14 and Nav1.2. Alterations in Nav channel expression or function modify neuronal membrane excitability and impair information processing in neuronal networks. As a general rule, mutations in genes encoding Nav channel subunits or alterations in the expression of proteins necessary for the localization of Nav channels affect the output properties of central neurons. These abnormalities could contribute to the deficits observed in FGF14.

Genetic ablation of FGF14 in mice ($FGF14^{-/-}$) causes ataxia, paroxysmal dystonia, and cognitive deficits. In fact, the similarities with the human symptoms led to the discovery of the mutation. The autosomal dominant nature of the $FGF14^{F145S}$ mutation and the analogy between the phenotypes of SCA27 patients and $FGF14^{-/-}$ mice further suggests that the $FGF14^{F145S}$ mutation induces a loss of FGF14 function, by blocking the interactions between wild-type FGF14 and Nav α subunits. In the hippocampus, FGF14 is expressed in pyramidal neurons and in the dentate gyrus, and loss of FGF14 in $FGF14^{-/-}$ mice results in an impaired long-term potentiation (LTP) at Schaffer collaterals–CA1 synapses and acquisition deficits in the Morris water maze. Globally, these transgenic mice exhibit altered presynaptic vesicle trafficking, docking, and synaptic protein expression.

Clinical Description

A large four-generation white family of Dutch descent with autosomal dominant ataxia was reported by van Swieten et al. Patients exhibit a high-frequency small-amplitude postural tremor of the hands starting in childhood, progressive ataxia involving the oculomotor system (dysmetric saccades, saccadic pursuit, gaze-evoked nystagmus), speech, limbs, posture and gait, as well as psychiatric manifestations or behavioral deficits (aggressive outbursts, depression), and facial- or orofacial-dyskinesias. Brisk knee jerks and diminished vibration sense at the ankles were noted for several patients.

Epidemiology

SCA-27 is a rare disorder. The precise incidence and prevalence of SCA-27 are unknown. Alterations of the FGF14 gene are not a major cause of SCA in Caucasians.

Ancillary Investigations

Brain MRI shows moderate cerebellar atrophy in some patients, but may also yield normal results. Reduced dopamine D2-receptor binding of the striatum may be

Table 2 Differential diagnosis of SCA27

Movement disorders	*Cognitive impairment/ behavioral symptoms*	*Axonal neuropathy*
Parkinsonism: SCA1, SCA2, SCA3, SCA12, SCA17, SCA21	SCA1, SCA2, SCA3, SCA13, SCA17, SCA19, SCA21, DRPLA, FXTAS syndrome, HDL-2	SCA1, SCA2, SCA3, SCA4, SCA6, SCA8, SCA12, SCA18, SCA22, SCA25
Dystonia: SCA3, SCA17		
Tremor: SCA8, SCA12, SCA16 (head/hand), SCA19, SCA20 (palatal), FXTAS syndrome		
Myoclonus: SCA2, SCA14, SCA19, DRPLA		
Chorea: SCA1, SCA17, DRPLA, HDL-2		
Paroxysmal ataxias (EAs)		

SCA, spinocerebellar ataxia; FXTAS, Fragile X associated tremor/ataxia syndrome; DRPLA, dentatorubral-pallidoluysian atrophy; Eas, episodic ataxias; HDL2, Huntington disease-like 2.

demonstrated by brain SPECT. Neuropsychological testing shows deficits in memory and executive functioning. Low IQ scores are found in about 20% of cases. Nerve conduction studies disclose a mild axonal neuropathy.

Differential Diagnosis

The main differential diagnoses of SCA-27 are summarized in **Table 2**.

Prognosis and Management

The ataxia of SCA-27 is slowly progressive over decades. Life expectancy is normal. Therapy is based upon rehabilitation. Symptomatic therapy of dyskinesias provides some relief. We are lacking in an effective therapy for ataxic symptoms. Several studies are currently performed in animal models of SCAs, especially in mice, with the aim of either preventing or reducing neurodegeneration.

See also: Ataxia; Dystonia; Multiple System Atrophy: Animal Models; SCA1; SCA2; SCA3, Machado–Joseph Disease; SCA4; SCA5; SCA6; SCA7, Spinocerebellar Ataxia with Macular Dystrophy; SCA8; SCA10; SCA11; SCA12; SCA13, 14, 15, and 16; SCA17; SCA27.

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Scale for the Assessment and Rating of Ataxia (SARA)

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Glossary

Ataxia – Literally (Greek) absence of order. Clinically referred to as a specific motor syndrome, with difficulty to stabilize the trunk against gravity, difficulty to stabilize gaze, difficulty in goal-directed limb movements, and dysarthria.
Cerebellar sign – Neurological sign attributed to lesions of the cerebellum.
Clinical rating scale – Assessment tool used to document and compare disease status, for example, in clinical trials, that is based on a standardized clinical examination of selected disease features. Standardization refers to instructions of test performance and rating.
Outcome parameter – Type of assessment that is chosen to document and compare the effects of an intervention in clinical trials. This can be a clinical scale or any instrumental or laboratory test known to change with disease severity.
Reliability – Accuracy of an assessment tool, that is, how consistent or repeatable are the measurements. For clinical rating scales, reliability is usually documented by good internal consistency and minimal variance between different raters (interrater) or between test and retest.
Validity – Appropriateness of content of an assessment tool, that is, does it measure what it is intended to measure. It is usually documented by good correlations with other assessments of the same construct: for example a clinical scale supposed to measure disease severity could be compared to other measures known to change with disease severity.
Sensitivity – Ability of an assessment tool to pick up differences between different disease states. Sufficient sensitivity (or responsiveness) to change over time is a prerequisite for use of a clinical rating scale as an outcome parameter in clinical trials.

Definition and History

The conduct of multicenter therapeutic trials requires reliable and sensitive assessment tools. For this purpose, clinical rating scales have been established for different diseases and for the testing of potential therapeutic agents. Spinocerebellar ataxias (SCAs) are a clinically and genetically heterogeneous group of autosomal-dominantly inherited progressive ataxia disorders. In the most common genotypes, the disease is caused by translated CAG repeat expansion mutations in different genes. The size of this repeat influences the age at onset, phenotype and disease progression in some genotypes.

The Scale for the Assessment and Rating of Ataxia (SARA) was first published in 2006 as a short and reliable clinical rating scale validated in a two large SCA cohorts (**Figure 1**). However, later studies have recommended its use also for other ataxia disorders including Friedreich ataxia (FRDA).

Development

The clinical group of the European integrated project on spinocerebellar ataxias (EUROSCA) developed and validated a clinical rating scale for ataxia, in preparation of a large multicenter study on the natural history of spinocerebellar ataxias. The authors argued that although the previously published International Cooperative Ataxia Rating Scale (ICARS) was developed by an international consortium for use in ataxia, it was not sufficiently validated at that time and was perceived to have shortcomings in practicality, rating instructions, and scale structure. The authors acknowledged that follow-up in the rare and slowly progressive SCAs would require most reliable and sensitive outcome parameter. Their new clinical scale should be easy to use by being short and close to a standard neurological exam, without instrumental testing. Items were selected by expert agreement for their specificity for cerebellar ataxia and their assumed sensitivity to change. For example, gaze-evoked

Rater: _____date: _____patient:_____

Scale for the assessment and rating of ataxia (SARA)

1) Gait	**2) Stance**
Proband is asked (1) to walk at a safe distance parallel to a wall including a half-turn (turn around to face the opposite direction of gait) and (2) to walk in tandem (heels to toes) without support. **0 Normal, no difficulties in walking, turning and walking tandem (up to one misstep allowed)** **1 Slight difficulties, only visible when walking 10 consecutive steps in tandem** **2 Clearly abnormal, tandem walking > 10 steps not possible** **3 Considerable staggering, difficulties in half-turn, but without support** **4 Marked staggering, intermittent support of the wall required** **5 Severe staggering, permanent support of one stick or light support by one arm required** **6 Walking > 10 m only with strong support (two special sticks or stroller or accompanying person)** **7 Walking < 10 m only with strong support (two special sticks or stroller or accompanying person)** **8 Unable to walk, even supported**	Proband is asked to stand (1) in natural position, (2) with feet together in parallel (big toes touching each other) and (3) in tandem (both feet on one line, no space between heel and toe). Proband does not wear shoes, eyes are open. For each condition, three trials are allowed. Best trial is rated. **0 Normal, able to stand in tandem for > 10 s** **1 Able to stand with feet together without sway, but not in tandem for > 10 s** **2 Able to stand with feet together for > 10s, but only with sway** **3 Able to stand for > 10 s without support in natural position, but not with feet together** **4 Able to stand for > 10 s in natural position only with intermittent support** **5 Able to stand > 10 s in natural position only with constant support of one arm** **6 Unable to stand for > 10 s even with constant support of one arm**
Score	**Score**
3) Sitting	**4) Speech disturbance**
Proband is asked to sit on an examination bed without support of feet, eyes open and arms outstretched to the front. **0 Normal, no difficulties sitting >10 sec** **1 Slight difficulties, intermittent sway** **2 Constant sway, but able to sit > 10 s without support** **3 Able to sit for > 10 s only with intermittent support** **4 Unable to sit for >10 s without continuous support**	Speech is assessed during normal conversation. **0 Normal** **1 Suggestion of speech disturbance** **2 Impaired speech, but easy to understand** **3 Occasional words difficult to understand** **4 Many words difficult to understand** **5 Only single words understandable** **6 Speech unintelligible / anarthria**
Score	**Score**

Figure 1 (Continued)

Rater: _____date: _____patient:_____

5) Finger chase

Rated separately for each side
Proband sits comfortably. If necessary, support offeet and trunk is allowed. Examiner sits in front of proband and performs 5 consecutive sudden and fast pointing movements in unpredictable directions in a frontal plane, at about 50 % of proband´s reach. Movements have an amplitude of 30 cm and a frequency of 1 movement every 2 s. Proband is asked to follow the movements with his index finger, as fast and precisely as possible. Average performance of last 3 movements is rated.

0 No dysmetria
1 Dysmetria, under/ overshooting target < 5 cm
2 Dysmetria, under/ overshooting target < 15 cm
3 Dysmetria, under/ overshooting target > 15 cm
4 Unable to perform 5 pointing movements

Score	**R**ight	**L**eft
Mean of both sides (R+L)/2		

6) Nose-finger test

Rated separately for each side
Proband sits comfortably. If necessary, support of feet and trunk is allowed. Proband is asked to point repeatedly with his index finger from his nose to examiner's finger which is in front of the proband at about 90 % of proband's reach. Movements are performed at moderate speed. Average performance of movements is rated according to the amplitude of the kinetic tremor.

0 No tremor
1 Tremor with an amplitude < 2 cm
2 Tremor with an amplitude < 5 cm
3 Tremor with an amplitude > 5 cm
4 Unable to perform 5 pointing movements

Score	**R**ight	**L**eft
Mean of both sides (R+L)/2		

7) Fast alternating hand movements

Rated separately for each side
Proband sits comfortably. If necessary, support of feet and trunk is allowed. Proband is asked to perform 10 cycles of repetitive alternation of pro- and supinations of possible. Movement is demonstrated by examiner at a speed of approx. 10 cycles within 7 s. Exact times for movement execution have to be taken.

0 Normal, no irregularities (performs <10 s)
1 Slightly irregular (performs <10 s)
2 Clearly irregular, single movements difficult to distinguish or relevant interruptions, but performs < 10 s
3 Very irregular, single movements difficult to distinguish or relevant interruptions, performs > 10 s
4 Unable to complete 10 cycles

Score	**R**ight	**L**eft
Mean of both sides (R+L)/2		

8) Heel-shin slide

Rated separately for each side
Proband lies on examination bed, without sight of his legs. Proband is asked to lift one leg, point with the heel to the opposite knee, slide down along the shin to ankle, and lay the leg back on the examination bed. The task is performed 3 times. Slide-down movements should be performed within 1 s. If proband slides down without contact to shin in all three trials, rate 4.

0 Normal
1 Slightly abnormal, contact to shin maintained
2 Clearly abnormal, goes off shin up to 3 times during 3 cycles
3 Severely abnormal, goes off shin 4 or more times during 3 cycles
4 Unable to perform the task

Score	**R**ight	**L**eft
Mean of both sides (R+L)/2		

Figure 1 Illustration of full SARA text. Sum score is formed by addition of cells highlighted in grey.

nystagmus, although specific for cerebellar dysfunction, was not included in the scale, as it can disappear in later disease stages with the progression of (noncerebellar) ophthalmoparesis. Further, nonataxia signs and symptoms frequently occur in ataxia disorders and may contribute to disease severity. In contrast to the previously published Friedreich Ataxia Rating Scale (FARS), which includes rating of some noncerebellar symptoms, SARA claims to measure ataxia only, irrespective of additional symptoms. However, the authors proposed a complementary 30-item Inventory of Non-Ataxia Symptoms (INAS) to account for such extracerebellar involvement in spinocerebellar ataxias.

Scale Structure

The scale consists of eight items that reflect neurological manifestations of cerebellar ataxia: gait, stance, sitting, speech, finger-chase, nose-finger-test, fast alternating hand movements, and heel-shin-slide. The ratings in each item range from 0 (= normal, absence of sign) to a maximum of 8 (gait), 6 (stance and speech) and 4 (for the remaining items). The items of limb coordination are performed and rated separately for right and left sides. The average of both sides is included in the SARA total score, a simple sum score of all eight items that ranges from 0 (= no ataxia) to 40 (= maximal ataxia or unable to perform).

Metric Properties and Validation Studies

The scale was originally published with data from two large validation trials performed in 167 and 119 SCA patients and 110 controls. The patient group covered a wide range of disease severity with SARA ratings of 15.9±8.5 (range 1.5–40) while controls had ratings of 0.4±1.1 (range 0–7.5). Thus, at the lower end of the scale, some overlap between mild cerebellar syndrome and no affection was seen with this scale. Practicality was good with time to administer reported as 14 min. Factorial analysis determined one factor that explained 80% of SARA variance after exclusion of one oculomotor item contained in an earlier version of the scale. This supports the concept of SARA as a one- dimensional scale that measures one single construct, ataxia. Internal consistency of the scale was high (Cronbach's alpha 0.94). In a subgroup of 95 patients, interrater reliability was excellent (ICC 0.98) for the sum score and most items (less for finger–nose test and heel–shin slide on the left side). The results of factorial analysis, high internal consistency and high interrater reliability (less for upper limb kinetic items) have later been replicated in a smaller validation trial in 64 moderately affected patients with different ataxia disorders (mainly sporadic adult-onset ataxia) and, recently, in a cohort of 96 FRDA patients. The test-retest reliability of SARA in a subset of 15 assessments of the original cohort with 1–34 days intervals was also high (ICC 0.9). The linearity of the scale has been evaluated by regression of SARA ratings versus global assessments of ataxia severity from 11 video cases. Results supported a linear model (r^2 0.98). The relation of SARA ratings with global ratings of mobility or with different measures of functional independence in the original SCA cohorts, but also in the sample of 64 cases with other ataxia disorders and in another study of 96 FRDA patients support validity of the scale and clinical relevance of score differences in different ataxia disorders. Further, in FRDA patients, SARA was highly correlated with ICARS and FARS (part III) sum scores. A correlation of SARA with disease duration reported for SCA as well as FRDA patients, suggests sensitivity to change in disease status over time.

Clinical Trials

SARA is currently used in a large European multicenter trial to evaluate the natural history of SCAs. Data from the baseline assessment have been published: SARA total was independently predicted by disease duration, age of onset and length of the expanded repeat in multivariate models that explained 60% (SCA1), 45% (SCA2), and 47% (SCA3) of the variance. In SCA6, SARA total was only determined by disease duration and age of onset. The 30-item Inventory of Non-Ataxia Symptoms (INAS) as a measure of noncerebellar affection was related to SARA in some genotypes. In addition, SARA was related to measures of subjective health status (EQ-5D) in the same study. The EUROSCA clinical group also devised the Spinocerebellar Ataxia Functional Index (SCAFI) as a composite of three timed performance measures −8 m walk, 9-hole peg test and PATA rate – that was highly correlated with SARA ratings in SCA patients over the whole range of disease severity. Likewise, another study in 141 autosomal-dominant ataxia patients reported a high correlation of SARA with (dominant-hand) performance in two measures of hand dexterity. To date, three interventional pilot studies used SARA to evaluate the effect of pregabalin, aminopyridine, or recombinant erythropoietin on ataxia severity in different disorders. SARA is also included as a secondary outcome measure in an ongoing pilot study of Lithium in SCA1.

Criticism

Estimates of progression rates, which are required for sample size calculations in clinical trials, have only been reported from regression with disease duration for SARA and the proposed complementary functional measure SCAFI. The ongoing EUROSCA natural history study will yield such estimates prospectively for the most common SCA genotypes: SCA1, SCA2, SCA3, and SCA6. Whether timed performance measures will be more favorable than SARA in terms of objectivity and sensitivity in therapeutic trials remains to be shown. Of note, separate evaluations of progression rates in other ataxia disorders than SCA will be needed for the planning of interventional trials in other target groups. As SARA did not differentiate well between mild ataxia and the performance of healthy controls, some limitation in specificity has to be considered when used in mildly affected patient groups.

Conclusion

SARA is an 8-item short and simple clinical rating scale for use in ataxia disorders. Oculomotor dysfunction was excluded from the scale during the validation process to improve its metric properties that are otherwise favorable

for use in clinical trials. Practicality was reported as superior to the ICARS, and the high reliability allows the use of SARA for interindividual and intraindividual comparisons. Further, linearity of the scale was reported in the original publication. Validation data are currently most abundant for spinocerebellar ataxia, including the ongoing evaluation of progression rates. However, favourable metric properties for SARA have also been confirmed in other ataxia disorders including FRDA.

See also: Ataxia; Ataxia with Isolated Vitamin E Deficiency; Friedreich's Ataxia and Variants; Friedreich's Ataxia Rating Scale (FARS); International Cooperative Ataxia Rating Scale (ICARS); Kuru; Multiple System Atrophy; Parkinson Hyperpyrexia Syndrome; Rating Scales in Movement Disorders; SCA1; SCA2; SCA3, Machado–Joseph Disease; SCA4; SCA5; SCA6; SCA7, Spinocerebellar Ataxia with Macular Dystrophy; SCA8; SCA10; SCA11; SCA12; SCA13, 14, 15, and 16; SCA17; SCA27.

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Relevant Websites

www.ataxia-study-group.net – European Integrated Project on Spinocerebellar Ataxia (EUROSCA).

www.eurosca.org – Ataxia Study Group, a consortium of scientific investigators for the study of ataxia disorders founded in 2008.

Schwab and England Activities of Daily Living Scale

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Glossary

Convergent validity – The ability of a measurement scale to correlate with other measures of the same variable.

Inter-rater reliability – The degree of agreement among raters using the scale.

Definition and History

The Schwab and England (S & E) Activities of Daily Living (ADL) Scale was originally used to evaluate response to basal ganglia surgery (see **Figure 1**). The intent was to describe the functional capacity of Parkinson's disease (PD) patients as a proportion of full, normal function. The scale was also meant to have 'interval properties' such that a change of 10% at the bottom of the scale is equivalent to a change of 10% at the higher end of the scale.

The S & E Scale may be administered in a variety of ways. Although the scale contains 100 possible points, most raters use either 11 steps (with 10 points between each step) or 21 steps (with 5 points between each step). Common variants are to use the scale to rate function in the medication 'on' or 'off' state for fluctuating patients, or to use either physician and/or patient input to generate a score. At the time of the scale's original publication, specific instructions were not included so that there was no official method of administration or application. In practice and research, the choices of administration depend on the purpose of the individual clinical evaluation or research study.

Although the S & E Scale is widely used in research and clinical practice, there is little information regarding its metric properties. However, the available data suggest

100%-Completely independent. Able to do all chores w/o slowness, difficulty, or impairment.
90%-Completely independent. Able to do all chores with some slowness, difficulty, or impairment. May take twice as long.
80%-Independent in most chores. Takes twice as long. Conscious of difficulty and slowing
70%-Not completely independent. More difficulty with chores. 3 to 4X along on chores for some. May take large part of day for chores.
60%-Some dependency. Can do most chores, but very slowly and with much effort. Errors, some impossible
50%-More dependant. Help with 1/2 of chores. Difficulty with everything
40%-Very dependant. Can assist with all chores but few alone
30%-With effort, now and then does a few chores alone of begins alone. Much help needed
20%-Nothing alone. Can do some slight help with some chores. Severe invalid
10%-Totally dependant, helpless
0%-Vegetative functions such as swallowing, bladder and bowel function are not functioning. Bedridden.

Figure 1 Schwab and England ADL Scale.

that it has high inter-rater reliability, convergent validity with other PD rating scales, and responsiveness to change over time. It has also shown significant changes in a variety of therapeutic settings.

Summary

The S & E Scale is a well-established and recognized outcome in clinical trials of PD. Its mode of application varies according to different uses, but it provides a clinically pertinent measure of the daily function for PD.

See also: Fahn–Marsden Rating Scale; Hoehn and Yahr Staging Scale; MMSE - Mini-Mental State Examination; Yale Global Tic Severity Scale (YGTSS).

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Senataxin

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Glossary

Aprataxin – Protein, encoded by the APTX gene, defective in ataxia with oculomotor apraxia type 1.
α-Fetoprotein serum level – Blood dosage of a tumor-associated fetal glycoprotein of 70 kD synthesized in the fetal yolk sac, liver, and intestines. α-Fetoprotein is the major protein of fetal serum, replaced by albumin after birth, and has a half-life of 5–7 days. α-Fetoprotein may bind and transport fatty acids, steroids, heavy metal ions, and drugs and plays a role as a growth regulator.
Oculomotor apraxia – Inability to generate volitional horizontal saccades with a characteristic compensatory headthrusting and synkinetic blinking. It is not a true apraxia, but rather an intermittent saccade failure responsible for dissociation between eyes and head movements during the rotation of the head, which reaches the target before the eyes.
Senataxin – Protein, encoded by the SETX gene, defective in ataxia with oculomotor apraxia type 2.

Clinical Features

Ataxia with oculomotor apraxia type 2 (AOA2) belongs to the autosomal recessive cerebellar ataxias (ARCA), which are rare and early disabling neurodegenerative diseases dominated by Friedreich ataxia. The onset of the disease

usually occurs between 12 and 20 years of age, and the patients become wheelchair bound near 30 years of age. The clinical phenotype, which is homogeneous, is characterized by cerebellar ataxia, which is the initial sign in more than 80% of cases and progressively worsens, axonal sensorimotor peripheral neuropathy (95%), oculomotor apraxia (OMA) characterized by hypometric horizontal saccades and normal or increased latencies (30–50%), strabismus (10–30%), chorea and/or dystonia (20–40%), and pyramidal signs (10–15%). Laboratory examination in AOA2 reveals prominently elevated α-fetoprotein (AFP) serum levels in 99% of patients and less frequently elevated creatine kinase (CK) serum levels. Slightly elevated AFP levels in healthy subjects with SETX heterozygous mutation have been reported. Brain magnetic resonance imaging (MRI) shows diffuse cerebellar atrophy with relative sparing of the brainstem (**Figure 1**) and electroneuromyography confirms the peripheral neuropathy. A postmortem study revealed a marked loss of cerebellar Purkinje cells as well as mild fibrous gliosis that was more severe in the vermis than in the hemispheres.

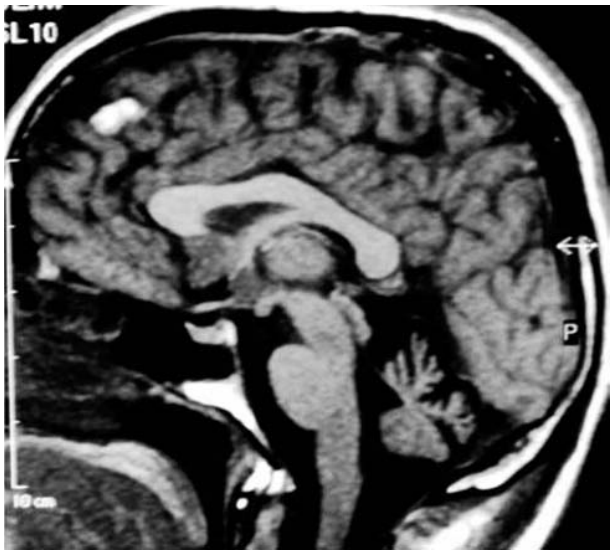

Figure 1 Sagittal T1-weighted brain magnetic resonance imaging of AOA2 patient: marked cerebellar atrophy.

Pathophysiology

The gene defective in AOA2 was localized to chromosome 9q34. AOA2 is caused by mutations in the SETX gene, which encodes a protein named senataxin due to its homology with the yeast protein SEN1p. SETX comprises 24 exons, and senataxin is 2677 amino acids long (with a large and poorly conserved domain encoded by the 4.2 kb-long exon 8) and contains at its C terminus a classical seven-motif domain found in the superfamily 1 of helicases. Senataxin is the ortholog of the yeast Sen1p, which is a helicase involved in tRNA, snRNA, and rRNA splicing and maturation. Senataxin is suspected to be a DNA/RNA helicase and is considered to be involved in the defense against DNA damage, in DNA double-strand breaks repair, and in the processing of noncoding RNAs. Senataxin belongs to a subfamily of helicases that comprises RENT1 involved in nonsense-mediated RNA decay and IGHMP2, which is mutated in spinal muscular dystrophy with respiratory distress. It has been demonstrated that senataxin is exclusively located in the nucleus but its nucleolus localization remains controversial. The conserved N-terminus of senataxin could be involved in protein–protein interaction and in subcellular localization. SETX missense mutations are mostly located either to the N-terminal domain or to the C-terminal helicase domain, supporting the fact they are both key functional domains.

Differential Diagnosis

AOA2 belongs to the group of ARCA with OMA, which are related to defect in DNA breaks repair and which also include ataxia-telangiectasia (AT) due to mutations in the ataxia telangiectasia mutated (ATM) gene with the first symptoms of the disease occurring mostly before 3 years of age, ataxia with oculomotor apraxia type 1 (AOA1) related to mutations in the aprataxin (APTX) gene with initial signs usually occurring early (between 2 and 5 years of age), and ataxia-telangiectasia-like disorder (ATLD), which is exquisitely rare and related to mutations in the MRE11 gene. AOA2 and AT patients also share elevated AFP levels but in contrast to AT, there is no increased sensitivity to ionizing radiation and no susceptibility to cancer in AOA2.

Mutations in SETX have also been reported to cause dominantly inherited juvenile amyotrophic lateral sclerosis (ALS4) and dominant tremor-ataxia. ALS4 occurs before 25 years of age and is defined by limb weakness, severe muscle wasting, pyramidal signs, normal sensation, the lack of bulbar and cerebellar signs, and a slow disease progression.

Diagnostic Work-up/Tests

Given the hurdles to sequence the large SETX gene, the strategy for AOA2 diagnosis in ataxic patients should be based on AFP serum level. In cases of ataxia with normal AFP levels ($< 7\ \mu g\ l^{-1}$) in the early stage of the disease, the diagnosis of AOA2 is unlikely, but a second assessment of AFP level, one year later for instance, is highly recommended. The AFP value of $7\ \mu g\ l^{-1}$ appears to be a good cutoff for selecting which patient should undergo sequencing of SETX.

Prognosis

Patients become wheelchair bound at a median age of 30 years (after a median disease duration of 15 years). No genotype-to-phenotype correlation or prognostic factors have been reported yet in AOA2, but the age of onset of the disease is negatively correlated to the severity of the disease (personal data). Strabismus is correlated to the severity, whereas OMA is negatively correlated to the severity of the disease. Missense mutations into the helicase domain, missense mutations outside the helicase domain, and deletion, truncating mutations were compared. There was a significant difference between the three groups considering the severity of the disease, the disease being more severe in the case of missense mutations out of the helicase domain than in the helicase domain. However, no difference was found for the severity between missense mutations out of the helicase domain and deletions or truncating mutations (personal data). Pyramidal signs and dystonia were more common and the disease was less severe with missense mutations in the helicase domain of *SETX* than with missense mutations out of the helicase domain and deletion and nonsense mutations.

See also: Aprataxin; Ataxia; Ataxia-Telangiectasia; ATM Gene; Friedreich's Ataxia and Variants; SCA1; SCA2; SCA3, Machado–Joseph Disease; SCA4; SCA5; SCA6; SCA7, Spinocerebellar Ataxia with Macular Dystrophy; SCA8; SCA10; SCA11; SCA12; SCA13, 14, 15, and 16; SCA17; SCA27; Scale for the Assessment and Rating of Ataxia (SARA); Spinocerebellar Ataxia Type 19, 20, 21, 22, 23, 26; Spinocerebellar Ataxias Genetics.

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Senile Chorea

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Glossary

Chorea – Abnormal involuntary movements that are brief, random, usually distal, and without purpose.

Huntington's disease – Autosomal dominant illness characterized by chorea and other movement disorders, behavioral disturbances and cognitive decline.

Sydenham's chorea – Chorea resulting from autoimmune process triggered by β-hemolytic Streptococcus.

Definition and History

'Chorea' (derived from the Latin choreus meaning 'dance') refers to abnormal involuntary movements that are brief, random, usually distal, and without purpose. Senile chorea (SeC) is the expression used to designate chorea with late onset, generalized distribution, lack of family history, and no dementia. This is an ill-defined concept, and the term is not frequently used in the current medical literature. It is now clear that SeC is a descriptor that applies to many patients with chorea, some with a diagnosed explanation and others with movements of unknown etiology in elderly patients. Most of reports of this subject are from the age before the availability of genetic testing for Huntington's disease (HD).

Etiology and Pathogenesis

At least half of the patients who meet the diagnostic criteria of SeC are diagnosed with HD. Other conditions, however, have been identified as responsible for some of these cases: HD-like disease, neuroacanthocytosis, late-onset Hallervorden–Spatz disease, Sydenham's chorea (SC), systemic lupus erythematosus, vascular disease (usually in association with diabetes mellitus), exposure to drugs (dopamine-receptor blockers, amphetamine, cocaine), hyperthyroidism, and infections (AIDS, syphilis, and viral encephalitis).

Because of the casual heterogeneity, there is no well-established underlying mechanism of pathogenesis responsible for SeC, aside the hypoactivity of the subthalamic nucleus, common to all forms of chorea. Of note, SC can occur as a result of exposure to hormone-replacement therapy in patients with a past history of rheumatic fever (not necessarily with presence of chorea). In the few patients with the diagnosis of SeC of uncertain cause who have come to autopsy, the results have been quite heterogeneous: no specific anatomic abnormality, spheroids in the striatum, findings typical of Hallervorden–Spatz disease, and striatal degeneration of nonvascular origin.

Epidemiology

There are no formal epidemiologic investigations of SeC performed either in the community or even in tertiary centers. In a study involving a few academic units in Spain during three years, the authors found six patients who met the diagnostic criteria of SeC. In half of them, however, genetic testing showed that the diagnosis was in fact HD. Taking into account this study, the scarcity of reports of SeC in the literature and the clinical experience of the author, it can be stated that it is a very rare condition.

Clinical Features and Diagnostic Criteria

The typical features of SeC are generalized chorea with onset in the elderly without family history or dementia. The chorea is usually mild but in a few patients it can be severe enough to be labeled as ballism. As to cognitive changes, although lack of dementia is mandatory criterion for the diagnosis of SeC, all patients who underwent formal neuropsychological evaluation have been found to display abnormalities in some domains.

Currently, there are no validated diagnostic criteria of SeC. Most authors, however, make the diagnosis when the onset of chorea is (1) in the elderly age, (2) the patient does not present with dementia and family history of a similar condition, suggesting Huntington's disease, and (3) investigation fails to identify a clear cause. There are to date unsolved problems in this set of criteria: the age limit has not been defined (my personal recommendation is 65 years) and the extent of the investigation that needs to be done to rule out an underlying recognizable cause. A minimal medical diagnostic evaluation is suggested below (see section Diagnostic Work-up).

Differential Diagnosis

The conditions which can mimic SeC are HD, HD-like disease, neuroacanthocytosis, late-onset Hallervorden–Spatz disease, SC, systemic lupus erythematosus, vascular disease (usually in association with diabetes mellitus), exposure to drugs (dopamine-receptor blockers, amphetamine, cocaine), hyperthyroidism, paraneoplastic chorea associated with colon or lung cancers, and infections (AIDS, syphilis and viral encephalitis).

Diagnostic Work-Up

Elderly patients with de novo chorea should undergo a complete neurologic history with attention to drug exposure, specifically antipsychotics or other dopamine-blocking agents (tardive dyskinesia. They should have a neurological examination to define if chorea is an isolated finding or whether other neurological signs, and especially dementia (Huntington's disease) are present. Diagnostic testing will help to investigate the myriad causes of this hyperkinesia: genetic testing for HD; genetic testing for

HD-like disease; genetic testing for Hallervorden–Spatz disease; search of acanthocytes on fresh blood smear, CPK levels and electromyography; tests of acute phase reactants such as erythrocyte sedimentation rate, C-reactive protein, leukocytosis, rheumatoid factor, mucoproteins, protein electrophoresis, supporting evidence of preceding streptococcal infection (increased antistreptolysin-O, antiDNAse-B, or other antistreptococcal antibodies; positive throat culture for group A *Streptococcus*; recent scarlet fever), Doppler echocardiogram; serologic studies for systemic lupus erythematosus and primary antiphospholipid antibody syndrome must be ordered to rule out these conditions; search for antibodies associated with paraneoplastic syndromes; and neuroimaging helps to define the vascular nature of chorea and identify findings suggestive of HD (atrophy of head of the caudate), Hallervorden–Spatz disease (the eye of the tiger sign) or neuroacanthocytosis (which can present with atrophy of head of the caudate or the eye of the tiger sign).

Management

If a cause is found, the underlying disease should be treated. In the absence of an identified cause, dopamine receptor blockers are the mainstay of the pharmacological management of SeC. Despite the lack of controlled studies, there is consensus among experts that the most effective agents are neuroleptics with significant D2 receptor blocker activity. The personal choice of the author is risperidone. Use of these agents, however, is warranted solely when chorea is associated with meaningful disability since even these new agents may be associated with side-effects, particularly in the elderly. Among the latter, the most important ones are drowsiness, parkinsonism, and tardive dyskinesia. There is one report describing the effectiveness and safety of deep brain stimulation of the pallidum and thalamus in one patient with SeC.

Prognosis

Little is known about the long-term prognosis of patients with SeC. Clinical experience suggests that there is little, if any, progression of chorea and cognitive decline in the majority of patients.

See also: Chorea; Huntington's Disease: Genetics; Huntington's Disease; Neuroacanthocytosis Syndromes.

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Serotonin and Tryptophan

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Glossary

Extrapyramidal symptoms – Extrapyramidal symptoms (EPS) are a variety of movement disorders such as tardive dyskinesia, akathisia, or bradykinesia, suffered as a result of taking dopamine antagonists, usually antipsychotic (neuroleptic) drugs, which are often used to control psychosis, especially schizophrenia. Other antidopaminergic drugs like the antiemetic metoclopramide or the tricyclic antidepressant amoxapine can also cause extrapyramidal side effects.

Myoclonus – Myoclonus is a movement disorder, characterized by brief, involuntary twitching of a muscle or a group of muscles.
Serotonin – Serotonin (5-hydroxytryptamine, or 5-HT) is a monoamine neurotransmitter synthesized in serotonergic neurons in the central nervous system (CNS) and enterochromaffin cells in the gastrointestinal tract.
Tryptophan – Tryptophan is one of the 20 standard amino acids, as well as an essential amino acid for humans.

Definition and History

The chemical name for serotonin is 5-hydoxytryptamine (5-HT) which is often abbreviated as 5-HT. In the late 1940s, the laboratory of Dr. Irving Page at the Cleveland Clinic isolated a vasoconstricting substance in serum and named it serotonin. The exact structure of serotonin was reported in 1949. In 1952, Dr. Betty Twarog joined the Page Laboratory, and her research resulted in the identification of serotonin in the brain.

Neurochemistry and Neuroanatomy

The neurochemical anatomy of brain serotonin neurons was first studied by fluorescence histochemical detection. Serotonin producing cell bodies are present largely within the brainstem raphe nuclei and particular regions of the reticular formation. Raphe clusters of 5-HT neurons are found rostrally from the level of the interpeduncular nucleus in the midbrain to the level of the pyramidal decussation in the medulla. 5-HT is synthesized from L-tryptophan, an essential amino acid. Hydroxylation in 5-hydroxytryptophan is catalyzed by tryptophan hydroxylase, which is the rate limiting enzyme of the synthesis. This enzyme requires for its activity the presence of tetrahydrobiopterine, oxygen, NADPH2, and a metal, iron or copper. Subsequently, L-aromatic amino acid decarboxylase with pyridoxal-phosphate as coenzyme catalyzes the decarboxylation of 5-hydroxytryptophan into 5-HT.

Central Serotonergic Systems and Serotonin Stores Outside the Central Nervous System

In the brain, serotonin biosynthesis depends on the quantity of tryptophan which crosses the blood–brain barrier (whereas 5-HT does not). Only free plasma tryptophan, that is, unbound to albumin, enters the brain, and decrease of its free ratio reduces its penetration. Moreover, other amino acids compete with free tryptophan and limit its entry in the brain. Plasma cortisol, increased in depressed patients, decreases free L-tyrosine and free L-tryptophan concentrations in plasma, resulting in alterations in tryptophan delivery to the brain. Insulin decreases the transfer of many amino acids centrally, but tryptophan transport is not affected. Serotonin is found in many tissues outside the brain, especially the digestive tract. The average adult human possesses only 5–10 mg of serotonin, and over 90% is in the intestine. The remaining is located in blood platelets and the brain. In the gastrointestinal tract, serotonin is also localized in enterochromaffin cells. In the central nervous system (CNS), higher concentrations are found in brainstem than in cortex. Serotonin, released by presynaptic serotonergic neurons into synaptic clefts, activates specific receptors and is removed from the synapse primarily by reuptake into presynaptic neurons. Platelets do not synthesize serotonin but absorbed serotonin release into the plasma from enterochromaffin cells. Serotonin released from platelets in plasma has a relatively localized effect on blood vessels where it is released, during migraine. While the half-life of serotonin is long in platelets and intestine (days), it is very short in the brain (a few minutes), Once 5-HT is actively transported into cells, it is inactivated by biotransformations, including oxydative deamination of the lateral amino chain by monoamine oxidase (MAO), both within and outside the cell. MAO-A plays a more prominent role in this process than MAO-B. The metabolism of serotonin leads to 5-hydroxy-indol-acetaldehyde which is then oxidized into 5-hydroxy-indol-acetic acid (5-HIAA). This metabolite can be found in urine in quantities normally lower than 10 mg per 24 h and is the usual measurement tool to reflect serotonergic metabolism. Inactivation also involves conjugation by glucuronic acid or sulfate of the hydroxyl group OH in 5-position.

Serotonergic Receptors

Serotonin receptors are classified into seven types, 5-HT1 through 5-HT7. Each type can have subtypes (A, B, etc.). These receptors are localized in the brain and in peripheral organs but their distribution is not homogeneous. The majority of 5-HT receptors are postsynaptic, with some exceptions, most notably 5-HT1A and 5-HT1B that are mainly presynaptic and modulate serotonin release. The signaling pathways to which these receptors are coupled are known, but it is has not been possible to link direct clinical effects systematically to their stimulation. Serotonin receptors are coupled to G proteins except 5-HT3 receptors which are receptor-channels, also called

ionotropic receptors, which, in the activated state, are open and permeable to sodium and potassium cations.

Clinical Disorders and Serotonin

Effects of serotonin on the CNS are numerous and complex and of considerable importance from a pharmacological point of view because many drugs act by its intermediary. Serotonin is a neurotransmitter involved in many pathways and plays a role in various different states, psychiatric, medical, and neurological. These conditions include aggression, pain, sleep, appetite (suppressant effect), depression (antidepressant action), migraine, anxiety, temperature regulation and emesis is involved in the regulation of sleep, learning and memory, mood (antidepressant action), temperature, and appetite (appetite suppressant effect). Overstimulation of 5-HT2 receptors can induce productive and negative symptoms of psychotic disorders. LSD (Lysergic acid diethylamide, a semisynthetic psychedelic drug of the ergoline family) or lysergide a potent agonist of 5-HT2 receptors with additional effects on D1 and D2 dopaminergic receptors, has hallucinogenic properties.

Drugs Affecting Serotonergic Pharmacology Used in Clinical Medicine

Serotonin, through its various types of presynaptic and postsynaptic receptors, modulates the activity of other transmitters. It plays a determining part in adaptation. L-Tryptophan and L-5-hydroxytryptophan, precursors of serotonin, are used as regulators of sleep and antidepressants, L-5-hydroxytryptophan, called oxitriptan, has been proposed for the treatment of certain types of postanoxic myoclonus.

The compounds which specifically inhibit serotonin reuptake by neurons are named SSRIs, selective serotonin reuptake inhibitors. The SSRIs have antidepressant properties in patients, but their mechanism of action is not completely elucidated, as their antidepressant effect appears only in 2 or 3 weeks, whereas their inhibiting effect on the reuptake is immediate. This delay in onset of antidepressant effect suggests the intervention of complex mechanisms. Some of SSRIs have also appetite suppressant properties. When serotonin reuptake is inhibited, its concentration in the synaptic cleft increases. This increase induces postsynaptic and presynaptic effects, in particular a stimulation of 5-HT1A receptors, which reduces 5-HT release and, thus offsets the inhibition of its reuptake. The combination SSRI and an antagonist of 5-HT1A presynaptic receptors increase the serotonin release. Pindolol, a drug with β-adrenergic blocking effects and nonspecific antagonism of 5-HT1A receptors, accelerates and improves the effect of SSRIs. The main SSRIs are fluoxetine, fluvoxamine, paroxetine, citalopram, escitalopram, and sertraline. They do not have atropinic (antimuscarinic) effects. In addition to their use in the treatment of depressive disorders in which their efficacy is equal or higher than that of other antidepressants, SSRIs are used in the treatment of compulsive obsessive disorders, of panic attacks and social phobia.

Movement Disorders and Serotonergic Agents

SSRIs are the most commonly prescribed antidepressants. Movement disorders induced by antidepressants are much less common than those induced by antipsychotic medications. Often, movement disorders following the use of antidepressants are the result of drug–drug interactions or tend to occur in patients who have a history of previously using neuroleptic medications. Patients with depression may have altered neurotransmitter function, which may make them prone to the development of certain movement disorders. Generally speaking, in contrast to antipsychotic medications, antidepressants do not commonly induce permanent movement disorders. The incidence of movement disorders caused by antidepressants is largely unknown, since there have been no systematic studies and most data are derived from case reports. Tricyclic and tetracyclic antidepressants act by blocking the reuptake of norepinephrine (NE) and serotonin (5-HT) and also block muscarinic acetylcholine (Ach) and histamine receptors (H1 and H2) in varying degrees. SSRIs block the reuptake of 5-HT more effectively than NE and lack significant effect on muscarinic cholinergic, and histaminergic receptors.

Myoclonus

Serotonergic pharmacology has been linked to the movement disorder of myoclonus. In most reported cases, the movement disorder develops shortly after the SSRI was started. The predominant receptors involved in mediating serotonin toxicity in humans appear to be 5-HT2 receptors, whereas 5-HT1 receptors are responsible for the therapeutic effects of SSRIs. Excessive levels of serotonin have been implicated in the development of myoclonus. 5-hydroxytryptophan (5-HTP) can induce a syndrome characterized by altered muscle activity with myoclonus. Similarly, myoclonus may be induced by L-tryptophan and coadministration of a monoamine oxidase inhibitor (MAO-I) or by serotonin receptor agonists. The 5-HTP-induced syndrome has been shown to be antagonized by a central decarboxylase inhibitor and by 5-HT receptor blockers such as methysergide and cyproheptadine.

Serotonin Syndrome

The serotonin syndrome is a medical emergency that is characterized by high fever, rigidity, and altered mental status. It may be confused with the neuroleptic malignant syndrome (NMS). The latter is typically associated with treatment with a neuroleptic medication or sudden withdrawal of a dopaminergic drug, such as levodopa (L-dopa). The NMS shares some clinical features with the serotonin syndrome, including mental status changes, fever, rigidity, and autonomic dysfunction. Tremor, dystonia, dyskinesias, and chorea may also be seen. The presence of myoclonus, however is particularly characteristic of the serotonin syndrome, although all cases of serotonin syndrome do not demonstrate myoclonus. Proposed diagnostic criteria for the serotonin syndrome are: Coincident with the new administration or increase of an existing SSRI, there is presence of at least three of the following clinical signs: mental status changes, agitation, myoclonus, hyperreflexia, rigidity, diaphoresis, shivering, tremor, diarrhea, incoordination, fever. Other etiologies, such as infectious, metabolic, drug withdrawal, or substance abuse, must be excluded. When a neuroleptic medication has been started or increased within a recent time period before symptom onset and an SSRI has likewise been added or increased, the two syndromes cannot be distinguished. Symptoms of Serotonergic excess can be caused by serotonin overdose, drug interaction or as a complication of therapy. More likely than pure SSRI overdose, the combination of an SSRI and a MAO inhibitor or a reversible MAO-A inhibitor may result in significant serotonin toxicity (16% vs. 55%). To avoid the serotonin syndrome, SSRIs should not be administered along with MAO-A inhibitors or with mixed MAO-A/MAO-B inhibitors. Although the metabolism of serotonin primarily involves MAO-A, when physicians treat patients on MAO-B inhibitors with SSRIs they usually introduce the antidepressant with caution and monitor for possible serotonin syndrome symptoms and signs carefully.

Serotonergic pathways in the CNS are intimately involved in the modulation of motor behavior, and in the pathophysiology of human involuntary movement disorders. These observations are supported by recent reports demonstrating large serotonergic innervation of the striatum and substantia nigra, and a close interaction between the activity of serotonergic neurons with the dopamine system in the striatum and nigra. There are several reports in the literature of other movement disorders, such as dystonia or chorea, associated with the use of SSRIs. Some of these may represent less severe cases of the serotonin syndrome. The serotonin syndrome may be encountered in Parkinson's disease. It is often precipitated by concomitant use of selegiline and other medications, including meperidine (mostly used in postoperative pain control), and antidepressants.

Other Movement Disorders

A study published in 1998 summarized 127 published reports of SSRI-induced movement disorders. The reports included akathisia ($n = 30$), dystonia ($n = 19$), dyskinesia ($n = 12$), tardive dyskinesia ($n = 6$), parkinsonism ($n = 25$), and 15 cases of mixed disorders. Ten isolated cases of bruxism were identified. Ten additional reports could not be classified. Treatment strategies included discontinuation of the SSRI; dosage reduction; or the addition of a benzodiazepine, β-blocker, or anticholinergic agent. An earlier report stated that among patients with Parkinson's disease treated with SSRIs, there were 16 cases of worsening parkinsonism. Patients who developed dystonia, parkinsonism, or tardive dyskinesia were older on average than patients with akathisia; 67.6% of affected patients were females. Fluoxetine, the most commonly prescribed SSRI to date, was implicated in 74.6% of cases of SSRI-induced EPS (extrapyramidal symptoms).

SSRI-induced EPS or movement disorders are probably related to agonism of serotonergic input to dopaminergic pathways within the CNS. Several patient-dependent and pharmacokinetic variables may determine the likelihood that EPS will emerge. Although these side effects are infrequent, clinicians should be alert to the possibility of their occurrence. SSRI use appears to be associated with the development of movement disorders, either as a direct result of the drug or exacerbation of an underlying condition. Predisposing factors may include the use of neuroleptics, existing neurological diagnoses, or preexisting movement disorders. Clinicians should be aware of the potential for these reactions, as prompt recognition and management is essential in preventing potentially significant patient morbidity.

See also: Antidepressants and Movement Disorders; Myoclonus; Serotonin Syndrome.

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www.wemove.org – WE MOVE.

Serotonin Syndrome

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Glossary

Enterochromaffine cells – These cells are present all along the digestive tract in the musoca. They represent about 5 % of the total number of the enterocytes. They are called paraneurons according to their biochemical properties: they are able to synthesize 5-HT from L-tryptophan, an active release process and reuptake of 5-HT were also demonstrated in this type of cell.
Fluoxetine – Commercial name Prozac®, is a specific inhibitor of 5-HT reuptake in serotonergic neurons. The use of fluoxetine leads to an increase of 5-HT concentration in the brain.
Inhibitors of monoamine oxidases (IMAO) – These drugs specifically block the enzymatic conversion of 5-HT into 5-hydroxyindol acetic acid (5-HIAA). Such a blockade results in a specific increase of 5-HT content in brain.
Raphe nuclei – Cells bodies of serotonergic neurons are located in the raphe nuclei. According to the classification of Falck and Hillarp they are located in the sagital plane of the brainstem, in nine nuclei named B1–B9 from the posterior to the anterior part of the brainstem. B1–B3 (obscurus, pallidus and magnus nuclei) give axons towards the spinal cord, whereas B7 and B8 (dorsalis and centralis superior nuclei) innervate, through the medial forebrain bundle, all cortical areas as well as sub-cortical structures such as: thalamus, hypothalamus, limbic system, striatum, and hippocampus.
Serotonergic neurons – Different histological methods have been used to identify serotonergic neurons in the central nervous system. Fluorescence, immunohistochemistry, as well as autoradiography, have revealed the presence of these neurons in the brainstem of various species. If their cell bodies are all located in specific neurons along the midline of the brainstem (the raphe nuclei) their axon terminals are present in all the regions of the brain, including spinal cord and forebrain.
Serotonine – Serotonin or 5-hydroxytryptamine (5-HT) was first identified in 1947 as a vasoconstrictor factor released by blood platelets. Its name was chosen because of its presence in blood serum and specific vasoconstrictor properties. In 1952, a similar compound was also detected in the gut and named 'enteramine.' That substance was shown to be present in the enterochromaffine cells and responsible for smooth muscle contraction all along the digestive tract. The presence of 5-HT in the brains of rat and rabbit was demonstrated by Twarog and Page, in 1953. This discovery started a long period of investigations related to serotonin as a neurotransmitter in the central nervous system.
Serotonin degradation – In parallel to 5-HT reuptake, serotonin homeostasis at the synaptic level is dependent on the action of monoamine oxidases. Degradation of 5-HT into 5-hydroxyindol acetic acid (5-HIAA) occurs both in nerve terminals and glial cells. 5-HIAA is then transported by blood flow and excreted through the urinary tract.
Serotonin receptors – Seven classes of 5-HT receptors (from 5-HT_1 to 5-HT_7) can be distinguished. Their existences was formally established by cloning of corresponding genes. Except for 5-HT_3, they all belong to the family of

seven transmembrane domain receptors coupled with G proteins. They modulate either an enzymatic membrane activity (adenylate cyclase, phospholipase C, or phospholipase A2) or an ion channel. In the 5-HT_1 family, the subtypes 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, and 5-HT_{1F} are characterized by a high affinity (Kd of nanomolar scale) whereas the 5-HT_2 receptors will bind 5-HT with a lower affinity. Serotonergic neurons bear 5-HT autoreceptors, the stimulation of which triggers an inhibition of their electrical activity or an inhibition of 5-HT release from nerve terminals. Distribution of 5-HT_3 seems to be exclusively neuronal, in contrast with the other types which can be detected both in the peripheral and central nervous systems on the neuronal and glial cell membranes.

Serotonin release – When the action potential is generated in the axon of a serotonergic neuron, induces calcium entry in the presynaptic terminal. Under these conditions vesicles move to the presynaptic membrane and release their content into the synaptic cleft through exocytosis. Released 5-HT can be bound to specific 5-HT receptors which are present on the postsynaptic membrane. Fixation of 5-HT to the receptor triggers the opening of ion channels with ionic exchanges between internal and external compartments. Such changes in the ionic permeability will give rise to a new potential which will be propagated all along the target neuron. As now has been clearly demonstrated newly synthesized 5-HT is preferentially released.

Serotonin reuptake – Inactivation of serotonin present in the synaptic cleft is partly accomplished by reuptake of the neurotransmitter in the presynaptic serotonergic terminal. Such a mechanism can be blocked by drugs such as fluoxetine or tricyclic antidepressants, leading to a substantial increase of 5-HT concentration in the synaptic cleft.

Serotonin synthesis – 5-HT is synthesized from the free fraction of L-tryptophan. The first reaction of 5-HT biosynthesis which concerns the transformation of tryptophan into 5-hydroxytryptophan (5-HTP) by tryptophan hydroxylase is the limiting step of 5-HT biosynthesis. Then 5-HTP is transformed into 5-HT by means of a non-specific decarboxylase. 5-HT is stored into synaptic vesicles where it is protected from monoamine oxidase (MAO) degradation. Synthesis of serotonin mainly occurs at the level of the terminal.

Tryptophan – Tryptophan is an essential amino acid derived from food. L-tryptophan is the amino acid precursor of 5-HT. Tryptophan is present in circulating blood where it is bound at 90 % to serum albumin. The free fraction of circulating L-tryptophan can be taken up via glial cells by serotonergic neurons, using a specific transporter system. Transformation of tryptophan into 5-hydroxytrypothan (5-HTP) by means of tryptophan hydroxylase, the specific enzyme of 5-HT synthesis, exclusively located in serotonergic neurons, is the limiting step of 5-HT synthesis.

Serotonin Neurons and Biochemical Mechanisms

Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter that is synthesized in specific neurons, located in the raphe nuclei, in the medial part of the brainstem. These neurons play a major role in sleep–wakefulness cycles, mood, emotion, food behaviors, and thermoregulation. Dysfunction of serotonin neurones is generally observed in depression. Following 5-HT release in the synaptic cleft, the neurotransmitter can be bound to various post- and presynaptic 5-HT receptors. Inactivation of 5-HT at the synaptic level is the result of reuptake in the presynaptic element and catabolism by monoamine oxidase (MAO) in both neurones and glial cells. Increased doses of L-trytophan, the amino acid precursor of 5-HT, will proportionally increase 5-HT formation. Amphetamines and related drugs increase the release of 5-HT stored in presynaptic vesicles. Inhibition of MAO activity will increase presynaptic 5-HT concentration, and impairment of 5-HT transport by uptake blockers increases synaptic 5-HT content. Serotonin agonists can directly stimulate postsynaptic receptors, and lithium is also known to increase postsynaptic receptor responses (**Figure 1**).

Serotonin syndrome is the result of an overstimulation of 5-HT_{1A} receptors which are present in the central grey nuclei and in the medulla. Such an excess of stimulation can be associated with the use of selective reuptake inhibitors, tricyclic antidepressants, MAO inhibitors, or other serotonin agents that act directly on 5-HT receptors. Overstimulation of 5-HT_2 receptors has also been demonstrated. A competitive inhibitor of 5-HT_2 receptors such as promethazine was shown to cause hyperactivation of 5-HT_{1A} receptors in the presence of selective inhibitors of 5-HT reuptake. In summary, excess of 5-HT precursors or 5-HT agonists, increased release, decreased reuptake and reduced metabolic of 5-HT can all be causative factors in the serotonin syndrome.

In parallel with the changes observed in serotonin metabolism, noradrenergic neuronal activity is enhanced,

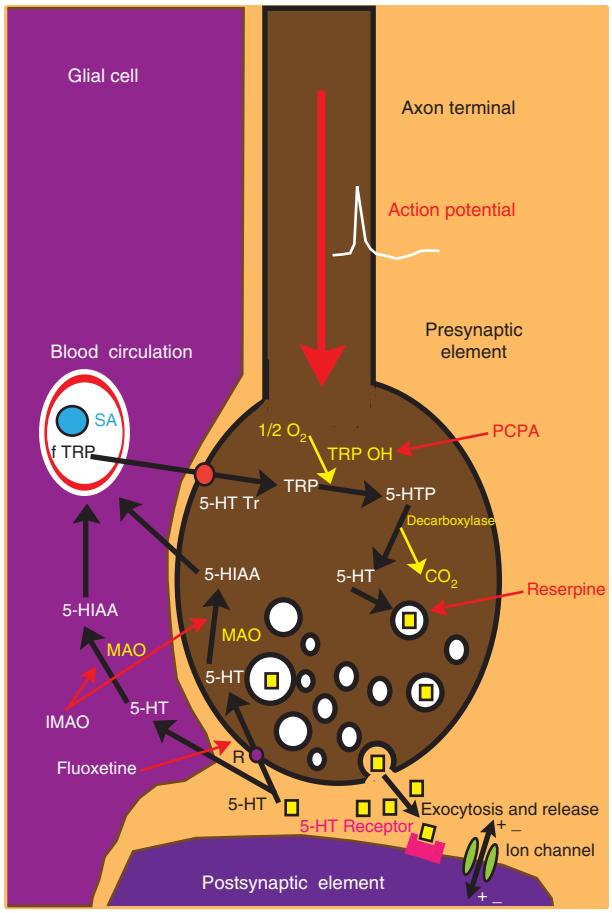

Figure 1 Schematic drawing of serotonin metabolism in serotonergic neurons. Serotonin (5-HT) is synthesized from L-Tryptophan (TRP). TRP is present in blood flow in two forms: 90 % of TRP is bound to serum albumin (SA) and the free fraction (f TRP) can be used for 5-HT synthesis in serotonergic terminals. Tryptophan is specifically transported in serotonergic neurons by mean of a 5-HT transporter (T) through the glial compartment. Tryptophan hydroxylase (TRP OH), in the presence of oxygen, catalyses the transformation of L-TRP into 5-hydroxytryptophan (5-HT). This biochemical reaction is the limiting step of 5-HT biosynthesis. 5-HTP is transformed in serotonin (5-HT) using decarboxylase. 5-HT is stored in vesicles. When the neuron is active, the action potential triggers the release of 5-HT in the synaptic cleft by an exocytosis mechanism. 5-HT which is released in the synapse can be bound to specific receptors. Inactivation of 5-HT can be the result of a 5-HT reuptake in the presynaptic terminal (R) or of an enzymatic degradation by monoamine oxidases (MAO) into 5-hydroxy indol acetic acid (5-HIAA). Such an enzymatic degradation occurs both in serotonin terminals and glial cells. 5-HIAA is transported through the blood flow and excreted in urine. Fluoxetine which blocks 5-HT reuptake, and inhibitors of MAO (IMAO) which reduce 5-HIAA formation, both enhance 5-HT concentration in the brain. Such drugs are suspected to be involved in the expression of serotonin syndrome.

and levels of norepinephrine in the brain appear to be correlated with clinical outcome. GABA and NMDA antagonists are also suspected to affect the development of serotonin syndrome, but their role is less clear.

Drugs Involved in Serotonin Syndrome Expression

A large number of pharmacological agents, used alone or in combination, have been reported to produce serotonin syndrome. These agents include antidepressant drugs such as: MAO inhibitors, selective serotonin transport inhibitors, tricyclic antidepressants (bupropion, nefazodone, tradozone), opioids (tramadol, pethidine, fentanyl, pentazocine, buprenorphine, oxycodone, hydrocodone), amphetamines and related molecules, and psychedelics (LSD, NMDA, MDA). LSD is an agonist of 5-HT_{2A} receptors, and the empathogen MDMA (ecstasy) releases 5-HT from synaptic vesicles of neurons and rather specifically targets the 5-HT_{1A} receptor. MDA (3,4 methylenedioxyamphetamine) also named 'psychedelic amphetamine' enters 5-HT neurons via the reuptake pump and affects 5-HT_2 receptor sites. Herbs (St John's Wort, Syrian rue, Panax ginseng, Nutmeg), and other molecules such as tryptophan, L-dopa, valproate, buspirone, lithium, 5-hydroxytryptophan, ritonavir, etc. were shown to produce large elevations in central serotonin levels. The combination of monoamine oxidase inhibitors with other serotonin agonists or precursors gives a high risk of causing serotonin syndrome.

Signs and Symptoms

Symptom onset is usually rapid, occurring within minutes of the administration of an overdose of serotonin pharmacological agents. Clinical manifestations of serotonin syndrome can range from mild to severe and even lethal symptoms. Serotonin syndrome is characterized by a triad of mental, autonomic and neurological disorders. While it can be fatal, in most cases there is a good prognosis when medication is immediately discontinued.

Mild symptoms generally include an increased heart rate, shivering, severe perspiration, and dilated pupils. Myoclonus and enhanced reflexes may also be present and lead, in some cases to impaired motor coordination. Hyperactive reflexes may be greater in the lower than the upper limbs. In moderate cases, additional features may include: hyperactive bowel sounds, diarrhea, high-blood pressure, and hyperthermia, which can reach 40 °C with moderate intoxication. Changes in mental status can also be noticed, including hypervigilance and agitation. In severe cases the increased heart rate and blood pressure may lead to shock. Agitated delirium, associated with rigidity and high muscular tension, has also been described. In such cases, the body temperature can reach 41.1 °C. Metabolic acidosis, rhabdomyolisis, seizures, renal failure, and disseminated intravascular coagulation have also been reported. These last symptoms, arising with hyperthermia, can be linked to metabolic 5-HT

peripheral changes occurring in both blood platelets and gut enterochromaffin cell compartments.

Diagnosis and Treatment

Serotonin syndrome has been reported in patients of all ages, including infants due to in utero exposure. The diagnosis of serotonin syndrome is guided by the criteria defined in 1991 by Harvey Sternbach, Professor of Psychiatry at UCLA. More recently, Australian researchers have developed the 'Hunter Serotonin Toxicity Criteria,' which have better sensitivity. There is no laboratory test for serotonin syndrome even if an elevation of the total creatine kinase and leukocyte count, elevated transaminase levels, or lower bicarbonate blood levels have been reported.

The most important clinical symptoms to be considered in serotonin syndrome are tremor, akathisia, or myoclonus. The physical examination of the patient should include assessment of deep tendon reflexes and muscle rigidity, the dryness of oral mucosa, the size and reactivity of the pupils, the intensity of bowel sounds, the skin color, and the quality of sweating. The physical examination must be complemented by a detailed history of any prescribed or illicit drug use. Serotonin toxicity usually gives a specific clinical picture, but at times may be mistaken for viral illness, an anxiety attack, neurological disorders, anticholinergic poisoning, sympathomimetic toxicity, or neuroleptic malignant syndrome (NMS). Serotonin syndrome and NMS can be distinguished by the fact that 5-HT toxicity has a rapid onset and responds to pharmacological blockade with drugs such as chlorpromazine and cyproheptadine. Dopamine blockade in NMS has a slow onset following the administration of a neuroleptic drug and responds to dopamine agonists such as bromocryptine.

The management of serotonin syndrome involves the removal of serotonergic agents. Supporting care includes the administration of intravenous electrolyte solution in order to maintain a physiological diuresis. Benzodiazepines may be used to control agitation and reduce anxiety. Upon initiation of therapy and discontinuation of serotonergic drugs, most cases of serotonin syndrome resolve within 24 hours. In some cases, muscle pain and weakness can persist for several months. Nevertheless, an appropriate medical management of serotonin syndrome is generally associated with a favorable prognosis.

See also: Antidepressants and Movement Disorders; Serotonin and Tryptophan.

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Shy–Drager Syndrome

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Glossary

Multiple system atrophy (MSA) – A term coined to describe the clinical and pathological overlap among three major neurodegenerative diseases which were previously described separately: (1) Shy–Drager syndrome, (2) striatonigral degeneration, and (3) sporadic olivopontocerebellar atrophy.

Olivopontocerebellar atrophy – Indicates primarily cerebellar defects due to degeneration of neurons in specific areas of the brainstem (pons and inferior olives) and the cerebellum, with minor degrees of parkinsonism. It may be sporadic or genetically determined.

Orthostatic hypotension – Sudden fall in blood pressure that occurs when a person assumes a

standing position manifested by dizziness, lightheadedness, blurred vision, and syncope.
Shy–Drager syndrome – Neurological syndrome characterized by severe autonomic failure (orthostatic hypotension, urinary retention or incontinence, and male erectile failure) combined with parkinsonism, cerebellar and pyramidal signs.
Striatonigral degeneration – A disease caused by the degeneration of the striatum and substantia nigra, clinically presenting as parkinsonism with or without some degree of autonomic and cerebellar dysfunction.

Definition and History

In May 1960, Milton Shy from the National Institutes of Health and Glenn Drager from Baylor College of Medicine described a neurological syndrome associated with orthostatic hypotension, termed later as the Shy–Drager syndrome (**Figure 1**). In their original article, they described the clinical features of two male patients who developed autonomic failure followed by other neurological symptoms. Their description of the new syndrome comprised of a complex series of symptoms and signs, including autonomic failure (orthostatic hypotension, urinary and rectal incontinence, impotence, loss of sweating, and iris atrophy), parkinsonism (rigidity, tremor, loss of associated movements), involvement of the anterior horn cells (fasciculations, wasting of distal muscles, evidence of a neuropathic lesions in the electromyogram, and in the muscle biopsy), and external ocular palsy. They were also able to carefully study the neuropathologic changes in one of these patients, in whom neuronal degeneration at many sites was found, including the intermediolateral columns of the spinal cord.

Numerous clinical details were cited in the text, though other parts of the article were discordant (description of the rectal incontinence and ocular muscle paresis in both patients, presence of fasciculations in patient 2 instead of patient 1, and presence of distal wasting in patient 2, whereas the text stated there was none). Although meticulously delineated in the article text, the 'full syndrome' description also failed to mention cerebellar and pyramidal signs. Shy and Drager recognized that there was a link between low blood pressure during erect posture (orthostatic hypotension) and disturbance in the central autonomic nervous system. Since their seminal report, growing interest in autonomic disorders has spawned studies outlining the clinical and neuropathologic findings in such patients.

Figure 1 (a) Milton Shy (b) Glenn Drager.

The eponym Shy–Drager syndrome became popular, but then it has been progressively replaced by the use of a new term, multiple system atrophy (MSA). This was first coined in 1969 by two British authors, Graham and Oppenheimer. The term MSA recognized the significant clinical and pathological overlap among three major neurodegenerative diseases which were previously described separately: (1) Shy–Drager syndrome, (2) striatonigral degeneration, and (3) sporadic olivopontocerebellar atrophy.

Clinical Features and Diagnostic Criteria

For various reasons, some uncertainty in the terminology generated over the following years. For instance, Wenning et al. described a series of 100 patients with clinically probable MSA (15 of them pathologically confirmed); in none of them, the 'full Shy–Drager syndrome' was found. These authors described fecal incontinence in only two patients, but neither of them had suffered painful muscle cramps or iris atrophy, and only one had fasciculations, weakness, and focal muscle atrophy. Although they admitted that rectal incontinence, iris atrophy, external ocular palsies, and signs suggestive of anterior horn cell involvement can occur occasionally in MSA, these features should not be considered typical of the disease. In addition, they suggested that the term Shy–Drager should be restricted to the situation in which severe autonomic failure (male erectile failure, orthostatic hypotension, urinary retention, or incontinence) is combined with parkinsonism, cerebellar and pyramidal signs. Respiratory stridor (high-pitched breathing sounds due to airway obstruction) and stimulus-sensitive finger myoclonus, developing each in one-third of cases, were included as optional diagnostic criteria. Unlike the original description (which antedated the introduction of levodopa), information on the response to levodopa treatment (which is often poor or absent in MSA, except for 20–30% of the cases in whom it may be transiently good) was also included.

In a subsequent commentary, Quinn et al. substantiated that the Shy–Drager syndrome signifies autonomic failure plus central nervous system dysfunction attributable to MSA, and that it is inappropriate to use the term simply as a shorthand for parkinsonism with autonomic failure.

However, it later became clear that the new complex classification was not well served by the term 'Shy–Drager syndrome.' Thus, a new terminology was needed. The American Autonomic Society and the American Academy of Neurology eventually disapproved the Shy–Drager syndrome as a disease entity in 1996, and existing cases were redefined as MSA with autonomic involvement.

However, the term 'Shy–Drager syndrome' is still used occasionally for MSA when the primary symptom is autonomic failure. At the very least, this nomenclature implies that several areas in the central nervous system are involved in the neurodegenerative process.

MSA is defined as a sporadic, progressive, adult-onset disorder characterized by autonomic dysfunction, parkinsonism, and ataxia in any combination. Onset usually takes place in the sixth or seventh decade, and most patients are severely disabled within 5–7 years. More males are affected than females, and prevalence is less than one in 10 000 persons. The etiology is unknown. Depending upon which part of the central nervous system is affected first, MSA may present in different ways. According to the current diagnostic criteria, MSA is divided into two main clinical categories: (1) MSA–parkinsonism type (MSA–P), which implies parkinsonism with or without some degree of cerebellar dysfunction (striatonigral degeneration), and (2) MSA–cerebellar type (MSA–C), which indicates primarily cerebellar defects with minor degrees of parkinsonism (olivopontocerebellar atrophy). In both conditions, autonomic failure could be a predominant or an associated manifestation of the clinical spectrum of the disease.

The most prominent symptom of autonomic failure in MSA is what is known as 'postural hypotension.' In cases of severe autonomic insufficiency, wide swings in blood pressure without modification in pulse rate are observed. Upon standing or sitting, patient's blood pressure drops to such a low level that they get dizzy, lightheaded, or momentarily blackout.

Urinary and erectile (in males) dysfunction symptoms are also prominent early features in MSA patients. Urogenital symptoms in MSA are usually due to a complex mixture of central and peripheral nervous abnormalities, sometimes superimposed on previous local pathological conditions such as benign prostatic hyperplasia and perineal laxity.

Unfortunately, although orthostatic hypotension and bladder disorders can be managed successfully, no effective treatment is available for the other manifestations of autonomic dysfunction or for the cerebellar and pyramidal symptoms. MSA usually concludes by the patient's death within 7–10 years after diagnosis. Breathing problems such as aspiration, stridor, or cardiopulmonary arrest are common causes of death.

See also: Multiple System Atrophy; Olivopontocerebellar Atrophy; Striatonigral Degeneration.

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Sialidosis

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Clinical Presentation

An inherited, primary deficiency of lysosomal sialidase was first demonstrated in the severe form of Sialidosis (type II). Shortly thereafter, several investigators described a similar deficiency in a clinically milder disorder, 'cherry-red spot-myoclonus syndrome,' now classified as Sialidosis type I, which becomes apparent during the second decade of life. Associated symptoms include cherry-red spots within the middle layers of the eyes; loss of visual clarity; and sudden, involuntary, 'shock-like' contractions (myoclonus) of muscles of the arms and legs. The myoclonus is progressive in nature and may be triggered by voluntary movements (action myoclonus) or certain external stimuli such as sound (reflex myoclonus).

Pathogenesis/Pathophysiology

In type I patients, increased excitability and reduced inhibition were found in some cortical motor pathways, but no abnormalities were found in the brain stem and spinal motor pathways tested. These findings suggest that the electrophysiological abnormalities are restricted to a level above the brainstem. While pathological features of lysosomal storage are apparent in the brainstem and spinal cord, circuits within the brainstem or spinal cord do not appear affected. Biochemically, this may be explained by the more profound role for Sialidase on the plasma membrane in the brain cerebellar cortex and the cerebellum.

Sialidase deficiency leads to defective lysosomal catabolism of sialoglycoconjugates with their subsequent accumulations in tissues and excessive excretion in the urine. The concentration of urinary oligosaccharides is reported to be correlated with the clinical severity of the affected patients, that is, over 3 times more in the infantile-type II Sialidosis patients than in the late-type I patients. Sialidosis patients will excrete high sialic acid conjugated molecules in the urine. Sialidosis has traditionally been diagnosed using enzyme assays that measure sialidase activity in blood leukocytes. Enzyme diagnostic tests for Sialidosis use a variety of both natural (sialyllactose, sialylhexasaccharides, and fetuin) and synthetic (3-methoxyphenyl-*N*-acetylneuraminic acid and 4-methylumbelliferyl-α-D-*N*-acetyl-neuraminic acid, muNANA) substrates. Only in recent times has it become possible to probe the disease at the level of the DNA lesion.

Human lysosomal sialidase (44 kDa) exists in a multienzyme complex consisting of β-galactosidase, cathepsin A, and sialidase (GCS complex). Cathepsin A is required to promote the formation of the enzyme complex. Mechanistically, the sialidase associates with cathepsin A in the endoplasmic reticulum and is then transported to the lysosomes. In fact, transport impaired cathepsin A prevents sialidase from reaching the lysosomes. The sialidase complex is also present on the cell membrane where it is involved in cellular signaling, particularly, in T-lymphocytes, where it activates the macrophage activating factor. Genetically, Sialidosis is inherited as an autosomal recessive trait. The human sialidase gene was mapped to chromosome 6p2l within the human major histocompatibility complex (MHC). The human and mouse sialidase genes are structurally similar (both about 4.5 kb). The two genes contain five introns which range in size from 96 bp to 1.2 kb. The levels of sialidase expression in different mouse tissues, evaluated by Northern blot analysis, were found to be high in kidney, epididymis, brain and spinal cord, and moderate to low in adrenal, liver, lung, spleen, and heart.

The isolation and cloning of the human lysosomal sialidase gene has allowed for the characterization of many disease-causing mutations. Thus far, more than

45 mutations have been identified. Previously, we have identified a frame shift mutation and two missense mutations (Phe260Tyr, Leu363Pro) in type II Sialidosis patients. Bonten et al. identified a point mutation that introduced a premature stop codon and the C-terminal truncation of 38 amino acids in two siblings with type I Sialidosis. The biochemical consequences of some of the identified missense mutations (such as Phe260Tyr) are difficult to explain, since they do not affect the putative active site residues of the enzyme and are not expected to introduce significant change in the conformation of the enzyme. Recently, Lukong et al. screened the genomic DNA of nine patients of diverse ethnic origin affected by type I and type II forms of Sialidosis for mutations in the sialidase gene. One patient had a frame shift mutation (G623delG deletion), which introduced a stop codon, truncating 113 amino acids. All others had missense mutations (Gly227Arg, Ala298Val, Gly68Val, Serl82GIy, Leu270Phe, and Gly328Ser). Two unrelated Japanese type I Sialidosis patients were found to have two missense mutations (Val217Met and Gly243Arg). Recently, we have identified five novel disease-causing mutations (Arg225-Pro, Ala298Val, Met1?, Arg341Gly, and Trp23Stop) and used diagnostic genetic technique to provide prenatal screening.

Treatment

While no effective therapy is available for lysosomal diseases so far, many innovative approaches have been used to slow down the disease or reduce its symptoms. Such approaches include enzyme replacement therapy, which provides functional enzyme through endocytosis. In addition, the use of chemical chaperones has shown to be effective in stabilizing misfolded enzymes and therefore increasing its transportation efficacy to the lysosome. The use of bone marrow transplantation is probably the most promising approach especially if used at the early stages of the disease. Finally, gene therapy utilizing adenoviruses or adeno-associated viruses is still in its infancy but holds much promise. However, progressive degeneration of multiple systems and somatic tissues, in clinical Sialidosis, including bone deformation, CNS, neuronal, sensory, skeletal muscle, and immunodeficiency, requires that potential therapies will need to correct a variety of cell and tissue types. This is not an easy task by any means.

See also: Myoclonus.

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Single Pulse TMS

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Glossary

CMCT – Central motor conduction time; conduction time of corticospinal fibers from the motor cortex to motor neurons in the spinal cord or brainstem.
iSP – Ipsilateral silent period; reduction or pause in ongoing voluntary EMG activity produced by transcranial magnetic stimulation of the ipsilateral motor cortex.
MT – Motor threshold; the lowest stimulus intensity capable of eliciting small motor evoked potentials.
SP – Silent period; reduction or pause in ongoing voluntary EMG activity produced by transcranial magnetic stimulation of the contralateral motor cortex.

Definition and History

Transcranial magnetic stimulation (TMS) is a noninvasive method of brain stimulation through magnetic pulses generated by a coil placed on the scalp. It was first described in 1985 by Barker and colleagues who demonstrated that TMS of the motor cortex produced contralateral limb movements.

Physics and Physiology of TMS

TMS has been used to study the complex circuitries and mechanisms in the brain, and as a possible treatment in a variety of neurological and psychiatric disorders. TMS works by passing a large, brief current through a wire coil placed on the scalp. The transient current produces a large and changing magnetic field with lines of flux passing perpendicularly to the plane of the coil. Thus, TMS is based on the principle that a changing electric current in a wire coil induces a changing magnetic field (Ampere's law) perpendicular to the current flow in the coil. This changing magnetic field passes unimpeded through the scalp and skull, and induces an electric current in the brain that flows in the opposite direction to the current in the coil (Faraday's law). The TMS apparatus mainly consists of boosters, control panel connected to a computer, and a stimulating coil. Boosters are made up of a capacitor discharge system which works with voltages of 500–4000 V and stores energy in the range of 400–2000 J. Stimulating coil is made up of wire loops encased in insulated plastic and connected through a cable to one or more capacitors. Electrical current passes through the coil for brief periods of 100–200 ms. When the current flows through the coil, magnetic field in the range of 1.5–2 Tesla is generated.

The strength of the induced current is a function of rate of change of the magnetic field, which in turn depends on the rate of change of current in the coil. Magnetic field penetrates the scalp and skull much more easily than electrical energy. The induced electrical current depolarizes axons, most likely at the sites of bending. The effects of TMS depend on the intensity of the induced magnetic fields, the shape and orientation of the induced current. Some coils such as a circular coil, stimulate a large brain area. Other coil designs such as a figure-of-eight coil, produce more focal stimulation with the maximum stimulation at the junction of the two loops. Different current directions activate different groups of cortical neurons.

Effects of Focal TMS

The effects of focal TMS depend on the function of the underlying brain region. While TMS over motor cortex results in generation of the motor evoked potential (MEP) in the target muscle, TMS of occipital cortex can produce phosphenes and transient scotomas. Several studies showed that TMS can transiently block the function of the stimulated region. For example, TMS of V5 area of the visual cortex can selectively interfere with motion perception, suggesting that this region is required for motion perception. Similarly, TMS over left dorsolateral prefrontal cortex (DLPFC) impaired working memory as detected by the three-back working memory task. Thus, these 'virtual lesions' experiments can be used to map the functioning of the brain. TMS can also be used to identify the functional connections. For example, connection between premotor and motor cortex can be studied by TMS to these areas at different interstimulus intervals and coil orientations.

Measures Derived from Single Pulse TMS

The following parameters can be used in diagnosis and research in neurological disorders.

Motor Threshold (MT)

MT refers to the lowest TMS intensity capable of eliciting small MEPs, and is usually defined as more than 50 μV in amplitude in the muscles at rest or 200 μV in active muscles in at least five out of 10 trials. MT likely reflects the excitability of neuronal membrane as it is increased by drugs that block voltage-gated sodium channels. MT reflects both cortical and spinal excitability, and can be used to assess corticospinal excitability in disorders such as amyotrophic lateral sclerosis, stroke, and Parkinson plus syndromes.

Central Motor Conduction Time

Central motor conduction time (CMCT) is the conduction time of corticospinal fibers from the motor cortex to motor neurons in the spinal cord or brainstem. It is calculated by subtracting the peripheral conduction time from the latency of the MEP elicited by motor cortical TMS. Upon stimulating a motor nerve, the M wave is the direct muscle response, and the F wave is the muscle response produced by the activation of the alpha motoneuron by the antidromic volley. Thus, peripheral conduction time may be calculated using the formula (F wave latency + M wave latency − 1)/2. Other methods of obtaining the peripheral conduction time include electrical or magnetic stimulation over the spine. CMCT may be useful in the diagnosis of multiple sclerosis, stroke, amyotrophic lateral sclerosis, and compressive myelopathies. Prolonged CMCT is also found in patients with parkinsonian syndrome secondary to the multiple system atrophy or progressive supranuclear palsy.

Silent Period

Silent period (SP) is a pause in the ongoing voluntary EMG activity produced by TMS. It is elicited by single pulse TMS delivered during voluntary muscle contraction. While the first part of the SP is due in part to decreased spinal cord excitability, the latter part is almost exclusively due to cortical inhibition. Prolonged SP suggests hyperactivity, whereas shortened SP suggests hypoactivity of inhibitory circuits in the motor cortex. This type of inhibition is likely mediated by $GABA_B$ receptors.

Ipsilateral Silent Period

Ipsilateral silent period (iSP) is generated through transcallosal inhibition and has been proposed as the diagnostic tool for callosal functions.

Recruitment Curve

This parameter also known as the input–output or stimulus-response curve refers to the increase in MEP amplitude with increasing TMS intensity. Compared to MT, this measure assesses neurons that are intrinsically less excitable or spatially further from the center of activation by TMS. Recruitment curves are likely related to the strength of corticospinal projections, and are generally steeper in muscles with low MT such as intrinsic hand muscles.

Mapping of Muscle Representation

Mapping is performed by stimulation at a number of different scalp positions with a focal figure-of-eight coil. The number of excitable scalp positions, location of the optimal position for stimulation, and the center of gravity (an amplitude-weighted representative position on the motor map) can be determined. Motor maps are affected by both the location and excitability of the motor representation.

TMS and Movement Disorders

TMS can provide useful information of patients with movement disorders. Studies have shown that MT

Table 1 Single pulse TMS measures in movement disorders

Disorder	*Motor threshold (MT)*	*Central motor conduction time (CMCT)*	*Silent period (SP)*	*Motor evoked potential (MEP) amplitude*	*Recruitment curve*	*Mapping of muscle representation*
Parkinson's disease	↓/↔	↔	↓	↓	↓	Anterior displacement of hand muscle area
Dystonia	↔	↔	↓	↓	–	Distorted hand muscle in FHD
Huntington's disease	↔	↔	C	↔	–	–
Wilson's disease	↑	↓	↓	↓	–	–
Friedreich's ataxia	↓	–	–	↓	–	–

↔, normal; ↓, decreased; ↑, increased; C, controversial/not established; –, not been studied; FHD, focal hand dystonia. These findings represent results from multiple studies. If studies showed conflicting results, the findings of the majority of studies are shown here.

measurements, input–output curves, SP, and CMCT frequently disclose abnormal findings, but are not specific for any disease (**Table 1**). TMS has a role in demonstrating CMCT abnormalities in patients with secondary forms of movement disorders in whom pyramidal signs may be clinically equivocal. TMS proved to be a very useful research tool to investigate the pathophysiology of movement disorders.

Future Directions

TMS has helped to advance the understanding of the complex circuitry of human brain. This noninvasive investigative tool coupled with advanced imaging techniques would throw more light into the neurophysiological mechanisms of neurological disorders.

See also: Dystonia; Electromyography (EMG); Huntington's Disease; Motor Evoked Potential; Paired Pulse TMS; Parkinson's Disease: Definition, Diagnosis, and Management; rTMS; Wilson, Samuel Alexander Kinnier.

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Sleep Attacks

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Glossary

Cataplexy – Sudden loss of voluntary muscle control triggered by an emotional stimulus such as laughter, surprise, or anger. Almost exclusively associated with narcolepsy.

Excessive daytime sleepiness (EDS) – Characterized by persistent sleepiness and general lack of energy compelling people to nap during the day.

Hypocretin – A neuropeptide hormone secreted by the lateral hypothalamus involved in wake promotion, also known as orexin. Often associated with narcolepsy.

Multiple sleep latency test (MSLT) – A series of 4–5 naps taken at 2 h intervals throughout the day after an overnight sleep study is performed in order to evaluate the extent of sleepiness in individuals.

Maintenance of wakefulness test (MWT) – A series of 20- or 40-min trials taken at 2 h intervals throughout the day after an overnight sleep study, during which the patient attempts to stay awake.

Polysomnography (PSG) – An overnight sleep study that typically includes electroencephalogram (EEG) to measure brain waves, electrooculogram (EOG) to measure eye movements, electromyogram (EMG) to measure muscle tone, electrocardiogram (EKG) to measure heart rate, limb electrodes to assess for leg movements, respiratory channels to assess for apnea, pulse oximetry to assess oxyhemoglobin saturation, and audiovisual recording.

Pathological hypersomnolence (PH) – Excessive sleepiness despite adequate amounts of nocturnal sleep. Includes narcolepsy, idiopathic hypersomnia, and Klein–Levin syndrome. Measured by MSLT.

Definition/History

'Sleep attacks' (SAs) are events of irresistible and overwhelming sleepiness. Any prodrome or warning of the attack

is typically absent so that preventative measures are useless in overpowering the urge to sleep. After much debate, SAs are no longer considered an exaggerated form of excessive daytime somnolence (EDS) but rather a severe form of pathological hypersomnolence (PH) similar to narcolepsy.

In the 1960s, SAs were described in narcolepsy and became pathognomonic for this disorder. The concept of SAs was specifically reintroduced in 1999 during investigations of Parkinson's disease (PD)-related motor vehicle accidents. SAs are now most commonly associated with dopaminergic agents (DAs), although they are also commonly reported with untreated obstructive sleep apnea (OSA) and restless legs syndrome (RLS). Assessment of PH is now considered crucial due to safety issues, particularly with regards to the medicolegal and psychosocial ramifications associated with SAs.

Pathogenesis/Pathophysiology

To discuss SA pathophysiology, it is essential to understand the basics of sleep and wake mechanisms. Although extensively interrelated, the drive for sleep and the processes for wake maintenance are essentially independent systems. Wake states are maintained by several neurotransmitters, including norepinephrine, dopamine, acetylcholine, and serotonin. Because these neurotransmitters also influence sleep, organization and communication among the nuclei that secrete these substances is critical. Orexin, a hypothalamic neuropeptide, helps coordinate and regulate these nuclei to allow for wake maintenance and to prevent sleep intrusion into wake periods. During sleep deprivation (SD), the drive for sleep increases but can be overcome by wake systems driven by certain motivational situations (e.g., interest, fear), as well as by substances (e.g., caffeine). For sleep onset to occur, the hypothalamic ventrolateral preoptic nucleus (VLPO) allows for coordinated dampening of wake systems, enabling coordination of various sleep systems to take over.

Narcolepsy research implicates loss of hypocretin neurons in as a cause of wake maintenance instability. Although SAs in PD are usually attributed to DAs, EDS can precede PD motor manifestations and drug treatment, leading to speculations that PH is inherent to PD pathophysiology. Pathological studies report early loss of hypocretin function in PD, which may be responsible for the early appearance of 'narcolepsy-like' symptoms, but hypocretin levels in the cerebrospinal fluid in PD are variably altered. As such, EDS in PD may not be solely due to hypocretin abnormalities, as the alerting properties of dopamine, norepinephrine, and serotonin are also affected.

Several studies correlate SAs in PD to disease severity, sleep fragmentation, and medication effect. One study evaluated sleep fragmentation by overnight polysomnograms (PSG), the drive to sleep by multiple sleep latency test (MSLT), and the drive for wake maintenance measured by the maintenance of wakefulness test (MWT). In PD, EDS correlated with overnight sleep fragmentation, but the degree of sleep fragmentation was independent of disease severity. PD patients compensated for EDS when asked to do so unless treated with high doses of DAs, which compromised their ability to stay awake. This suggests that PD-pathophysiology causes sleep fragmentation, thereby increasing sleep drive, but use of DA in combination with sleep fragmentation also alter wake mechanisms, causing PH. Although this theory may apply to PD, it does not explain DA-induced SAs in other cases, such as RLS. Further investigations should assess whether DA-sensitivity confers susceptibility to SAs and whether this carries implications for neurodegeneration.

Epidemiology/Risk Factors

Community-based studies report EDS in over 15% of PD patients. However, SAs are seldom differentiated from EDS, prompting one study to classify EDS into the following: sudden irresistible SA, definite SA, probable SA, possible SA, sleep episode, and sleep event not otherwise specified. In this article, DAs were implicated in SAs in 30% of PD patients. Despite admitted overestimation, this study highlights the need for evaluation of SAs apart from EDS.

Aside from DA, little is known about risk factors. Dysautonomia likely confers a higher risk, but age, disease severity, and sedatives are not considered specific risk factors in PD-related SAs. Sensitivity of subjective screening tools is low in evaluating EDS in PD.

Clinical Features and Diagnostic Criteria

In contrast to prodromal symptoms of sleepiness in traditional EDS, SAs are described as irresistible and sudden attacks with little, if any, warning. One description likened SAs to a 'short circuit' rather than 'falling asleep,' consistent with absence of EEG slowing preceding the SAs. Recovery from SAs is refreshing, which is not always reported with EDS-induced naps.

Diagnosis should begin with clinical interview, evaluating medical history, sleep habits, nocturnal sleep time, potential causes of sleep fragmentation, and daytime function. Overnight PSG is recommended to identify SD secondary to nocturnal sleep disorders such as OSA. Quantification of EDS is recommended with a next-day MSLT.

Differential Diagnosis

SAs are considered to be a disorder of PH, which includes narcolepsy and idiopathic hypersomnia. Before assigning a diagnosis of PH, assessment and resolution of SD is

recommended. SD can be due to several causes, including, but not limited to, primary sleep disorders, chronic insufficient sleep, and substances that influence sleep or promote wakefulness, such as alcohol or caffeine. Clinical interview and work-up should also include neurological history for seizures.

Diagnostic Work-up/Tests

Prior to PSG, clinical history should evaluate nocturnal sleep habits, substances and medications, and daytime habits. SD should be corrected with a regular sleep–wake schedule, allowing for 7–8 h of sleep per night. If a nocturnal sleep disorder is present, appropriate treatment should be instituted. After the above is complete, a PSG with a next-day MSLT is recommended to quantify the extent of PH. A urine drug screen should accompany the MSLT. MWT can also be clinically useful to assess the ability to maintain the wake and alert state despite situations, such as medication effect.

For those with clinical history suspicious for narcolepsy, MSLT is considered diagnostically definitive. Hypocretin levels and HLA genotype are generally reserved for atypical and research cases.

Management

Switching DAs, reducing DA dose, or adjusting DA intake may help reduce SA severity. Additional pharmacological management consists of wake-promoting medications such as modafinil and stimulants. Modafinil has an unclear mechanism of action, although norepinephrine and dopamine systems are likely involved. Dose typically starts at 100–200 mg each morning, with upward titration according to clinical symptoms. The most common side effect of modafinil is headache, exacerbated if dose titration occurs too quickly. Most patients take modafinil upon awakening, although a second dose is occasionally taken to sustain the wake-promoting effect into the late afternoon. Modafinil is FDA-approved for doses up to 400 mg for certain sleep disorders such as narcolepsy, shift-work sleep disorder, and OSA. If modafinil is ineffective, stimulants such as methylphenidate may be prescribed, but side effect profiles often limit their use. Despite reported effectiveness in narcolepsy, modafinil seems less effective in preventing SAs in PD. Few studies have evaluated stimulant effectiveness in controlling SAs in PD to warrant comment.

Nonpharmacological management must be emphasized. Patients should institute proper sleep hygiene, avoid SD, and avoid substances interfering with sleep. Sedating medications should be avoided, including limiting or lowering use of DAs. Safety habits should be routinely discussed, particularly driving. Scheduled naps may be helpful.

Prognosis

Although systematic reviews of SAs are limited, patients can respond to intervention. Follow-up studies are needed to determine whether SAs can be eliminated on a long-term basis with these techniques.

See also: Dopaminergic Agonists in Parkinson's Disease; Parkinson's Disease: Definition, Diagnosis, and Management.

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Somatoform Disorders

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Glossary

Body dysmorphic disorder – Involves the preoccupation with a perceived defect in appearance that causes clinical distress and impairment in social and occupational functioning. Even If a slight physical anomaly is apparent, the individual's concern is markedly exaggerated and not better accounted for by anther psychiatric disorder.
Conversion disorder – Describes patients who present with symptoms affecting voluntary motor or sensory function that inappropriately suggest a neurological or other general medical condition. It inherently has all the features of somatoform disorders, including primary psychogenic etiology of an unconsciously based nature, being unexplainable on a physiological basis and not being due to the direct effects of a substance or a culturally sanctioned experience. Furthermore, the clinically impairing symptoms are not limited to pain or sexual dysfunction; are not part of a somatization disorder; and are not better accounted for by another mental disorder.
Hypochondriasis – Describes individuals who are debilitated by fear that they have a serious disease despite appropriate medical reassurance to the contrary. The fear is often based on catastrophizing normal bodily signs or symptoms as indication of serious illness. While beliefs cause clinical distress or functional impairment, they are not of delusional intensity: patients can often acknowledge that their concerns may be excessive, yet feel unable to stop worrying and seeking reassurance. To meet criteria for diagnosis of hypochondriasis, the preoccupation, and fear must persist for at least 6 months and not be better accounted for by another psychiatric disorder.
Somatoform disorder – A psychiatric disorder describing patients who experience distressing physical symptoms suggestive of a medical condition, yet without objective findings or adequate explanation by an existing general medical condition. Despite this, the symptoms lead to impairment in social, occupational, or other areas of functioning. Furthermore, the symptoms are not intentionally produced by the patient (i.e., are not under conscious, voluntary control).
Somatization disorder – Connotes a chronic history, lasting several years, of many physical complaints, beginning before age 30, that result in active treatment or significant impairment of social, occupational, or other important areas of functioning. As with all somatoform disorders, patients with somatization disorder have symptoms with primary psychogenic etiology of an unconsciously based nature, being unexplainable on a physiological basis and not being due to the direct effects of a substance or a culturally sanctioned experience. In addition, criteria for somatization disorder require the presence of at least four pain symptoms, two gastrointestinal symptoms, one sexual symptom, and one pseudo-neurological symptom.

Definition and History

Patients with somatoform disorders experience distressing physical symptoms suggestive of a medical condition, yet without objective findings or adequate explanation by an existing general medical condition. Despite this, the symptoms lead to impairment in social, occupational, or other areas of functioning. Furthermore, the symptoms are not intentionally produced by the patient (i.e., are not under conscious, voluntary control), distinguishing them from *factitious disorders* and *malingering* (see cross references) (**Table 1**).

The most important initial and continuing task in the evaluation of this group of disorders is the clarification of whether an underlying, initially undiagnosed physical condition exists that may be overlooked and that may coexist with a superimposed somatoform disorder. A second vital task is that of maintaining a therapeutic rapport with patients whose initial inclination is often to doubt or dismiss the possibility that psychological factors may underlie some or all of their presenting physical symptoms. A combination of tact on the part of the primary medical physician and continuing collaboration with the consulting and cotreating mental health professional is crucial to allow for a thorough and open-minded diagnostic process as a prelude to effective treatment. Maintaining a 'neuropsychiatric perspective' that emphasizes the universal impact of stress on physical processes is a helpful way of avoiding the defensive turnoff that leads some patients to flee precipitously if they feel that they are being viewed as either 'crazy' or malingering when the possibility of psychogenic contributions to their symptoms is raised.

Historically, somatoform disorders were a particular interest of both Charcot and Freud, with Freud having

Table 1 The somatizing disorders: defining characteristics

	Conscious intentionality	*Motivational factors*	*Coexisting psychopathology*	*Prognosis*
Somatoform disorders	Absent	1. Repress unacceptable wishes, feelings or conflicts 2. Any pragmatic benefits, if present, are secondary	Highly variable: may include affective, anxiety, dissociative, psychotic, developmental or personality disorders	Highly variable: depending on chronicity, coexisting psychopathology, patient resilience, support network, and treatment
Factitious disorders	Present	1. Assume the sick role 2. Any pragmatic benefits, if present, are secondary	Often includes dependent, histrionic, borderline or antisocial personality features	Often poor, especially if chronic
Malingering	Present	Pragmatic benefits: financial, legal, drugs; Circumvent authority	Often includes antisocial personality disorder	Symptoms are relinquished only when the goal is either obtained or seen as clearly unobtainable
Psychological factors affecting a medical condition	Variable	None. Any pragmatic benefits, if present, are secondary	Highly variable	Highly variable, depending on the medical condition, chronicity, patient resilience, support network, and treatment
Undiagnosed Medical Condition	Absent	None. Any pragmatic benefits, if present, are secondary	Highly variable	Depends on the medical condition and the stage at which diagnosed and treated

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contributed substantially to our understanding of the unconsciously based dynamics involved and the possibilities of alleviation of disabling symptoms through supportive, insight-oriented psychotherapeutic intervention. More recent psychotherapeutic and pharmacological interventions have enhanced therapeutic leverage in treating coexisting and contributory anxiety, depression, and other psychopathology. Contemporary functional MRI studies have documented the presence of unconscious processes whereby emotional stressors can distort cognitive perceptions in ways clearly relevant to our better understanding the pathogenesis of these disorders.

Clinical Features and Diagnostic Criteria

The term 'somatoform disorders' is a grouping of related disorders involving medically unexplained symptoms.

Conversion disorder describes patients who present with symptoms affecting voluntary motor or sensory function that inappropriately suggest a neurological or other general medical condition. It inherently has all the features of somatoform disorders as outlined earlier, including primary psychogenic etiology of an unconsciously based nature, being unexplainable on a physiological basis and not being due to the direct effects of a substance or a culturally sanctioned experience. Furthermore, the clinically impairing symptoms are not limited to pain or sexual dysfunction, are not part of a somatization disorder (see next subsection), and are not better accounted for by another mental disorder. Commonly encountered conversion symptoms presenting to neurologists as 'movement disorders' include tremor, gait abnormality, dystonia, paroxysmal dyskinesias, and myoclonus, among others. Prospective studies of children and adolescents with untreated or unresolved mono-symptomatic conversion disorder disclose a pattern of symptom proliferation over time, suggesting that this is a developmental path leading to somatization disorder and its chronic variant, undifferentiated somatoform disorder.

Somatization disorder connotes a chronic history, lasting several years, of many physical complaints, beginning before age 30, that result in significant impairment of social, occupational or other important areas of functioning. As with all somatoform disorders, patients with somatization disorder have symptoms with primary psychogenic etiology of an unconsciously based nature, being unexplainable on a physiological basis and not being due to the direct effects of a substance or a culturally sanctioned experience. In addition, criteria for somatization disorder require the presence

of at least four pain symptoms, two gastrointestinal symptoms, one sexual symptom, and one pseudo-neurological symptom.

Undifferentiated somatoform disorder connotes the presence of one or more physical complaints of at least 6 months duration that manifest primary psychogenic etiology of an unconsciously based nature, being unexplainable on a physiological basis and not being due to the direct effects of a substance or a culturally sanctioned experience. This will include patients who are similar to, but do not meet all the criteria of, patients with somatization disorder.

Pain disorder involves pain where psychological factors play a major role in the onset, severity, or maintenance of the pain and requires clinical attention. The pain causes significant functional impairment and is not intentionally produced nor better explained by another psychiatric disorder. There are two subtypes of pain disorder: (1) *Pain disorder associated with psychological factors*, where psychological factors have a predominant role in the onset, severity, or maintenance of the pain and general medical conditions play either no role or a minimal one and (2) *Pain disorder associated with both psychological factors and a general medical condition*, where both psychological factors and a general medical condition have important roles in the clinical course.

Hypochondriasis describes individuals who are debilitated by fear that they have a serious disease despite appropriate medical reassurance to the contrary. The fear is often based on catastrophizing normal bodily signs or symptoms as indication of serious illness. While beliefs cause clinical distress or functional impairment, they are not of delusional intensity: patients can often acknowledge that their concerns may be excessive yet feel unable to stop worrying and seeking reassurance. To meet criteria for diagnosis of hypochondriasis the preoccupation and fear must persist for at least 6 months and not be better accounted for by another psychiatric disorder.

Body dysmorphic disorder (BDD) involves the preoccupation with a perceived defect in appearance that causes clinical distress and impairment in social and occupational functioning. Even If a slight physical anomaly is apparent, the individual's concern is markedly exaggerated and not better accounted for by anther psychiatric disorder.

Pathogenesis/Pathophysiology

Conceptualizations regarding pathogenesis of somatoform disorders have addressed considerations of predisposition, precipitating influences, and perpetuating influences.

Predisposition includes biological factors (e.g., genetics and emerging data on immunological factors influencing amplification of symptom sensitivity), past experiences (e.g., trauma, abuse, or exposure to disabling physical illness in oneself or others), and personality factors (e.g., internalizing, as opposed to externalizing style). A variety of family studies show higher rates of somatoform and related disorders (i.e., depression and obsessive compulsive disorder) in first-degree relatives. For instance, genetic factors are suggested by pedigree studies finding a higher incidence of somatization disorder in female first-degree relatives of index cases, whereas male first-degree relatives have a higher incidence of alcoholism and antisocial (externalizing) personality features. Additionally, recent advances in understanding of psychoneuroimmune pathophysiology, including the role of cytokines in illness behavior, suggest that some individuals are more vulnerable to experiencing amplified somatic symptoms and pain sensitivity. Past experiences such as trauma or illness may underlie chronic activation of the immune system. Comorbid psychiatric or neurological disorders may also be contributory. Biologic factors can be compounded by limitations of communicative ability due to intellectual, emotional, or social constraints predisposing some to a 'body language expression of distress.'

Precipitating stressors may involve proximate activation of psychological conflicts, such as those regarding sexual, aggressive, or dependency issues. Traumatic events, such as those threatening one's physical integrity or self-esteem, are commonly cited precipitants.

Perpetuating factors include 'primary gain' or the ways in which the symptom may resolve or diminish the psychological conflict that generated the symptom, as well as 'secondary gain' or the pragmatic benefits of the symptom.

Somatoform disorders embody dissociative features, since they involve development of somatic symptoms or preoccupations based on psychological mechanisms outside the individual's conscious awareness. One may conceptualize such an individual as overwhelmed with stress beyond the capacity for effective, conscious processing of the related affect, leading to communication of distress via 'somatic metaphor' or symptom production.

Epidemiology

Psychogenic neurological symptoms have been estimated to account for between 1% and 9% of all neurological diagnoses. In psychiatric epidemiologic studies, children have an equal incidence of conversion disorders in boys and girls, which shifts in the direction of female preponderance as age progresses. Somatization disorder appears more commonly among women (lifetime prevalence 0.2–2%, vs. 0.2% in men). When the number of symptoms required for a somatoform diagnosis is reduced, however, (e.g., in undifferentiated somatoform disorder) an

increased prevalence is encountered: in primary care patients, this is estimated at ~16.6%. Pain disorder is relatively common (estimated 12 month prevalence of 8%) and is also noted to be more common in females (11%) than males (4%). Hypochondriasis is seen in ~4–6% of patients in general medical practice. It presents typically in adulthood and is found equally commonly in men and women. Body dysmorphic disorder has a prevalence estimated ~1–2%; however, prevalence may be significantly higher in some dermatologic and plastic surgical populations. It occurs equally commonly in males and females and typically presents in adolescence or early adulthood.

Differential Diagnosis

Undiagnosed medical illness is the most crucial category of differential diagnosis for the somatoform disorders, presenting substantial hazards for patients as well as clinicians. While it is beyond the scope of this article to address the complex issue of what constitutes an adequately thorough medical workup for movement disorders with initially uncertain etiology, it is clear that this is a crucial foundation for the diagnosis of any somatoform disorder and for the effectiveness of any therapeutic intervention. Certainly, the presence of nonphysiologic features on physical examination does not rule out the possibility of an underlying undiagnosed physical illness coexisting with a superimposed somatoform disorder. Furthermore, the patient's need for reassurance that all plausible organic causes of the presenting symptoms have been considered and evaluated is a prerequisite to seriously considering a judiciously introduced discussion of possible psychogenic contributants.

Factitious disorders involve the *intentional, or conscious,* production of physical or psychological symptoms with the primary purpose of *being cared for medically.* Patients with factitious disorders may seek numerous medical evaluations and treatments, including hospitalizations, invasive procedures, and surgery. Factitious disorders differ from malingering in that pragmatic incentives for this behavior, such as economic gain or evasion of responsibility, are absent or subsidiary. A more chronic and intractable pattern of factitious disorder is known as 'Munchausen's Syndrome.' These patients may migrate to different treatment sites to avoid detection that would be more likely in a single follow-up site. Duplicity in assuming the patient role is often associated with severe dependent, histrionic, borderline, and antisocial personality characteristics. Prognosis is generally less favorable than in cases of somatoform disorder.

Malingering involves purposeful production of physical or psychological symptoms in pursuit of a pragmatic goal, which may include financial gain, avoidance of school or military duty, evasion of prosecution, or obtaining controlled substances. Associated features include poor cooperation during diagnostic evaluation and treatment, pending litigation, and antisocial personality disorder. Although there may be underlying psychopathology, malingering is not considered as a mental disorder.

Psychological factors affecting a medical condition is a diagnosis that requires documentation of a general medical condition. Psychological factors can impact a general medical condition in two main ways: (1) the psychological factors influence the development of the medical condition, as reflected by a close temporal proximity between the psychological factors and the evolution of the medical condition; or (2) stress-related physiological responses exacerbate the medical condition. A neurologically relevant example is the exacerbation of a parkinsonian or essential tremor by anxiety.

Coexisting psychiatric conditions, such as affective disorders, anxiety disorders, dissociative disorders, psychotic disorders, developmental disorders and personality disorders, may mimic, contribute to, or exacerbate somatoform disorders. Examples include cardiovascular symptoms seen in panic disorder, vegetative symptoms of depression suggesting a neurodegenerative, endocrine or metabolic disorder, or somatic delusions seen in schizophrenia. In addition to inquiring about contemporary psychosocial stressors and psychiatric symptoms, clinicians should ask about histories of physical, sexual, or emotional abuse or neglect, which may predispose to somatization.

Diagnostic Workup

It is inevitable that medical illness will sometimes be missed on initial assessment by the primary medical clinician who suspects a possible somatoform disorder. This fact may lead some clinicians to an overly aggressive medical diagnostic workup and an untoward delay in seeking psychiatric consultation. This, in turn, may lead the patient to the presumption that there must be some esoteric medical cause for the unexplained symptoms that has simply not yet been found at the conclusion of the workup, prompting migration to a new medical specialist. On the other hand, premature presentation of a firm diagnosis of psychogenic etiology before adequate medical workup has been completed can lead to an alienation of the patient and an embarrassment for clinicians who have prematurely grasped a misdiagnosis, undermining the patient's confidence in the treatment team. A more judicious path, requiring seasoned judgment of the primary medical physician, is to introduce the recommendation of a psychiatric consultation when a somatoform disorder is strongly suspected, with the psychiatrist presented as another specialty consultant seeking elucidation of symptoms that may have multifactorial causation, including the possible role of 'stress.'

Management

Conversion Disorder

Physical therapy can be a valuable face-saving intervention in cases of fixed postures, weakness, or gait abnormalities. This physically based format of recovery may be particularly helpful for patients who have difficulty in assimilating psychodynamic interpretations. The physical therapist provides hands-on encouragement and reassurance. Physical therapy is also crucial in treating disuse atrophy or contractures that complicate persistent somatoform motor symptoms.

Psychotherapy allows patients to manage conflicts that led to symptom formation through a process of emotional and cognitive 'restructuring.' Such treatment ideally addresses as many relevant etiological variables as possible, with a strategy that strengthens the patient's capacity to impact relevant psychological, biological, and social variables to generate a healthier mode of adaptation. Patients may be receptive to 'stress management techniques,' which utilize cognitive behavioral strategies, as a contemporary adaptation of the traditional psychodynamic treatment of these disorders.

Hypnosis is a psychotherapeutic technique that provides patients with a benign desensitizing experience of dissociation under the protective supervision of the therapist along with suggestions for symptomatic improvement. Initial assessment of hypnotizability provides a 'mind-body' dissociative experience that conveys a model for understanding and experiencing the dissociation central to conversion symptoms. Self-hypnosis techniques provide a confidence-building strategy of enhanced self-control and healing.

Behavior modification strategies address the contingencies of reinforcement that contribute to symptom formation and perpetuation. Insight-oriented psychotherapy and positive suggestion have more motivational traction when combined with the alteration of environmental forces that generated primary and secondary gain benefits that precipitated the symptoms. Behavior modification often requires collaboration of motivated family members, who are often inadvertent 'contributants' to the symptomatic pattern, either by aversive influence or by 'enabling' of the sick role. This route of therapeutic influence via family intervention is often easier with child and adolescent patients, by working with parents. However, it should not be overlooked with adults, where spouses or significant others can often wield a crucial influence.

Pharmacotherapy is often indicated for coexisting psychiatric conditions, such as depression, anxiety, or psychosis. These *neuropsychiatric* medications can reasonably be presented as an aid to attenuate abnormalities of neurotransmitter balance that appear to play a central role in many *neuropsychiatric conditions,* including somatoform disorders.

Other treatment interventions include family therapy, which addresses conflicts, dependency, abuse, or enabling issues; intravenous infusions, such as amobarbital or loazepam, to evaluate for possible contractures in fixed, dystonic posturing; electroconvulsive therapy for treatment-resistant depression or mania; or speech therapy when indicated.

Somatization and Pain Disorders

Practical outpatient strategies for patients with chronic medically unexplained symptoms include centering the treatment with the primary care physician, who maintains a dual role of monitoring the patient's physical status, while supportively encouraging that exploratory attention be paid to those psychosocial stress factors that inevitably impact on this chronic condition. Helpful adjunctive techniques include scheduling patients in a time-contingent rather than symptom-contingent manner and avoiding unnecessary treatment and repetition of tests. While approaching patients with somatization and pain disorders with empathy and an appreciation for their genuine suffering, one does not want to be overly reassuring. It is helpful to reframe treatment expectations from symptom 'cure,' if that is unattainable, to improved accommodation.

Psychosocial treatments: Cognitive behavioral therapy (CBT) is a moderately effective treatment for somatization disorder. The CBT model of somatization stresses the interplay of sensory physiology, cognition, emotion, behavior and environment. CBT aims at facilitating patients' identification of their incorrect beliefs about their symptoms and bodily functioning as well as identification of related dysfunctional, avoidable behaviors. One then moves to challenge these beliefs and behaviors, eventually replacing them with more realistic and adaptive ones. The efficacy of treatment for somatoform disorders was recently addressed in a review by Kroenke et al. of 34 randomized controlled trials involving 3922 patients. Two thirds of the studies involved somatization disorder and its variants. Cognitive behavior therapy was effective in most studies (11 of 13), as were antidepressants in a small number (4 of 5).

Pharmacotherapy: Since there is frequent comorbidity with somatization and chronic pain disorders involving anxiety, depression, and personality disorders, the use of antidepressant medication may be helpful in treating these comorbid conditions, as well as in having some impact on the associated somatoform disorder. Some added, independent benefit from antidepressant medication regarding unexplained pain disorder may also ensue. There may be advantage in this regard for medications that enhance both serotonin and norepinephrine reuptake inhibition, such as duloxetine and venlafaxine.

Other potential treatment interventions, including physical therapy, hypnosis, and family therapy, as discussed earlier regarding conversion disorders, may similarly be helpful.

A well-formulated treatment strategy involves drawing upon all relevant interventions that may constructively impact on these chronic syndromes with multifactorial determinants. These combined initiatives, reflecting concerted efforts by the collaborating clinicians, can foster a therapeutic alliance that engenders hope for gradual improvement, based on systematic efforts, further extended by the patient, to attenuate chronic distress and disability. A calm and reassuring therapeutic optimism, supported by regular monitoring and reinforcement of the patient's progress, can be helpful.

Hospitalization: An outpatient setting for the evaluation and treatment of somatoform disorders is favored by the current 'managed care model' that seeks to minimize the time in hospital. In clinical experience, however, the diagnosis of a somatoform disorder may be first entertained when the patient has been admitted to a medical service for the evaluation and treatment of undiagnosed, disabling symptoms. Precipitous discharge without adequate diagnostic clarification to the patient and family, and without establishment of an acceptable, coordinated treatment plan, can be quite counterproductive, generating patient resentment, resistance to appropriate treatment, and prolongation of the course of illness.

Alternatively, a consulting physician may conclude at initial office visit, based on the patient's response to the physician broaching this subject, that while a somatoform disorder is indeed the most likely diagnosis, the patient is resistant to accepting this diagnosis and the associated recommended treatment without a more intensive, integrated evaluation, which can more effectively be done on an inpatient setting. Although there have not been any controlled clinical trials done to systematically evaluate this, it has been the impression of our movement disorder group that such an admission has enabled us to afford a transformative therapeutic opportunity to some patients, who by reasons of geography or other limitations of access to integrated diagnosis and treatment, would not otherwise have achieved symptomatic remission. Under the rubric of a 'multidisciplinary inpatient diagnostic and treatment approach,' such patients have been seen intensively by the admitting neurologist, the consulting psychiatrist, and a physical therapist. This hospitalization removes the patient from those environmental influences that contributed to the symptom formation and perpetuation, while it also allows us to evaluate the patient more thoroughly in a controlled environment. Further, the introduction of the psychiatrist as a routine member of the evaluation and treatment team makes it more difficult for the patient to reject this intervention and allows for the development of a therapeutic alliance while multiple diagnostic and treatment strategies are ongoing simultaneously, assuring the patient that no organic contributions to symptoms are being overlooked.

Within a few days of admission, with our initial diagnostic impressions usually further clarified, we arrange for a conjoint debriefing session with both the neurologist and psychiatrist present, to supportively present to the patient our diagnostic impressions and treatment recommendations. If neurological workup was negative or disclosed a substantial somatoform component, this is supportively reviewed, together with the more favorable prognosis for recovery than would be the case with a degenerative neurological disorder. We observe further that stress of various types can contribute to physiological aberrations that generate clear physical symptoms despite the absence of structural lesions on the various diagnostic tests performed. Commonly encountered clinical examples of how stress can activate the symptoms of hypertension, peptic ulcer disease, and asthma, among others, facilitates patient recognition of the plausibility and relevance of this conceptual model. A treatment plan is then outlined, tailored to the needs of the individual patient. Elements of this treatment plan, generally including psychotherapy, pharmacotherapy, and physical therapy, are started in the hospital in an effort to achieve as much symptomatic improvement as possible, to be continued on an outpatient basis as individually needed. A follow-up appointment is recommended with both the neurologist and the psychiatrist, to assure the patient and family that both spheres are being appropriately monitored in an effort to achieve full symptom resolution.

While there are substantial expenditure and associated insurance hurdles inherent in this intervention, it can be argued from a public health perspective that for some patients who are not otherwise effectively engaged in treatment, the cost of chronic care for years of unremitting somatization disorder far outweigh the cost of a 1–2 week admission, which in our experience, is sometimes dramatically transformative in generating a 'sprint into health.'

Hypochondriasis and Body Dysmorphic Disorder

Cognitive-behavioral therapy and serotonin reuptake inhibitors (SRIs) have the most empirical support for both the treatment of hypochondriasis and Body Dysmorphic Disorder. Both can also be helpful for reducing comorbid symptoms of anxiety and depression.

Psychotherapies: CBT improves patient functioning by modifying dysfunctional thoughts and behaviors in response to symptoms. Therapy may focus on areas such as learning to tolerate and attenuate symptoms without necessarily chasing an unobtainable 'cure.'

Pharmacotherapy. There is increasing evidence that SRIs, such as fluoxetine, fluvoxamine, and paroxetine, help to attenuate both hypochondriasis and BDD. Much like the treatment of obsessive–compulsive disorder,

symptoms of hypochondriasis and BDD may be most responsive to higher does of these medications (e.g., fluoxetine 60 mg day^{-1}).

Prognosis

The prognosis for patients with a somatoform disorder is determined by many factors: Contributants include the nature, chronicity, and severity of the comorbid psychopathology; the nature, chronicity, and severity of life environmental stressors; the intrinsic resilience of the patient; the strength of the available support system; and the effectiveness of treatment.

Follow-up studies of patients with impairing, undiagnosed illness presenting as 'neurological disorders,' the majority of which are apparently somatoform, report a low rate of spontaneous remission and a high rate of long-term impairment in patients not receiving active psychiatric treatment. It therefore behooves the physician who has a clinical suspicion regarding the possible existence of a somatoform illness to document this diagnostic impression clearly to the referring clinician, to communicate it tactfully and empathically to the patient, as well as to make sustained efforts to implement psychiatric referral for further evaluation and treatment. Neurological follow-up is advisable to avoid the patient's feeling abandoned and to reassure all concerned that relevant neurological illness has not been missed.

See also: Factitious Disorders; Malingering; Psychogenic Movement Disorders.

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Spasm

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Glossary

Amyotrophic lateral sclerosis (ALS) – A group of adult onset degenerative conditions resulting in both upper and lower motor neuron findings. ALS causes degeneration of the anterior horn cells with secondary degeneration of the pyramidal tracts.

Dystonia – A condition caused by abnormalities in the basal ganglia. This condition results in involuntary contraction of muscles. The muscular contractions may occur at rest, but are

often worsened after activation of the affected muscles.

Spasticity – Increased tone in muscles due to disruption of descending motor pathways resulting in increased extensor tone in the lower extremities and increased flexor tone in the upper extremities.

Overview

Muscle spasms are defined as involuntary contractions of a muscle group. These spasms can often be forceful and painful. The etiology of muscle spasms may range from benign conditions such as electrolyte disorders that alter muscle physiology to more severe neurological and degenerative conditions such as motor neuron disease and stroke where muscles spasms occur because of abnormalities in the pathways that normally activate muscles. **Table 1** contains a list of conditions that may result in muscular spasms and presents these conditions from the perspective of the primary anatomical site of involvement.

The evaluation of muscular spasms should begin with a history of the distribution, onset, severity, occurrence, and frequency of cramps. A thorough review of systems should be completed for underlying neurological or medical illness and a complete list of medications and supplements. Physical examination can help to elucidate benign from more severe conditions, and the examination must pay close attention to tone, reflexes, bulk of muscles, and sensory changes. In patients with abnormalities on examination, further evaluation is warranted with neuroimaging, laboratory testing, electromyography, and possibly, muscle biopsy. Treatment of muscular spasms is usually directed at the underlying cause, although some treatments may be beneficial regardless of etiology.

Table 1

Electrolyte, metabolic disorders, and toxins
Hypokalemia
Hypomagnesemia
Hypocalcemia
Thyroid abnormalities
Parathyroid abnormalities
Addison's disease
Renal disease
Tetanus
Strychnine poisoning
Medications (diuretics, anesthetics, antipsychotics, laxatives)
Peripheral nerve, nerve root, and plexus
Hemifacial spasm
Radiculopathy
Plexopathy/plexus Injury
Peripheral neuropathy
Muscle disorders
Benign fasiculations and cramps syndrome (myoadenylate, deaminase deficiency)
Myopathy
Myotonia congenita
Malignant hyperthermia
Stiff person syndrome
Anterior horn cell
Motor neuron disease
Post polio syndrome
Spinal cord
Multiple sclerosis
Trauma
Tumor or mass
Infarction
Infection/inflammation
Central nervous system
Dystonia
Tics/Tourette syndrome
Infarction
Traumatic brain injury
Tumor or mass
Infection/inflammation
Neurodegeneration with iron deposition (PANK 2)
Neuroacanthocytosis
Wilson's disease
Cerebral palsy
Other
Nocturnal leg cramps
Exercise induced cramps

Primary Muscle Impairments

Contraction of muscles at the cellular level is a complex process through electrical potentials at the cell membrane and release of calcium with subsequent contractile protein interaction and fiber shortening. This process may be disrupted by electrolyte abnormalities and muscle disorders. Electrolyte disorders and medical illnesses are often acute and short lived. Even in normal people without neurological disease, overuse of muscles from intense exercise can generate mild degrees of lactic acidosis and cause muscle spasms. Single episodes of spasms do not require neurological evaluation in most cases. Recurrent or chronic spasms are best assessed with laboratory studies of muscle enzyme levels and electrolytes, especially immediately during an episode of cramping. In more prolonged medical conditions such as thyroid disease, electromyography may be helpful.

Primary muscular diseases may cause longer term spasms often with accompanying symptoms such as weakness or muscular tenderness. These disorders tend to be progressive over months to years. Muscle diseases can be assessed with electromyography and possibly muscle biopsy.

Peripheral Nerve Impairments

Neurogenic causes are likely the most common type of spasm. This condition results from denervation of the

motor unit with resultant hyperactivity of uninhibited muscle fibers. Neurogenic cramps are seen in a number of peripheral nervous system disorders, including radiculopathy, neuropathy, plexopathy, and anterior horn cell disorders such as amyotrophic lateral sclerosis and spinal muscular atrophy. These conditions can be diagnosed on clinical examination with confirmation by electromyogram.

Hemifacial spasm is a particular form of spasm involving one side of the face and can be associated with a prior history of facial nerve (cranial nerve VII) palsy. In some cases, hemifacial spasm is due to compression of the facial nerve by aneurysm or an ectatic basilar artery. This can be assessed with an MRI and MRA of the brain. Hemifacial spasm may be treated with anticonvulsants, but the most effective therapy remains botulinum toxin injections into the affected facial musculature.

Central Causes of Muscular Spasms

Spasticity is an increase in muscle tone due to lesions of the descending motor pathways at any level from the cerebral hemispheres to the spinal cord. Spasticity is the result of a number of disorders, including, but not limited to cerebral palsy, multiple sclerosis, stroke, and trauma. It is most often associated with other upper motor neuron signs such as increased reflexes, paresis, Babinski signs, and clonus. Spasticity results in increased extensor tone in the lower extremity and increased flexor tone in the upper extremity. The exact pathophysiology of spasticity is not understood, but may be due to the loss of inhibition in descending pathways from the brainstem. Treatments of spasticity and resultant spasms are aimed at reduction of the hypertonicity to facilitate activities of daily living and improve quality of life. Treatment of spasticity includes physical therapy and medical therapy. Medications, including baclofen, tizanidine, benzodiazepines, gabapentin, dantrolene, and botulinum toxin, have been used to decrease tone and spasms.

Dystonia is a movement disorder seen as a primary or secondary disorder due to abnormalities in the basal ganglia. Dystonia is discussed in further detail in its own entry, but its symptoms are primarily those of muscle spasm and deviation of postures, often with pain.

Summary

Spasms that are recurrent require laboratory evaluations to assess electrolytes, acid–base balance, and muscle enzyme levels. If weakness accompanies spasms, electromyography is needed to assess the possibility of myopathy, plexopathy, or neuropathy. If the neurological examination shows increased or decreased reflexes, alterations in ambient tone, or other neurological findings, further evaluations of the spinal cord, brain stem, and brain are needed.

See also: Dystonia; Hallervorden–Spatz Syndrome (PKAN); Hemifacial Spasm; Neuroacanthocytosis Syndromes; Stiff Person Syndrome and Variants; Wilson's Disease.

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Spasmodic Dysphonia: Focal Laryngeal Dystonia

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Glossary

Abductor laryngeal dystonia – Focal dystonia of the laryngeal muscles causing a 'whispering' dysphonia or speech with breathy breaks.
Adductor laryngeal dystonia – Focal dystonia of the laryngeal muscles causing a 'strain-strangled' voice.
Adductor breathing dystonia – Focal dystonia of the laryngeal muscles causing paradoxical motion with adduction on inspiration.
Botulinum toxin – A neurotoxin produced by the bacterium *Clostridia botulinum* which blocks the release of acetyl choline into the neuromuscular junction.
Electromyography – Measurement and recording of mini end plate potentials from muscle.

Definition and History

Spasmodic dysphonia (SD) is an action-induced, laryngeal motion disorder producing interference with a fluent speech pattern. Most cases represent manifestations of primary dystonia, but many are secondary to other neurologic entities. In 1871, Traube coined the term 'spastic dysphonia' when describing a patient with nervous hoarseness. Schnitzler, in 1895, used the terms 'spastic aphonia' and 'phonic laryngeal spasm' to describe such patients. Fraenkel, in 1887, used the phrase 'Mogiphonia' for a slowly developing disorder of the voice characterized by increasing vocal fatigue, spasmodic constriction of the throat muscles, and pain around the larynx. In 1899, Gowers described functional laryngeal spasm whereby the cords were brought together too forcibly while speaking (adductor type) and contrasted this to phonic paralysis whereby the vocal cords could not be brought together while speaking (abductor type). Critchley, in 1939, described the voice pattern as a condition in which the patient sounds as though he were 'trying to talk whilst being choked.' Jacome, in 1980, associated SD with Meige disease, and this association with dystonia was confirmed by Blitzer, Marsden, and others in the 1980s.

Epidemiology

SD is a rare disorder (1 per 100 000). It typically begins in the mid to late 1930s and is more common in women (63%). Almost 12% of the patients have a positive family history for dystonia. More than 80% of these patients remain focal, but almost 15% will develop other cranial involvement (usually blepharospasm), and less than 5% will progress to an extracranial site.

Clinical Features

Two main types of SD have been identified. The adductor type produces an irregular hyperadduction of the vocal folds during speaking, producing a 'strain-strangled' voice with harshness and voice breaks. There is also a less common abductor type in which there are irregular and inappropriate abductor spasms during speaking, producing breathy breaks, or whispering. There are also cases of compensatory or pseudoabductor patients who whisper as a compensatory strategy for the tight adductor spasms they experience. Therefore, these patients may need to be seen several times and put through various challenging vocal tasks to make the correct diagnosis. Cannito et al. believe that all of the patients are a mixed adductor/abductor with a predominance of one form. We have seen several patients who are truly mixed and have both adductor and abductor spasms. We also have seen several patients in whom their primary form changed with time (e.g., adductor to abductor). Many other laryngeal functions, including breathing, laughing, swallowing, and, at times, singing and humming, are usually unaffected.

In addition, we have identified a 'Singer's laryngeal dystonia' in which the vocal abnormalities occur during singing. There is also a rare form of laryngeal dystonia in which there are adductor spasms during respiration. The paradoxical motion during breathing produces stridulous noises during inspiration, but usually does not produce hypoxia. Other laryngeal activities in these patients are normal.

Dystonic movements can be rapid and repetitive, and tremor may be seen in dystonia affecting any segment of the body. The tremors are typically irregular and have a directional preponderance, and thought to be produced by simultaneous agonist/antagonist actions. Many patients with SD have an irregular vocal tremor that is both audible and can be recorded on EMG. This tremor is to be differentiated from the regular tremor that is commonly seen in benign essential voice tremor that often occurs with tremor in other body parts.

Sensory tricks, often, can ameliorate dystonic movements and postures. A sensory trick is also known as

'geste antagonistique' or 'gegendruckphaenomen.' Many laryngeal patients speak better after a yawn or sneeze, or when they sing or yell.

Differential Diagnosis

The differential diagnosis is important because there are no quantitative tests to secure the diagnosis, unless the condition is the result of a secondary dystonia (e.g., head trauma, stroke, Wilson's disease, and tardive dystonias). Patients with a strain-strangled voice or whispering dysphonia include tremor disorders, including essential tremor, cerebellar disorders, muscle tension dysphonia, Parkinson's disease, laryngeal myoclonus, and psychogenic voice disorders.

Diagnostic Evaluation

Diagnostic evaluation should include speech analysis and a fiberoptic endoscopy. The endoscopy will reveal an irregular tremor in some patients and hyperadduction at the glottal level, the false cord level, and/or at supraglottic closure. In the abductor group, there will be abductor spasms producing aphonic breaks in connected speech. In the adductor respiratory laryngeal dystonia, there will be paradoxical adductor closure with inspiration. Brain scans and blood analysis are not very valuable in the diagnosis.

Management

Specific pharmacotherapy to treat underlying identified etiology is available only for a limited number of symptomatic dystonias (secondary dystonias) such as Wilson's disease. For the other patients, the current treatment strategy is aimed at the management of symptom complexes.

Management of focal dystonias has been attempted through a variety of local surgical procedures. Dedo theorized that if sustained contractions of the vocal cords prevented normal phonatory activity, impairing one of the cords would allow for more normal speech. He also found that injection of one recurrent laryngeal nerve (RLN) with lidocaine that cause a paresis could provide temporary speech improvement. Dedo then performed and advocated RLN section as a permanent therapy. Although initial reports of the RLN section technique were promising, many surgeons found late-onset failures. Aronson and DeSanto's review of the Mayo Clinic series found that, by 3 years, only 36% of the patients continued to have some improvement and only one patient maintained a normal voice. Others have suggested a role for laser myectomy, implantable nerve stimulators, and selective dennervation–reinnervation procedures with limited data available.

Botulinum toxin was first given by Blitzer et al., in 1984, for the management of SD. Although not curative, botulinum toxin may significantly ameliorate the muscle spasms and restore a patient's function and quality of life. Some patients require a combination of an oral agent and botulinum toxin. The botulinum toxin is administered through the anterior neck, using a 27 gauge hollow bore, Teflon-coated EMG needle. The active part of the muscles is identified by the interference pattern heard and visualized on the EMG machine while the patient is phonating. The adductor SD patients receive injections into the thyroarytenoid muscle, and some in the lateral cricoarytenoid or interarytenoid muscles. For the abductor SD patients, injections are given into the posterior cricoarytenoid muscles.

Botulinum toxin injections have several advantages over surgical therapy. The patient remains awake and avoids the risks associated with general anesthesia. Graded degrees of weakening can be achieved by varying the dose injected. Dosing begins with small amounts and can be increased until good voice is achieved without prolonged weak voice after the injection. Some patients may have transient dysphagia to liquids. Most adverse effects are transient and are due to diffusion of the toxin. If there is too much weakening produced, the patient will recover with varying amounts of time. If a new and better treatment emerges, the toxin may be stopped and the patient would return to full function. The disadvantage is that the results are not permanent. The adductor SD patients achieve, on average, better than 90% of normal function for a period of 3–4 months. The abductor patients achieve about 70% of normal function. This is because of the limit to how much weakness can be achieved in the posterior cricoarytenoid (PCA) muscle before they begin to have stridor and dyspnea.

Prognosis

SD is a chronic neurologic disorder for which there is presently no cure. There is a very small number of patients who have spontaneous remissions. All of the other patients require management of their symptoms to allow them continued function.

See also: Botulinum Toxin; DYT4, Autosomal Dominant Type Dystonia or Whispering Dysphonia.

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Spastic Paraparesis

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Glossary

Ataxia – Lack of coordination in movements due to cerebellar disorders or loss of proprioception.
Leukodystrophy – Progressive degeneration of brain's white matter due to defective development of the myelin sheath that surrounds neural axons.
Nystagmus – Eye movements characterized by alternating slow movements in one direction and fast (saccade-like) phases in the opposite direction.
Spastic paraparesis – A condition by which continuous muscle activity causes stiffness in lower limbs and gait impairment.
Spasticity – A state of continuous muscle activity of agonistic and antagonistic muscular groups that causes stiffness, and interferes in the normal movement.

Definition and History

Spastic paraparesis results from restless muscle activity of lower limbs that hinders leg movements, causing impaired gait. In this article, we will mainly focus on the hereditary spastic paraplegia (HSP).

HSP, also called as familial Strümpell–Lorrain syndrome, was described by Ernest A. Strümpell and Maurice Lorrain in the late nineteenth century. It comprises a heterogeneous group of inherited neurodegenerative pyramidal tract dysfunctions causing progressive spasticity and weakness of the lower limbs.

HSP can be classified according to the clinical presentation or the mode of inheritance. Clinically, HSP is classified as either pure (uncomplicated) or complex (complicated). HSP most often presents with an autosomal dominant inheritance (ADHSP), but can also be inherited by autosomal recessive (ARHSP) or X-linked transmission. In the last 10 years, identification of the causative genes linked to HSP has provided an essential aid in classifying HSP, despite the fact that the frequent phenotypical variability of mutations located in the same gene, as seen in *PLP1*, *paraplegin*, or *spastin* mutations, can give rise to either pure or complex HSP. Fifteen different genes and 22 different loci with unknown gene have been associated with HSP to date (**Tables 1** and **2**). Some genes cause a specific phenotype such as *atlastin*, associated with pure ADHSP starting in childhood, or *spatacsin*, which causes mental retardation, thin corpus callosum, and polyneuropathy.

Pathogenesis and Pathophysiology

HSP is characterized by corticospinal tract degeneration caused by the derangement of microtubule dynamics and organelle transport. Neuronal degeneration starts distally in the axons of pyramidal neurons that have synapses with spinal interneurons. These neurons activate the second motor neurons, which are located at the ventral horn of the spinal cord, whose axons run through the peripheral nerves and end in the neuromuscular junctions. Functional loss or gain of mutated proteins impairs mitochondrial metabolism, axonal transport, and cytoskeletal organization.

Table 1 Hereditary spastic paraplegias caused by mutations of known genes

Locus	*Chromosome region*	*Type of inheritance*	*Gene*	*Function*	*Pathway*	*Pure/ complex*	*Age at onset*	*Clinical features*
SPG3A	14q12–q21	AD	SPG3A/ *Atlastin*	Transmembrane GTPase, Golgi apparatus	Trafficking	Pure	Predominantly early onset	Common cause of dominant hereditary spastic paraplegia
SPG4	2p22–p21	AD	*Spastin*	Microtubule severing protein	Trafficking	Pure and complex	Variable from second to seventh decade	Most common form of autosomal dominant hereditary spastic paraplegia. Some cases with cognitive impairment. Lower motor neuron dysfunction may be found. Occasional bulbar dysfunction and respiratory insufficiency. Mild cerebellar signs may occur
SPG6	15q11.2–q12	AD	*NIPA1*	Transmembrane protein	Unknown	Pure	Predominantly adult onset, as early as second decade	
SPG8	8q24	AD	*KIAA0196*			Pure	Predominantly adult onset	
SPG10	12q13	AD	*KIF5A*	Molecular motor	Trafficking	Pure	Predominantly adult onset	
SPG13	2q24–q34	AD	*HSP60* (heat shock protein 60)	Mitochondrial heat shock protein	Mitochondria	Pure	Predominantly adult onset	
SPG17 (Silver syndrome)	11q13	AD	BSCL2/ *Seipin*	Endoplasmic reticulum transmembrane protein	Unknown	Complex	From childhood to adulthood	Wasting of small muscles in the hands, weakness of shoulder muscles
SPG31	2p12	AD	*REEP1* (receptor expression enhancing protein 1)	Transmembrane protein	Mitochondria	Pure	Variable from second to fifth decade	
SPG5A	8q21.3	AR	*CYP7B1*			Pure	From childhood to adulthood	
SPG7	16q	AR	*Paraplegin*	Mitochondrial metalloproteinase	Mitochondria	Pure and complex	From childhood to adulthood	Cerebellar signs, polyneuropathy, pes cavus, optic atrophy
SPG11 (autosomal recessive hereditary spastic paraplegia with thin corpus callosum)	15q21.1	AR	*Spatacsin*			Pure and complex	First and second decades	Mental retardation or cognitive impairment, polyneuropathy, thin corpus callosum

Continued

Table 1 Continued

Locus	*Chromosome region*	*Type of inheritance*	*Gene*	*Function*	*Pathway*	*Pure/ complex*	*Age at onset*	*Clinical features*
SPG15 (Kjellin syndrome)	14q24.1	AR	ZFYVE26/ *Spastizin*			Complex	Childhood to adulthood	Pigmented maculopathy, distal amyotrophy, pes cavus, dysarthria, cerebellar signs, mental retardation, dementia, saccadic pursuit, thin corpus callosum, axonal peripheral neuropathy, extrapyramidal signs, white matter abnormalities
SPG20 (Troyer syndrome)	13q12.3	AR	*Spartin*	Microtubule and mitochondria associated	Trafficking	Complex	Early childhood	Distal muscle wasting, dysarthria, mental retardation, cerebellar signs, developmental delay and short stature
SPG21 (Mast syndrome)	15q22.31	AR	ACP33/ *Maspardin*	Vesicular transport, Golgi apparatus	Trafficking	Complex	Childhood-early adulthood	Premature aging, developmental delay, dementia, dysarthria, pseudobulbar, cerebellar, and extrapyramidal syndrome, thin corpus callosum, periventricular white matter hyperintensities, cataract, dystonia, polyneuropathy, chorea, distal wasting
ARSACS (autosomal recessive spastic ataxia of Charlevoix Saguenay)	13q11	AR	*Sacsin*	Chaperone-mediated protein folding		Complex	Early childhood	Pyramidal and cerebellar progressive symptoms, distal muscle wasting, peripheral neuropathy, dysarthria, nystagmus, retinal striation
SPG1 (MASA syndrome, CRASH syndrome or L1 syndrome)	Xq28	X-linked	*L1CAM* (L1 cell adhesion molecule)	Neurite outgrowth, myelination	Signaling	Complex	Infancy	Mental retardation, aphasia, shuffling gait, absence of extensor pollicis longus muscle, microcephaly, or macrocephaly with hydrocephaly, exaggerated lumbar lordosis
SPG2	Xq22	X-linked	*PLP1* (myelin proteolipid protein)	Myelination	Myelination	Pure and complex	First and second decades	Mental retardation, optic atrophy, nystagmus, diplopia, dysarthria, hypoestesia, cerebellar signs

AD, autosomal dominant; AR, autosomal recessive; SPG, spastic paraplegia.

Table 2 Hereditary spastic paraplegia caused by unknown genes to date

Locus	*Chromosome region*	*Type of inheritance*	*Pure/ complex*	*Age at onset*	*Clinical features*
SPG9	10q23.3–q24.2	AD	Complex	Infancy to adulthood	Cataract, motor neuropathy, short stature, skeletal abnormalities, gastroesophageal reflux
SPG12	19q13	AD	Pure	Predominantly adult onset	Trend to earlier age of onset in subsequent generations
SPG19	9q33–q34	AD	Pure	Predominantly adult onset	Slow and relatively benign progression, polyneuropathy
SPG29	1p31–p21	AD	Complex	Second decade	Sensorineural hearing impairment, pes cavus, urinary urgency due to detrusor muscle hyperactivity, neonatal hyperbilirubinemia without kernicterus, hiatal hernia. Hyperreflexia may also affect upper limbs
SPG37	8p21.1–q13.3	AD	Pure	Variable, from childhood to seventh decade	Affects both lower and upper limbs, slowly progressive, incomplete penetrance
SPG38	4p16–p15	AD	Complex	Second decade	Pes cavus, amyotrophy of small hand muscles, polyneuropathy
SPG14	3q27–28	AR	Complex	Adult	Distal motor neuropathy, mental retardation, pes cavus, visual agnosia
SPG23 (Lison syndrome)	1q24–32	AR	Complex	Early childhood	Skin and hair pigmentary abnormalities, facial and skeletal dysmorphia, postural tremor, cognitive impairment, premature aging, cerebellar signs, perypheral neuropathy
SPG24	13q.14	AR	Pure	Early childhood	
SPG25	6q23.3–24.1	AR	Complex	Adult	Prolapsed intervertebral disks, multiple disc herniation, bilateral cataract, congenital glaucoma
SPG26	12p11.1–q14	AR	Complex	Adult	Intellectual impairment, distal muscle wasting, dysarthria, polyneuropathy, pes cavus, wasting of small muscles
SPG27	10q22.1–q24.1	AR	Pure and complex	Adult	Polyneuropathy, dysarthria, abnormal somatosensory-evoked potentials
SPG28	14q21.2–22.3	AR	Pure	First and second decades	
SPG30	2q37.3	AR	Complex	Second and third decade	Slow progression, cerebellar signs and atrophy, saccadic eye movements, distal sensory loss
SPG32	14q12–q21	AR	Complex	Childhood	Pontine dysraphia, mental retardation, thin corpus callosum, cortical and cerebellar atrophy
SPG35	16q21–q23.1	AR	Complex	Childhood	Dysarthria, epilepsy, cognitive decline
Thin corpus callosum and epilepsy	8q	AR	Complex	Childhood	Thin corpus callosum, mental impairment, epilepsy
SPOAN (spastic paraplegia, optic atrophy, and neuropathy)	11q13	AR	Complex	Infancy	Optic atrophy, polineuropathy, dysarthria, distal amyotrophy, exacerbated startle response, scoliosis
ARSAL (autosomal recessive spastic ataxia with frequent leucoencephalopathy)	2q33–34	AR	Complex	Variable	Highly variable severity. Ataxia from onset, spasticity, leucodystrophy, scoliosis, dystonia, cognitive impairment, urinary urgency, dysathria, horizontal nystagmus, optic atrophy, cataract, mild hearing impairment
SAX2 (spastic ataxia 2)	17p13	AR	Complex	Variable	Dysarthria at onset, ataxia, spasticity in all limbs, muscle fasciculations, horizontal nystagmus
SPG16	Xq11.2	X-linked	Pure and complex	Infancy	Mental retardation, visual impairment, motor aphasia, nystagmus
SPG34	Xq25	X-linked	Pure	Second and third decade	Slow progression, sensory polyneuropathy late in evolution.

AD, autosomal dominant; AR, autosomal recessive; SPG, spastic paraplegia.

The ongoing identification of several genes responsible for HSP is providing a better understanding of the pathological mechanisms involved, and opens the way to discovery of future therapies targeted at the specific causes of HSP.

Proteins such as atlastin (SPG3A), spastin (SPG4), NIPA1 (SPG6), KIAA0197 (SPG8), KIF5A (SPG10), BSCL2 (SPG18), spartin (SPG20), and ACP33 (SPG21) are involved in neuronal trafficking. Mutated spastin protein leads to microtubule disassembly and accumulation of organelles and cytoskeletal components, producing axonal swelling and cell death.

Paraplegin (SPG7), HSP60 (SPG13), spartin (SPG20), and REEP1 (SPG31) mutated proteins impair the mitochondrial metabolism. Paraplegin protein is a metalloprotease localized in the inner mitochondrial membrane, which acts as a molecular chaperone. Mutated paraplegin protein increases the sensitivity to oxidative stress by decreasing complex I activity in the mitochondria. HSP60 is another mitochondrial chaperone that prevents protein misfolding, especially in an oxidative environment. REEP1 is a mitochondrial transmembrane protein involved in protein folding. Spartin protein may be involved in endocytosis, vesicle trafficking, mitogenic activity, and protein binding. Loss-of-function *spastin* mutations cause mitochondrial dysfunction.

One similarity is shared by some HSP clinical forms linked to different genes. *KIF5A*, *spastin*, *spartin*, and *atlastin* all impair the intracellular membrane trafficking.

The function of spatacsin protein remains unknown, but its highly conserved leucine-zipper motif and Myb domain suggest it may have a role in regulating the DNA replication and transcription.

Epidemiology and Risk Factors

Studies on prevalence have yielded different figures, depending on the clinical criteria used to distinguish between pure and complex forms.

The prevalence of HSP varies across the world (0.004–0.01%). When clinical criteria are followed, the prevalence of HSP is 2–10 out of 100 000. Even when similar patient selection methods are used, there is variability among different populations: figures such as 18.4 in Guam, 2.0 in Zealand (Denmark), 2.1 in Benhazi (Libya), 9.6 in Cantabria (Spain), 2.7 in Molise (Italy), 4.3 in Valle d'Aosta (Italy), 2.0 in Viano do Castelano (Portugal), or 1.27 in Ireland have been described. These differences are probably due to the geographical origin of the HSP related genes.

HSP clinical subtypes have a different prevalence according to geographical distribution and depending on the model of inheritance considered. There are 10 000 cases of HSP in the United States and 10% of them are complex forms. The most common genetic form of HSP among the Europeans is the autosomal dominant form. The frequency of HSP in Europe is estimated at 1–9 out of 100 000. Pure ADHSP is the most frequent form in Europe, and complex ARHSP is more prevalent in Southern Europe that in Northern Europe.

Autosomal Dominant Forms

About 70% of HSP cases have an autosomal dominant inheritance. *Spastin* gene mutations (SPG4) are the most frequent cause of ADHSP accounting for 50% of HSP. More than 130 *spastin* gene mutations have been described. Nonsense, splicing, or frameshift mutations truncate spastin protein. Missense mutations are less common (29%). *Atlastin* gene is the second most frequent cause of ADHSP, explaining ~10% of pure HSP. *Atlastin* testing should precede *spastin* analysis in HSP when ADHSP starts before the age of 10 (**Table 1**).

Several other genes have been found to be involved in ADHSP such as *NIPA1* (SPG6), *KIAA0196* (SPG8), *KIF5A* (SPG10), *HSP60* (SPG13), *seipin* (SPH17), and *REEP1* (SPG31) (**Table 1**). Several other chromosomal loci (SPG9, SPG12, SPG19, SPG29, SPG37, and SPG38) have been identified, although the genes responsible still remain unknown (**Table 2**).

Autosomal Recessive Forms

About 30% of HSP show an autosomal recessive inheritance. Some cases may have an apparently sporadic presentation of disease and consanguinity is often associated with ARHSP. In a Portuguese and Algerian family study, 53% of the families had pure ARHSP, whereas 47% had complex ARHSP. The most frequent gene was *spatacsin* gene (SPG11), in which homozygous or compound nonsense, frameshift, and heterozygous exonic rearrangements can cause a loss of spatacsin function. SPG11 produces a rapidly progressive HSP with onset in the first or second decades. SPG21 and SPG32 are also associated with thin corpus callosum and mental retardation.

Homozygous mutations of *CYP7B1* (SPG5A), *paraplegin* (SPG7), *ZFTVE26* (SPG15), and *spartin* (SPG20) genes have been associated with ARHSP (**Table 1**). Other loci, such as SPG14, SPG23, SPG24, SPG25, SPG26, SPG27, SPG28, SPG30, SPG32, and SPG35 have been linked to ARHSP, but the gene responsible has not yet been found (**Table 2**).

X-linked Forms

The X-linked inherited HSP forms are rare. Mutations in *L1CAM* gene (SPG1) and *PLP1* (SPG2) are involved in HSP disorders. The SPG16 and SPG34 loci have both been associated with a few isolated families, but the gene is still unknown (**Table 2**).

In SPG1, the spastic paraplegia is always complicated by other features (**Table 1**). About 200 mutations in the *L1CAM* gene that causes L1 syndrome have been described. These mutations change the L1 protein structure which plays an important role in the nervous system development such as neuronal migration, differentiation, and formation of myelin and synapses.

More than ten mutations in the *PLP1* gene have been identified. The deletion of the entire *PLP1* gene causes a more severe clinical phenotype. SPG16 can also be associated with complex and pure HSP forms. SPG34 has been associated with pure spastic paraplegia affecting only the lower limbs in a large Brazilian family spanning five generations.

Clinical Features and Diagnostic Criteria

HSP is characterized by clinical manifestations derived from the degeneration of corticospinal axons. Corticospinal track degeneration starts distally and advances in retrograde direction, so that fibers of the lower limbs are most severely affected. Muscle weakness is most noticeable at the iliopsoas and tibialis anterioris muscles. Hip weakness causes the pelvis to tilt down on the contralateral leg during the stance phase of gait (Trendelenburg sign). Weakness and spasticity hamper foot dorsiflexion and hip flexion, frequently causing lumbar hyperlordosis while walking. There may be stumbling, tripping, and gait circumduction. Progressive weakness and spasticity are predominantly found in the lower limbs wherein brisk tendon reflexes and extensor plantar responses are found. Pes cavus is often present. Muscle contractures may develop over time.

Sensory manifestations, such as paresthesias and decreased perception in the lower limbs, are often present, and urinary sphincter disturbances may occur in pure HSP. Individuals sometimes complain of fluctuating stiffness and temperature in the lower limbs. As in other spinal diseases, stress or tiredness may exacerbate the symptoms. HSP is clinically divided into pure and complex forms.

Pure HSP

Pure HSP forms only have motor symptoms arising from corticospinal track dysfunction. The age of onset varies from infancy to old age, though most patients start in second through fourth decades of life. Diagnostic criteria for the pure type and a clinical severity scale have been suggested (**Tables 3** and **4**).

Complex HSP

Complex HSP forms have additional neurological and extraneurological findings. Corticospinal symptoms are combined with different signs, such as mental retardation, cognitive decline, deafness, amyotrophy, cerebellar ataxia, epilepsy, dysarthria, ichthyosis, optic atrophy, peripheral neuropathy, pigmentary retinal degeneration, and cataracts.

Table 3 Diagnostic criteria of hereditary spastic paraplegia

A subject is definitely affected if all of the following occurs:
1. Alternative disorders have been excluded
2. Family history supports inheritance of an X-linked, autosomal recessive, or autosomal dominant disorder
3. Patient reports progressive gait disturbance
4. Neurologic examination shows frank corticospinal tract deficits in the lower limbs, including grade 4 hyperreflexia and extensor plantar responses
A subject is probably affected if all of the following occurs:
1. The subject is asymptomatic
2. There is lower-extremity hyperreflexia associated with extensor plantar responses
3. It is not possible to know whether these findings have been present from birth (raising the suspicion of an alternative diagnosis, such as spastic cerebral palsy)
A subject is possibly affected if:
1. The subject is asymptomatic
2. The subject belongs to a HSP kindred
3. Neurologic examination is questionably abnormal, showing possible corticospinal tract deficits (mildly hyperactive deep tendon reflexes and 3–4 beats of ankle clonus), but plantar responses are flexor

HSP, Hereditary Spastic Paraplegia. See Fink et al. (1996) *Neurology* 46:1507–1514.

Table 4 Classification of severity of hereditary spastic paraplegia

Grade 1	Spastic gait without functional limitation
Grade 2	Abnormal gait with functional limitations but not requiring consistent use of an assisting device
Grade 3	Gait abnormality requiring a consistent use of a cane, crutches, or a walker, or occasional use of a wheelchair only for long distances (up to 10% of the time) but still with an ability to walk short distances using assistive devices
Grade 4	Gait abnormality requiring frequent use of a wheelchair (up to 50% of the time) but still with an ability to walk short distances using assistive devices
Grade 5	Marked functional impairment with an inability to walk with crutches, requiring a wheelchair more than 50% of the time

See Hedera et al. 1999 *Neurology* 53:44–50.

Differential Diagnosis

Diagnosis of HSP is clear when there is family history of progressive spastic paraparesis, though sometimes differential diagnosis with other hereditary neurological diseases can prove difficult.

However, spastic paraparesis can also be caused by noninherited neurological conditions. Incomplete penetrance, de novo mutations, autosomal recessive, or X-linked inheritance can cause the disease in the absence of a family history of HSP.

Magnetic resonance imaging (MRI) of the brain and spinal cord, serum vitamin levels, and viral antibody levels are recommended before establishing a diagnosis in cases where the diagnosis of HSP is very unlikely or screening of appropriate genes is negative. Neurophysiologic studies can be helpful in distinguishing pure and complex HSP forms.

Familial Disorders with Spasticity other than HSP

Other neurological entities can be confused with HSP. Spinocerebellar ataxias can show spasticity, as is the case with Machado–Joseph's disease, but in this case ataxia is pronounced. Adrenoleukodystrophy and adrenomyeloneuropathy show white matter abnormalities in brain MRI and high plasma long-chain fatty acid levels. Krabbe's disease is an autosomal recessive condition due to galactocerebrosidase deficiency; it can also be diagnosed by MRI, slow nerve conduction velocities, and delay in visual and auditory evoked potentials.

Hereditary progressive dystonia with diurnal variation, also known as dopamine-responsive dystonia (Segawa's disease), is caused by mutations either in the *GTP cyclohydrolase I* or *tyrosine hydroxylase* genes. Segawa's dystonia improves with L-dopa treatment. Therefore, a trial of low dose L-dopa is advised in children with progressive gait disturbance.

Sporadic Spastic Paraparesis

Multiple sclerosis (MS) can mimic spastic paraplegia. MS individuals show demyelinating white matter lesions in brain MRI, oligoclonal bands in the cerebrospinal fluid (CSF), and impairment of evoked potentials. Amyotrophic lateral sclerosis (ALS) predominantly impairs the motor function of the upper limbs and bulbar muscles, and shows fasciculations, amyotrophy, and muscle denervation. Interestingly, *spastin* mutations have been reported to cause a clinical picture resembling juvenile-onset ALS. Spastic diplegic cerebral palsy secondary to complicated birth delivery can be confused with HSP.

Structural spinal cord or brain abnormalities, such as Arnold-Chiari or other cervical spinal cord conditions, can be diagnosed by cranial or spine MRI.

Subacute combined degeneration, due to vitamin B12 deficiency, causes peripheral neuropathy and dorsal column involvement. Vitamin E deficiency can cause distal muscle weakness and sensory deficits, visual-field constriction, nystagmus, ophtalmoplegia, arrhythmia, and dementia.

Differential diagnosis with infectious diseases, such as tertiary syphilis, tropical spastic paraparesis, and HIV myelopathy, can be performed by serologic tests.

Diagnostic Work-up and Tests

In patients with spastic paraparesis, cerebral and spinal MRI are useful to differentiate HSP from other diseases.

The diagnostic work-up in HSP includes neuroimaging, blood and electrophysiological tests, including reflex studies to detect abnormal responses of the lower limbs, electrophysiological studies such as electromyography, nerve conduction tests, or electroencephalography. CSF analysis could be performed in some cases. A genetic evaluation is recommended when family history of a similar condition is present.

Spinal MRI can show atrophy of the spinal cord, and in some complex HSP cases such as SPG11, SPG21, and SPG32 and autosomal recessive spastic ataxia with leukoencephalopathy (ARSAL) syndrome, brain MRI can show cortex atrophy and a thin corpus callosum.

SPG11 is characterized by mild frontal and temporal cortical atrophy, mild ventricular dilatation, widening in the frontal fissure, thin corpus callosum, decreased number of methylation fibers, axonal degeneration, abnormal Schwann cell inclusions, thalamic and cortical glucose hypometabolism on positron PET scan, and supratentorial symmetric white matter lesions.

Some forms of spastic paraparesis have abnormal nerve conduction as in autosomal recessive spastic ataxia of Charlevoix Saguenay (ARSACS), which shows reduced motor conduction velocities, a decrease in amplitude of sensory potentials, and vermian cerebellar atrophy. Spastic paraplegia, optic atrophy and neuropathy (SPOAN) syndrome is associated with axonal neuropathy.

ARSAL syndrome has abnormal brain MRI findings, such as cerebellar atrophy and sometimes brain atrophy, corpus callosum atrophy, and leukodystrophy.

Neurophysiological studies of HSP are consistent with the degeneration of long motor pathways.

Transcranial magnetic stimulation (TMS) responses are abnormal in HSP. TMS responses can vary from decrease or delay of potentials to their complete absence in the lower limbs. Less often, TMS responses are impaired in the upper limbs. TMS also can show a shorter cortical silent period. Similarly, somatosensory evoked potentials are frequently abnormal in the lower limbs.

Management

Unfortunately, there is no treatment that can modify the natural course of HSP. Symptomatic and supportive medical treatment should be offered. Muscle relaxants such as

the γ-aminobutyric acid receptor agonist Baclofen and Dantrolene, available in some countries, could lessen spasticity. Baclofen can be administered orally and intrathecally. Benzodiazepines and Tizanidine, a centrally acting α-2 adrenergic agonist, can be used to treat muscle spasms. Programmed bladder evacuation can help in urinary symptoms. Intramuscular botulinum toxin can alleviate spasticity. Orthopedic surgery to lengthen ankle plantar flexors and hip adductors may help some patients. Physical activity should be encouraged, including aerobic and strengthening-stretching exercises to reduce atrophy and maintain muscle strength as well as a range of joint motion. As the disease progresses, assistive devices such as canes, crutches, or walkers may be necessary.

Prognosis

Prognosis of HSP is highly variable. In pure HSP forms, age of onset is not a good predictor of disability and the rate of progression varies depending on the gene involved.

Life expectancy can be normal in some pure HSP, though there is an increased morbidity due to an increased risk of falls and urinary infections.

Though adult onset is most common, SPG4 HSP can have a wide range of ages of onset (2–70 years) suggesting incomplete penetrance. Some SPG4 mutation carriers are asymptomatic, whereas others are severely disabled. SPG4 produces moderate disability proportional to time since onset, but some cases of SPG4 develop bulbar weakness and respiratory insufficiency.

SPG3A HSP usually has an onset in early childhood, although some cases begin in adult life. These patients may very early become clinically stable. Though this type has almost full penetrance, intrafamilial variability of the severity of HSP associated with the same mutation is frequent.

Some of the complex HSP forms such as SPG1, SPG2, SPG11, SPG21, SPG23, SPG26, and SPG32 have a more disabling disease course due to the presence of cognitive impairment.

See also: Amyotrophic Lateral Sclerosis/Parkinsonism-Dementia Complex of Three Pacific Isolates; Ataxia; Ataxia with Isolated Vitamin E Deficiency; Botulinum Toxin; Dysarthria; DYT5; Electroencephalography (EEG); Electromyography (EMG); Epilepsia Partialis Continua; HIV Infection and Movement Disorders; MMSE - Mini-Mental State Examination; SCA3, Machado–Joseph Disease.

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SPECT Imaging in Movement Disorders

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Glossary

Brain perfusion – Perfusion is defined as the passage of fluid through the lymphatic system or blood vessels to an organ or a tissue. Perfusion scanning is the process by which this perfusion can be observed, recorded, and quantified. The term perfusion scanning encompasses a wide range of medical perfusion modalities. In the case of brain perfusion, cerebral blood flow is coupled to local brain metabolism and energy use. The tracers ECD (99mTc-ethylcysteinate dimer and HMPAO (99mTc-hexamethyl propyleneamine oxime) are commonly used to assess brain metabolism regionally.

Dopamine Transporter (DAT) – A membrane protein that binds dopamine. DAT provides the primary mechanism through which dopamine is cleared from synapses, transporting dopamine from the synapse into the dopamine nerve terminal. DAT is present in the peri-synaptic area of dopaminergic neurons in areas of the brain where dopamine signaling is common. Because DAT terminates the dopamine signal, it is implicated in a number of dopamine-related disorders, in addition to Parkinson's disease including attention deficit hyperactivity disorder or bipolar disorder. The gene that encodes the DAT protein is located on human chromosome 5.

SPECT – Single photon emission computed tomography is a nuclear medicine tomographic imaging technique using γ-rays. It is similar to the conventional nuclear medicine planar imaging using a gamma camera. However, it is able to provide 3D information. This information is typically presented as cross-sectional slices through the patient but can be freely reformatted or reconstructed as required.

Its application to the study of movement disorders regards the investigation of the dopamine system as well as brain perfusion.

FP-CIT or (^{123}I)-Ioflupane ([I-123] *N*-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane).

A cocaine derivate used as neuroimaging radiopharmaceutical for the differentiation of Parkinson's disease from essential tremor. It is injected into a patient and viewed with a SPECT gamma camera. It binds to dopamine nerve terminals in the striatum. Ioflupane is distributed under the tradename DaTSCAN and is manufactured by GE Healthcare. It is not marketed outside of Europe.

SPECT Utilization for Movement Disorder Diagnosis

Diagnosis of Parkinson Disease: Motor Symptoms

The clinical diagnosis of Parkinson's disease (PD) is based on the presence of characteristic motor symptoms: bradykinesia, rigidity, postural instability, and resting tremor but neuropathology is still considered the gold standard for definite diagnosis. Differentiating PD from other movement disorders (e.g., essential tremor and atypical parkinsonism) can be challenging throughout the disease course, because signs and symptoms often overlap. Indeed, neuropathology studies reveal that clinical diagnosis of PD can be confirmed with an accuracy of about 75%. Good response to levodopa is often used to support the diagnosis of PD. However, cases of pathologically proven PD with poor response to levodopa have also been reported.

Misdiagnosis of PD can occur for several reasons. In a community-based study of patients taking antiparkinsonian medication, the most common misdiagnosis were essential tremor, Alzheimer's disease, and vascular parkinsonism. In addition, many of the prominent features of PD (e.g., rigidity, gait disturbance, bradykinesia) may also occur as a result of normal aging or from comorbid and multifactorial medical conditions (e.g., diabetes, cancer).

Diagnosis of Parkinson Disease: Premotor Stage

A number of nonmotor symptoms, not explained by dopamine deficiency alone, can precede the classical features of PD. Premotor symptoms in PD include constipation, loss of smell, sleep disturbances such as REM sleep behavior disorder, and mood disturbances such as depression. Many of these symptoms find a possible explanation in the theory introduced by Braak and colleagues, suggesting a caudal–rostral progression of Lewy body pathology in PD, from brainstem to the cortex. According to this theory, at least two stages precede the onset of motor signs and involve the serotonin and norepineprhine systems. Briefly, at stage 1, there is a degeneration of the olfactory bulb and

nucleus, which can clinically manifest as olfactory dysfunction. Stage 2 shows a progression to the lower brainstem with lesions in the lower raphe nuclei, magnocellular portions of the reticular formation, and locus coeruleus, areas that could mediate symptoms such as olfaction, sleep homoeostasis, and other autonomic symptoms. The pedunculopontine tegmental nucleus and dopaminergic neurons of the substantia nigra (relay centers of the visceromotor system and nuclei of the somatomotor system) are damaged at stage 3. In stage 4, the disease extends to anterior and posterior thalamic intralaminar nuclei that project to the striatum and cerebral cortex and in stages 5–6 neocortical association areas and the premotor areas are damaged.

SPECT Imaging as a Biomarker for Early Parkinson's Disease

A biomarker (biological marker) is an indicator of normal biological processes, pathogenetic processes, or pharmacological responses to a therapeutic intervention. In the past decade, the search for treatments of PD that protect against disease progression (neuroprotectors) has intensified, raising the issue of the need for biomarkers of both disease and severity of disease in PD.

Single photon emission tomography (SPECT) with radioligands binding selectively to striatal dopamine nerve terminals provides an objective and reproducible measurement of the nigrostriatal dopaminergic system in early PD patients with additional high sensitivity to disease progression. Uncertainty about an interaction between therapeutical drugs and tracer binding, however, has raised debate on whether imaging is a valid biomarker for progression of nigrostriatal pathology in PD. These unresolved issues are the focus of current research efforts.

SPECT with Receptor-Binding Tracers

Dopaminergic System: Presynaptic Issues

Target and tracers

Available presynaptic ligands for SPECT bind selectively the dopamine transporter (DAT). The DAT is a 620-amino acid protein with 12 α-helical hydrophobic transmembrane domains, two to four extracellular glycosylation sites, and up to five intracellular phosporylation sites. Ex vivo studies have shown the expression of DAT in the dopaminergic neurons of the substantia nigra and in the ventral tegemental dopaminergic neurons. DAT controls dopaminergic neurotransmission by spatial and temporal buffering, making the molecule an imaging target for diseases affecting the dopaminergic nigrostriatal pathway. DAT levels correlate with striatal dopamine concentration.

Introduction of radioactive iodine (^{123}I) into the tracer molecules provides a suitable method for DAT-SPECT imaging. A large number of ^{123}I-labeled compounds have been prepared, and DAT receptor-specific imaging agents are routinely used for SPECT imaging studies. All of the successful agents for imaging DAT belong to a group of tropane derivatives that share a similar backbone structure of cocaine. The first successful DAT imaging agent for SPECT, [^{123}I]β-CIT, was reported in the early 1990s, and studies suggested a strong correlation between the decrease in localization in the putamen area and PD symptoms. Currently, [^{123}I]β-CIT, [^{123}I]FP-CIT, [^{123}I]IPT, and [^{123}I] altropane are being developed for this purpose.

The two most widely used ligands to study PD patients are [^{123}I]β-CIT and [^{123}I]FP-CIT. A direct comparison of the two compounds has been attempted in only a few studies; briefly: (1) the nonspecific uptake of [^{123}I]FP-CIT is greater than [^{123}I]β-CIT, causing [^{123}I]β-CIT to have a lower ratio of specific to non-displaceable striatal uptake (V''_3); (2) [^{123}I]β-CIT shows a lower selectivity for DAT, having an equivalent affinity for the serotonin transporter (SERT), which results in a higher thalamic/midbrain [^{123}I]β-CIT uptake; (3) washout period of [^{123}I]β-CIT is about 1% per hour and of [^{123}I]FP-CIT is 5–8% per hour, making striatal V''_3 values of [^{123}I]FP-CIT stable as early as 3–6 h, whereas [^{123}I]β-CIT stabilizes only after 18–27 h. In Europe [^{123}I]FP-CIT (DatScan, Amersham PLC, Buckinghampshire, UK) is commercially available for routine clinical use.

One of the major drawbacks of using ^{123}I-labeled compounds for routine imaging is the availability of the isotope. Produced by cyclotrons or by accelerators, it is not readily available in standard nuclear medicine clinics and requires overnight shipment from production sites. As a consequence, it is relatively expensive and inaccessible. As an alternative, ^{99m}Tc-labeled tropane derivatives have been investigated. Only [^{99m}Tc] TRODAT-1 has been tested successfully in normal subjects and parkinsonian patients. This compound has some logistical advantages over the most commonly used SPECT ^{123}I-ligands, including absence of thyroid uptake, ready availability, ease of use, and lower cost.

Clinical application

Diagnosis of PD

The effectiveness to demonstrate changes in presynaptic DAT sites in vivo in PD patients has been demonstrated by using [^{123}I]β-CIT, [^{123}I]FP-CIT, [^{123}I]IPT, [^{123}I]altropane, and [^{99m}Tc]TRODAT-1.

At the point when cardinal motor signs required for a clinical diagnosis of PD appear, as many as 58–64% of dopaminergic neurons in the substantia nigra (SN) have been lost, and striatal dopamine content has been reduced by 60–80%. Imaging studies of the dopaminergic system and postmortem cell counts of pigmented neurons in the SN suggest that the onset of dopaminergic neuronal loss

precedes the clinical diagnosis of PD by approximately 4–6 years. Abnormalities have been shown in individuals at risk for the disease years before disease onset.

In some large clinical drug trials of PD where patients were enrolled based on their clinical diagnosis of early 'untreated' PD, a significant proportion of patients has normal scans. These individuals have been defined 'subjects with scans without evidence of dopaminergic deficit' (SWEDD) and represented from 5.7% to 14.7% of cases clinically diagnosed as early PD. Uptake values measured by fluorodopa PET (REAL-PET study) and by [^{123}I]β-CIT (ELLEDOPA study) remained normal after 2- and 4-year follow up respectively, thus questioning the diagnosis of a progressive and neurodegenerative disorder as PD in these subjects. Alternative explanations on false-negative PD at DAT SPECT are the theoretical possibility of scans in the normal range at a very early stages of the disease and greater specificity of quantitative versus qualitative analysis of the SPECT scans.

Differential diagnosis

Essential tremor

Although distribution, frequency, severity, age of onset, and evolution of symptoms should ensure a correct separation of PD from essential tremor (ET) overlapping features may make differential diagnosis a challenge. Both [^{123}I]β-CIT and [^{123}I]FP-CIT showed no evidence of PD-like dopaminergic disruption in ET, and [^{123}I]FP-CIT/SPECT proved a specificity of 95% and sensitivity of 80% in discriminating ET from PD patients (**Figure 1**). Comparable results have been recently shown with SPECT and [^{99m}Tc]TRODAT-1. Recent evidence suggests that DAT imaging is cost effective for separating PD and ET.

Atypical parkinsonism

Presynaptic tracers have low accuracy in differentiating PD from atypical neurodegenerative parkinsonism (APS) (e.g., multiple system atrophy (MSA) and progressive supranuclear palsy (PSP)). However, marked asymmetry in reductions of putaminal DAT finding is more typical for PD when compared to APS. A recent study found reduced midbrain [^{123}I]β-CIT uptake in patients with the Parkinson variant of multiple system atrophy (MSA-P), and the authors were able to correctly classify 95% of MSA-P and PD patients.

Vascular parkinsonism

Presynaptic dopaminergic circuitry is generally preserved in vascular parkinsonism (VP) although a slight reduction in lateral substantia nigra may occur probably due to transneuronal degeneration. Because VP is a somewhat controversial clinical concept and there are no clear cutoff values to separate VP from PD according to striatal DAT availability, conventional techniques such as CT and MRI are still considered necessary diagnostic tools.

Drug-induced parkinsonism

Drug-induced parkinsonism (DIP) is a frequent cause of secondary parkinsonism, developing in patients during treatment with antipysychotic or dopamine receptor blocking agents. The same syndrome can develop after treatment with agents that deplete dopamine. About 60–70% of patients recover after medication withdrawal in 2 months. In the remaining cases, motor symptoms persist or sometimes worsen in the following months suggesting that DIP unmasked an already low dopaminergic state that was preclinical before drug exposure and that the patients had very early PD. DIP is clinically not easily distinguishable from PD because similar clinical signs may occur in both diseases

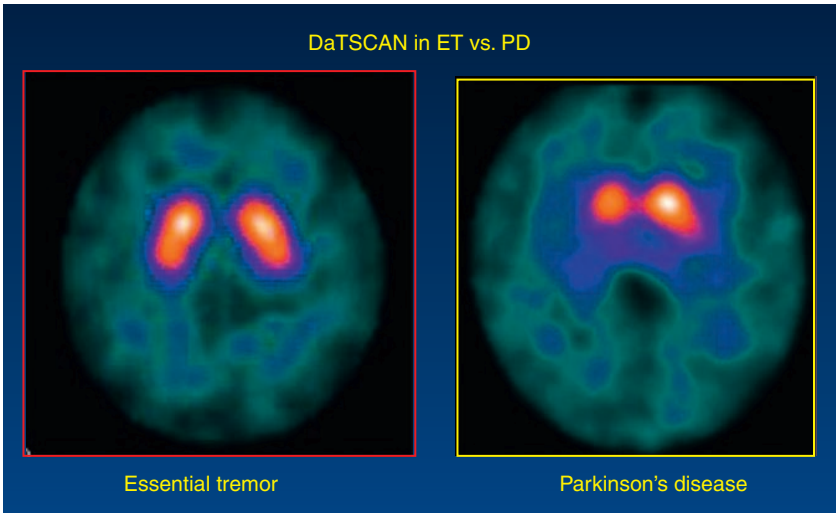

Figure 1 DAT binding in patients with essential tremor (left: normal tracer distribution in the head of the caudate nucleus and the putamen) and Parkinson's disease (right: reduced uptake mainly in the right putamen).

making the differential diagnosis a challenge Few SPECT studies are available on DIP and all with [^{123}I]FP-CIT/SPECT. Significant putaminal [^{123}I]FP-CIT/SPECT binding abnormalities may be found in some DIP patients, consistent with loss of dopamine nerve terminals.

Assessment of disease progression

Disease progression in PD was originally evaluated with [^{123}I]β-CIT/SPECT. The mean reduction of [^{123}I]β-CIT binding in PD patients versus healthy controls was reported of 5.8% for a period of 15 months and, when calculated for 1 year, 5.6%. Further studies with [^{123}I]β-CIT showed similar results with an annual rate of progression ranging between 5% and 8%, although one report documented a higher rate of 11.2% per year. One study with a 2 years follow up reported striatal [^{123}I]IPT binding decreases of 6.6% in the first year and 5.3% in the second year. Similarly, [^{123}I]FP-CIT/SPECT showed a mean annual decrease in striatal binding ratios of about 8% (of the baseline mean) (**Figure 2**).

Dopaminergic System: Postsynaptic Issues

Target and Tracers

Dopamine receptors (D_1–D_5) are a class of metabotropic G protein-coupled receptors. D_2 receptors are the major target for in vivo imaging studies. Among the radiotracers proposed for D_2 quantification, the benzamide derivative [^{123}I]IBZM gained wide acceptance for SPECT imaging. Although [^{123}I]IBZM has a high nonspecific brain uptake, it offers the advantage of a fast kinetic profile and a great susceptibility to synaptic dopamine release. It is also approved and commercially available for clinical use in some countries. The best analogue of [^{123}I]IBZM is [^{123}I]IBF. [^{123}I]IBF affinity for D_2 and basal ganghia-to-frontal cortex ratio are higher than [^{123}I]IBZM.

Clinical applications

There is little clinical value of postsynaptic studies with SPECT to confirm the clinical diagnosis of PD or to measure progression over time. The main (and only) clinical application for postsynaptic SPECT imaging is the differential diagnosis of PD from APS. At an early stage of PD, postsynaptic receptors are normal or upregulated in the putamen, but decreased in APS (**Figure 3**). At a later stage of PD, with increasing disease severity, binding values are in the range of control subjects or lower, possibly due to the decline in the presynaptic dopaminergic drive, [^{123}I]IBZM SPECT cannot discriminate among different APS. Similarly [^{123}I]IBF does not provide accurate discrimination between PD and APS.

Serotonergic System

Among the many premotor symptoms in PD patients, depression is the most common and disablin. It is generally accepted that alterations in serotonergic neuronal function occur in patients with major depression, and SPECT imaging of the serotonin transporter (SERT) may play an important role to study depression in PD patients at an early stage of the disease.

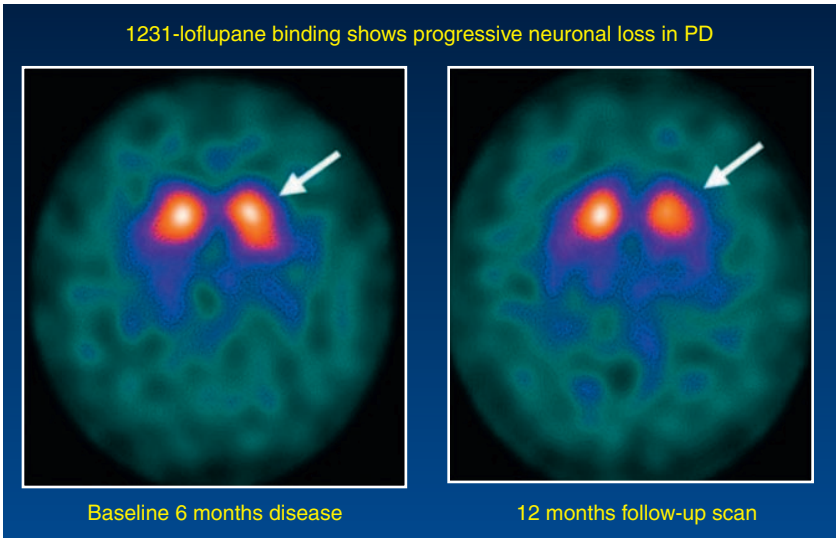

Figure 2 Progressive loss of dopamine nerve terminals in the putamen in a patient with Parkinson's disease. The loss (see arrow becomes evident at the 12-month follow-up scan in the left putamen).

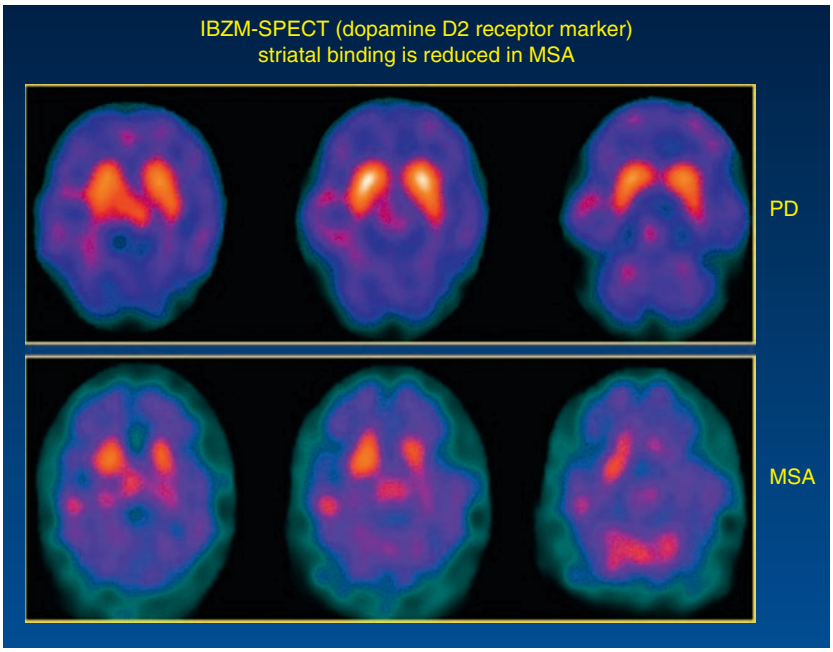

Figure 3 IBZM Binding to striatal dopamine D2 receptors is normal in Parkinson's disease (upper row) but reduced in multiple system atrophy (lower row).

The SERT is an integral membrane protein that transports the neurotransmitter serotonin (5-HT) from synaptic spaces into presynaptic neurons in a sodium-dependent manner. The first successful ligand to target the SERT was [^{11}C]R(+)McN5652 for PET imaging. It showed excellent inhibition of 5-HT reuptake, good correlation with known densities of SERT sites in the human brain and moderate selectivity toward other monoamine transporters (DAT and norepinephrine transporters, NET). The main disadvantage of this ligand is the presence of active metabolites, which appear to penetrate the brain, enhancing background activity and limiting quantitative measurement.

Several iodinated compounds have been evaluated in the search for a SPECT ligand for SERT. Previously, investigators suggested that [^{123}I]β-CIT binds to both DAT and SERT, thus allowing a tool to detect pathological changes in both dopaminergic and serotonergic systems. However, further studies documented overlapping uptake regions and differential kinetics of [^{123}I]β-CIT binding to DAT and SERT. Recently, [^{123}I]β-CIT/SPECT imaging showed a significant reduction (30%) of SERT binding in the midbrain area in depressed PD subjects compared with the controls. More selective compounds, such as nor-β-CIT (*N*-demethylated analog of β-CIT), improved SPECT imaging for SERT, but binding to both DAT and SERT still occurred with insufficient selectivity to distinguish between the two monoamine transporter sites in vivo.

Finally, investigators have been working with a series of derivatives based on the substituted phenylthiophenyl core structure. Among them [^{123}I]IDAM and [^{123}I]ADAM are the most promising candidates. Preliminary SPECT imaging with [^{123}I]IDAM demonstrated an excellent localization of regions in the midbrain area known to have a high concentration of SERT binding sites and excellent affinity to SERT sites over the norepinephrine transported (NET) and DAT. A small modification of the substitution group on the benzene rings of [^{123}I] IDAM produced significant improvements on the imaging properties, producing a new ligand, [^{123}I]ADAM. Currently, [^{123}I]ADAM has been tested only on healthy volunteers.

Noradrenergic System

Many nonmotor symptoms of early PD may be related to a dysfunction of the norepinephrine system, and the possibility of in vivo imaging the norepinephrine (NE) transporter (NET) would be of great value in the early diagnosis of PD. The NET is a protein with 12 transmembrane-spanning domains, located at the presynaptic terminal of noradrenergic neurons. The principal physiological function of NET is to remove NE from the synaptic cleft into the presynaptic neuron. There is no successful NET imaging agent for SPECT currently available for human study. The only tracer available for SPECT, [^{123}I]INER, has been tested in nonhuman primates. The in vivo specificity, selectivity, and kinetics of [^{123}I]INER make it a promising agent for imaging NET in vivo by SPECT imaging.

SPECT and Brain Perfusion

Presynaptic and postsynaptic imaging may not fully describe the complexities of neural systems involved in a neurodegenerative process and their modulation with treatment. On the contrary, cerebral blood flow (CBF) can be used to quantify the effect of nigrostriatal degeneration on brain regions functionally related to the dopaminergic system. Regional cerebral perfusion is determined by both the density of synapses in a certain brain area and the state of activity of these synapses. In general terms, decreases of CBF indicate reductions in neuronal activity because of local cell loss or deafferentation of these regions by lesions in remote brain areas.

Targets and Tracers

There are three compounds available to investigate CBF with SPECT: [^{99m}Tc]ECD, [^{123}I]IMP, and [^{99m}Tc]HMPAO. [^{99m}Tc]ECD has high initial cerebral extraction and very slow clearance from the brain. Brain uptake is rapid, and peak brain activity compares favorably with that of other brain perfusion agents, reaching 6% of the injected dose by 5 min after intravenous injection. Blood clearance is also rapid, resulting in high brain-to-soft-tissue activity ratios early after injection.

[^{123}I]IMP is highly lipophilic, and moves across the blood–brain barrier with almost complete extraction during a single passage through the cerebral circulation. It distributes proportionally to CBF under normal physiologic conditions and over a wide range of flow. Brain uptake of [^{123}I]IMP is rapid, reaching 6–9% of the injected dose by 30 min. The clearance of the tracer from the brain is relatively slow. Thus, brain activity remains constant from 20 min to at least 60 min after injection. Uptake of unbound ^{123}I by the thyroid gland should be blocked by Lugol's solution given orally before injection.

[^{99m}Tc]HMPAO is a lipid soluble macrocyclic amine. Brain uptake of the radiotracer is rapid and reaches its maximum within 10 min post-injection time. The distribution of the radiotracer remains constant for many hours post-injection. Once it crosses the blood–brain barrier it is converted into a hydrophilic compound in the presence of intracellular glutathione and is trapped, with slow blood clearance. Limitations of this compound are perfusion defects and chemical instability in vitro by 30 min after preparation.

Both [^{99m}Tc]HMPAO and [^{99m}Tc]ECD exhibit less brain extraction than [^{123}I]IMP, but its more favorable dosimetry permits a substantially higher dose (20–30 mCi) and a higher photon flux.

Clinical Application

[^{99m}Tc]ECD/SPECT can discriminate PD patients from healthy age-matched controls; it is also of great value in the diagnosis of MSA-P (MSA parkinsonian variant) where scans show a significant perfusion decrement in the striatum, mainly in the posterodorsal putamen. However, due to the high overlap between PD and MSA patterns, [^{99m}Tc]ECD/SPECT cannot be used without other tests, and additional morphologic information (e.g., 1.5 T MRI), are often needed to discriminate between PD and MSA (**Figure 4**). [^{99m}Tc]ECD/SPECT may have some

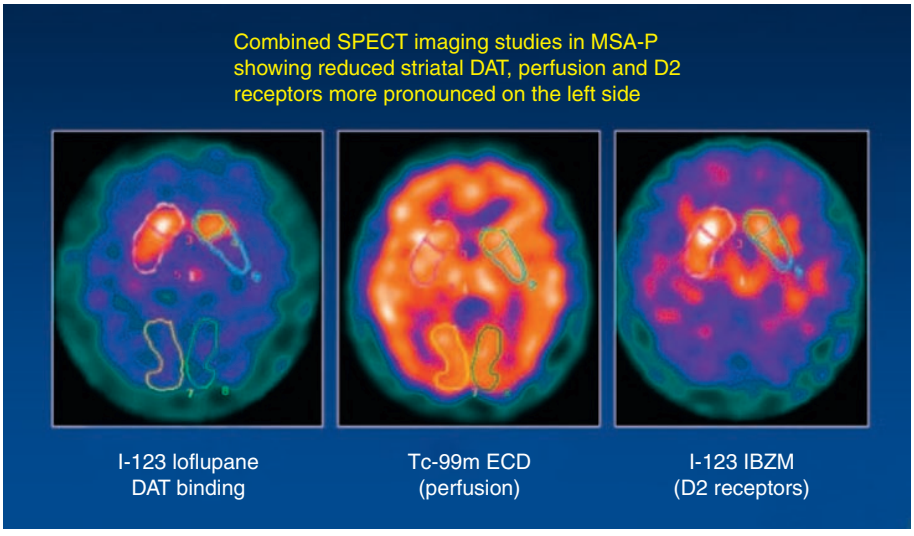

Figure 4 This figure shows loss of DAT (image on the left), reduced perfusion (middle image) and decreased striatal dopamine D2 receptors (image on the right) in the left putamen of a patient with multiple system atrophy.

clinical value in detecting patterns distinctive to early-stage dementia in PD patients, but this application is still a research tool.

Limited data are available on [^{123}I]IMP, and conflicting results preclude its clear clinical applications. Early-PD patients showed occipital hypoperfusion in comparison to healthy controls, but this result was not validated. Two studies reported parietal and occipital hypoperfusion and cerebellar hyperperfusion in PD, and frontal and cerebeller hypoperfusion in MSA-P. Recently, [^{123}I]IMP showed a significant CBF reductions in the left frontal association cortex in PD with dementia.

[^{99m}Tc]HMPAO/SPECT is not able to differentiate among parkinsonian syndromes, nor can it detect early PD. However, clear defects in energy metabolism can be seen in PD with a dementing process, and a correlation was suggested between region-specific CBF decreases and dementing conditions such as Alzheimer type, diffuse Lewy body dementia, frontotemporal dementia, and PSP (**Figure 5**).

Cardiac Perfusion SPECT

Targets and Tracers

Metaiodobenzylguanidine (MIBG) is an analog of noradrenaline without pharmacologic activity. MIBG can be labeled with ^{131}I ([^{123}I]MIBG) or ^{123}I ([^{123}I]MIBG). MIBG is actively taken up across the membrane of adrenergic cells by the sodium-dependent and energy-dependent human norepinephrine transporter. It is then actively taken up into intracellular storage vesicles by an ATPase-dependent proton pump via the vesicular monoamine transporter and is secreted after stimulation of the neurons with acetylcholine. Thus, [^{123}I]MIBG acts as a tracer not only for the localization but also for the functional integrity of the catecholaminergic structures.

Clinical Application

In PD, neuronal degeneration is not only restricted to the central nervous system, but also affects the peripheral autonomic nervous system. [^{123}I]MIBG scintigraphy is useful for the diagnosis of PD, being markedly reduced even in the early stages. It is less useful than DAT binding SPECT ligands for ranking disease severity. At present, it remains to be determined at which phase PD reductions in MIBG uptake occur, and particularly whether changes in [^{123}I]MIBG scintigraphy can be detected prior to the occurrence of motor signs in PD. Other than the heart, no organ, with sympathetic innervations, such as the lung, muscles, or glands, show [^{123}I]MIBG uptake reduction. The reason for the reduction in cardiac [^{123}I]MIBG tracer uptake is unclear. This finding does not likely reflect damage and degeneration of postganglionic sympathetic neurons, and more reasonable explanation is a change in monoaminergic metabolic pathways, as indicated by a higher wash-out rate in sympathetic neurons of PD patients. In addition to the early diagnosis of PD, quantification of cardiac [^{123}I]MIBG uptake appears to be a valuable tool to discriminate PD from other neurodegenerative disorders. Indeed, MSA, PSP, corticobasal degeneration and vascular parkinsonism show normal or only mild reduction of cardiac [^{123}I]MIBG uptake (**Figure 6**).

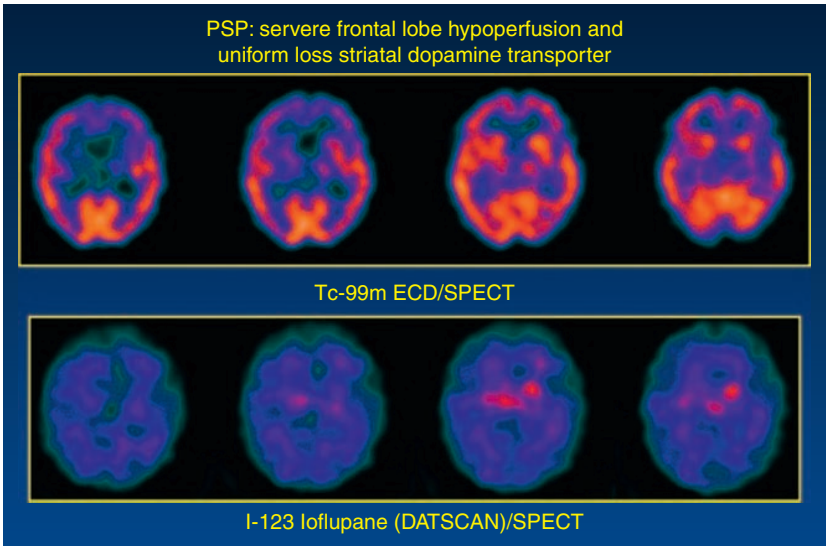

Figure 5 Reduced brain perfusion (upper row) primarily in the frontal lobe and the basal ganglia associated with severe DAT loss in the whole striatum of a patient with progressive supranuclear palsy.

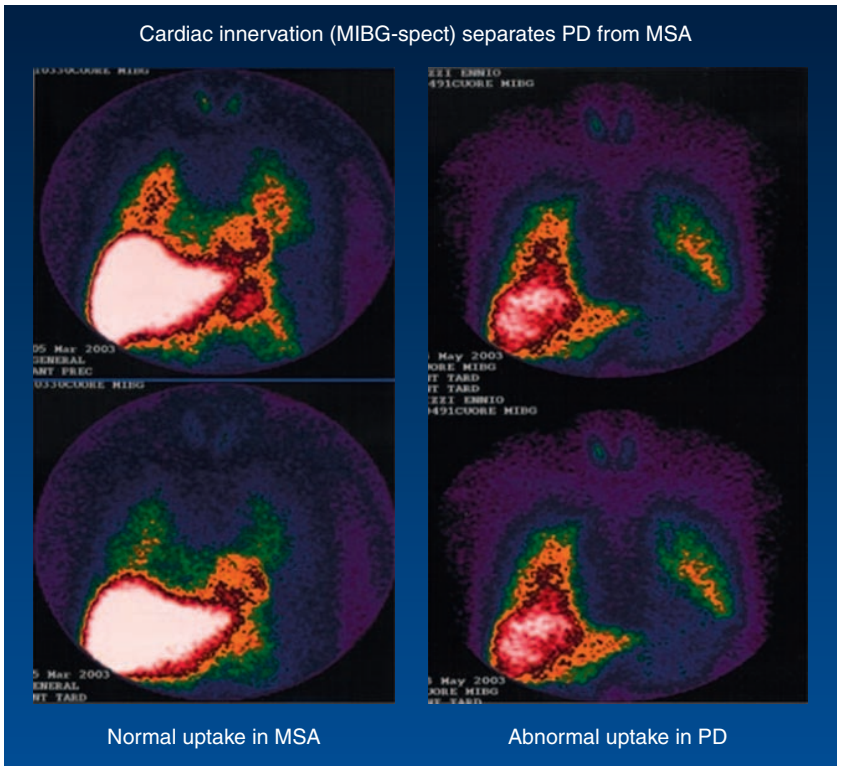

Figure 6 Reduced MIBG is observed in the heart of a patient with Parkinson's disease (right panel) vs. normal control subject (left panel).

The main drawback of [^{123}I]MIBG/SPECT is low specificity (37.4%) while the sensitivity of is relatively high (87.7%). One study directly comparing [^{123}I]MIBG and [^{123}I]FP-CIT in early-stage PD subjects showed higher sensitivity for [^{123}I]FP-CIT (83% vs. 72%).

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www.nlm.nih.gov/medlineplus – MedlinePlus.
www.nuccast.com – The Nuclear Medicine and Molecular Medicine podcast.

Spinal Segmental Myoclonus

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Glossary

Myoclonus – Lightning movements of muscles sufficient to move a body part.
Spinal myoclonus – Myoclonic activity originating within the spinal cord.
Segmental myoclonus – Myoclonic activity involving multiple contiguous muscle groups over several spinal segments.

Clinical Characteristics

Segmental myoclonus is characterized by myoclonic activity at a particular segment or at multiple contiguous muscle groups over several spinal segments. The generators are thought to be at a particular segment of the spinal cord and are therefore classically relatively unaffected by the state of consciousness, motor activity, or stimulus. These movements often occur spontaneously and rhythmically, but irregular jerks may also occur. Segmental myoclonus may occur bilaterally and if it does, it is usually synchronous in corresponding body parts on each side, but asynchronous bilateral myoclonus has also been described. Unilateral segmental myoclonus has been described as well in a case of right arm myoclonus involving the deltoid, biceps, supinator, and triceps muscles of a patient who had a cervical cord astrocytoma. The frequency of this type of jerk is usually in the range of 0.5–3 Hz. The myoclonic discharge ranges from 50 to 500 ms. Some consider the palatal tremor a type of segmental myoclonus.

Pathophysiology

Various structural and pathologic processes in the spinal cord are known to cause this phenomenon, including arteriovenous malformations, tumors and cysts, infections, multiple sclerosis plaques, spondylitic myelopathy, inflammatory processes, and trauma. The precise mechanisms for the spinal myoclonus are not fully understood, but in general, spinal interneuron dysfunction is thought to be a primary cause, via reduced inhibitory mechanisms. In some cases, dysfunction in motor neurons in the spinal cord has been suggested to be the cause of repetitive muscle jerks. In one case report, spinal myoclonus was associated with a systemic cancer not localized to the central or peripheral nervous system.

Treatment

Treatment of spinal myoclonus should first be directed towards treating the cause. Symptomatic treatments have included levetiracetam, clonazepam, valproic acid, tetrabenazine (recently approved in the United States), baclofen, carbidopa–levodopa, 5-HTP, carbamezapine, diazepam, propofol, and topiramate. Chemodenervation with botulinum toxin has shown to be of some benefit. Of these listed, clonazepam is often considered to be the drug of first choice.

See also: Myoclonus; Propriospinal Myoclonus.

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Spinocerebellar Ataxia Type 19, 20, 21, 22, 23, 26

T Klockgether, University Hospital Bonn, Bonn, Germany

Glossary

Ataxia – Impaired coordination leading to problems of balance, finger and hand movements and speech.
Cerebellum – Part of the brain that receives afferent fibres from the cortex, brainstem and spinal cord and sends efferent fibres via the cerebellar deep nuclei towards the thalamus and cortex. The cerebellum has an essential role in coordinating movements.
Dysphonia – Hoarseness or other disorders of phonation.
Linkage analysis – Genetic method that allows to map disease causing gene mutations on chromosomes.
Lod score – Lod score stands for logarithm of the odds and describes the likelihood that a disease causing gene is in close vicinity to a chromosomal locus. A lod score larger than 3 is considered significant for linkage.
Myoclonus – Involuntary, short muscle contraction resembling the muscle twitch caused by electrical nerve stimulation.

SCA19

Schelhaas et al. identified a four-generation Dutch family with autosomal dominant inherited ataxia associated with cognitive impairment, postural tremor, and myoclonus. In all examined patients, cerebellar ataxia was relatively mild. Ataxic speech was an early feature, while limb ataxia occurred only in the later course of the disease. Two out of 10 patients had additional neurological features in the form of a slow irregular postural tremor (Holmes tremor) and myoclonus. All patients had mild cognitive impairment that did meet the criteria of dementia. Neuropsychological testing revealed impaired frontal executive function. Age of onset ranged from 20 to 45 years with a median of 31 years. Disease progression was estimated to be relatively slow. MRI showed marked cerebellar atrophy and in some patients mild cerebral atrophy. The brainstem was not affected. A genome-wide linkage analysis allowed assignment of the disease locus to a 35 cM region on the short arm of chromosome 1.

SCA20

Knight et al. described a four-generation Australian family of Anglo-Celtic origin with autosomal dominant inherited ataxia. The clinical syndrome was that of a largely pure cerebellar syndrome with ataxic speech, often occurring as the presenting symptom, ataxia of gait and stance, incoordination of limb movements and oculomotor disturbances including impaired smooth pursuit, hypermetric downward saccades, and impaired suppression of the vestibulo-ocular reflex. Five out of 14 examined family members who were affected had minor pyramidal signs consisting of exaggerated tendon reflexes in the lower extremities without extensor plantar responses or spasticity. Apart from that, most patients were presented with dysphonia reminiscent of adductor spasmodic dysphonia and a 2 Hz palatal tremor. Disease onset ranged from 19 to 64 years with a median of 46 years. Disease progression was slow: only one patient required a wheelchair 40 years after the onset of first symptoms. A highly characteristic imaging feature was pronounced dentate calcification on CT that was not regularly accompanied by calcifications in other brain regions. MRI showed diffuse cerebellar atrophy and increased signal in the region of the inferior olives as a correlate of palatal tremor.

A genome-wide linkage analysis revealed a chromosomal locus in the pericentromeric region of chromosome 11 with a maximal lod score of 4.47 at marker D11S4191. Although the critical region partially overlapped with the SCA5 region, the locus was provisionally assigned as SCA20 due to the distinct clinical phenotype. After identification of mutations in β-III spectrin gene (*SPTBN2*) causing SCA5, the exons, intron–exon boundaries, the 5′UTR and parts of the 3′UTR of the *SPTBN2* gene were sequenced in an affected family member. Sequencing did not yield causative mutations making it unlikely that SCA20 is allelic to SCA5.

A survey of Portuguese families suffering from dominant inherited ataxia revealed six families with cerebellar ataxia and spasmodic cough. One patient had dentate calcification on CT. Thus, these families share phenotypical features with SCA20. As linkage data for these families are not yet available, it remains a matter of speculation whether the Portuguese families correspond to SCA20.

SCA21

Devos et al. described a four-generation French family with autosomal dominantly inherited ataxia and mild cognitive impairment. The clinical syndrome consisted of gait and limb ataxia as well as ataxic speech. In some patients, ataxia was associated with akinesia, tremor, and rigidity. In almost all patients, a mild degree of cognitive impairment was evident. Disease onset ranged from 6 to 30 years with a median of 20 years. An analysis

of 10 parent–sib pairs revealed a median anticipation of 10 years between generations. Disease progression was slow. The index case was still able to walk unassisted after a 40 year disease history. MRI revealed an isolated cerebellar atrophy without brainstem involvement.

A genome-wide linkage analysis yielded a locus on the short arm of chromosome 7 flanked by markers D7S2464 and D7S516 named SCA21. Direct sequencing of a number of candidate genes in this region did not reveal causative mutations.

SCA22

Chung et al. described a four-generation Chinese Han family with autosomal dominantly inherited ataxia. The clinical syndrome was purely cerebellar in all examined patients. The age of onset ranged from 10 to 46 years. Disease progression was reported to be slow. Only one affected individual was unable to walk unassisted 20 years after onset of first symptoms. An MRI was available in one patient and showed an isolated cerebellar atrophy.

Genome-wide linkage analysis revealed linkage to a 43 cM region on the short arm of chromosome 1 with a maximal lod score of 3.78. Schelhaas et al. pointed out that this locus named SCA22 overlaps with the SCA19 locus to which a Dutch family with ataxia, cognitive impairment, postural tremor, and myoclonus had been previously mapped.

SCA23

Verbeek et al. reported a Dutch three-generation family with autosomal dominantly inherited ataxia. All examined patients had gait and limb ataxia. In addition, slowed saccades, impaired vibration and position sense, and extensor plantar responses were encountered in about half of the patients. Disease onset ranged from 43 to 56 years with a median of 51 years. One subject who had a disease duration of 23 years required a wheelchair. All other affected members with a disease duration ranging from 1 to 13 years still walked unassisted. MRI was available in one subject and showed isolated cerebellar atrophy and multiple small subcortical white matter lesions. Neuropathological examination of one brain showed neuronal loss in the Purkinje cell layer, dentate nuclei, and inferior olives. Posterior and lateral columns of the spinal cord were demyelinated.

A genome-wide linkage analysis showed linkage with a region on the short arm of chromosome 20 with a maximal lod score of 3.46.

SCA26

Yu et al. reported a six-generation family of Norwegian origin with autosomal dominantly inherited ataxia. All affected family members had a pure cerebellar syndrome including gait and limb ataxia, ataxic speech and impaired smooth pursuit. Disease onset ranged from 26 to 60 years with a median of 42 years. Disease progression was reported to be slow. Only 2 out of 15 examined patients were wheelchair-bound. MRI showed isolated cerebellar atrophy without brainstem involvement.

By genome-wide linkage analysis, the disease was assigned to a 15 cM region on the short arm of chromosome 19 flanked by the markers D19S886 and D19S894. Maximal lod score was greater than 15. Although the SCA26 locus maps close to SCA6, *CACNA1A*, the gene affected in SCA6, does not lie into the SCA26 region. In addition, the CAG repeat expansion mutation causing SCA6 was not found. Sequencing of the exonic regions of four candidate genes did not reveal any mutations.

See also: Ataxia; Ataxia with Isolated Vitamin E Deficiency; Creutzfeldt–Jacob Disease; SCA1; SCA2; SCA3, Machado–Joseph Disease; SCA4; SCA5; SCA6; SCA7, Spinocerebellar Ataxia with Macular Dystrophy; SCA8; SCA10; SCA11; SCA12; SCA13, 14, 15, and 16; SCA17; SCA27; Spinocerebellar Ataxias Genetics.

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Spinocerebellar Ataxias Genetics

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Glossary

Gain and loss of function – Mechanism by which a genetic mutation exerts its pathogenic effect. Gain of function means that the disease is caused by a new deleterious function acquired by the mutated gene. In a loss of function mechanism, the pathogenesis is due to a loss of the physiological function of the mutated gene.

Ion channel – Pore forming membrane protein that allows and regulates the flow of ions across membranes of excitable cells.

Neuronal nuclear inclusions – Small, light microscopically visible accumulations of proteins present in the nuclei of neurons. Neuronal nuclear inclusions are the pathological hallmarks of polyglutamine disorders.

Polyglutamine disorders – Group of inherited neurodegenerative diseases that are caused by translated CAG repeat expansion mutations which lead to the formation of polyglutamine-containing disease proteins.

Repeat mutation – Disease causing gene mutation characterized by a pathological expansion of a repetitive gene sequence.

Translated and untranslated regions – Translated regions are the exonic parts of a gene that are transcribed and translated into a protein. The untranslated regions are the parts in the 3′ and 5′ region of a gene that are not translated into a protein. They have regulatory functions.

Ubiquitin protease – Enzyme that removes ubiquitin molecules from ubiquitinaned proteins.

Genetics

Of the mutations that have been identified, spinocerebellar ataxias, SCA1, 2, 3, 6, 7, 17 are translated CAG repeat expansions coding for an elongated polyglutamine tract within the respective proteins. These diseases belong to a larger group of polyglutamine disorders that also include Huntington's disease, dentatorubro-pallidoluyisian atrophy and spinobulbar muscular atrophy. Three SCAs, SCA8, 10, 12 are caused by untranslated repeat expansions in non-coding regions of the respective genes. In SCA5 (beta-III spectrin, SPTBN2), SCA11 (tau tubulin kinase-2, TTBK2), SCA13 (voltage-gated potassium channel, KCNC3), SCA14 (protein kinase Cγ, PKCγ), SCA15 (inositol 1,4,5-triphosphate receptor type 1, ITPR1), SCA27 (fibroblast growth factor 14, FGF14), and 16q22-linked autosomal dominant cerebellar ataxia (ADCA) (puratrophin), nonrepeat mutations have been found in the respective genes. In all other SCAs, the affected genes and mutations have not yet been identified.

The genetic heterogeneity of the SCAs implies an even greater heterogeneity of their molecular pathogenesis. Even the polyglutamine SCAs that were initially assumed to share a common mechanism of polyglutamine toxicity, have diverse pathogenic mechanisms that are related to the specific properties of the respective disease proteins. While there has been considerable progress in the understanding of the pathogenesis of the polyglutamine disorders, there is still very limited knowledge of the mechanisms that underlie the SCAs due to untranslated repeat expansions and to nonrepeat mutations.

Epidemiology

There are only few prevalence studies of SCAs. According to these studies, the prevalence ranges between 0.8 and 3.0: 100 000 inhabitants. Due to founder effects, the prevalence may be much higher in certain regions. For example, the prevalence of SCA2 is 43:100 000 in the Cuban province Holguin. The worldwide most frequent SCAs are the polyglutamine SCAs SCA1, 2, 3, and 6 which together account for more than half of all SCA families.

Polyglutamine SCAs

Genetics: The polyglutamine SCAs (SCA1, 2, 3, 6, 7, 17) are caused by CAG repeat expansions in the coding regions of the respective genes. The critical threshold above which the expansion causes the disease ranges from 20 in SCA6 to 51 in SCA3. In all polyglutamine SCAs except SCA3 and SCA7, the normal and pathological range border at each other, or may even have some overlap, as in SCA1. In contrast, the largest normal SCA3 alleles have a length of 40 CAG repeats, while the shortest pathological SCA3 allele observed so far has 51 repeats. There is an inverse correlation between CAG repeat length and age at disease onset. Statistical analyses of large cohorts of SCA patients showed that the repeat length explains 56% (SCA6) to 80% (SCA2) of the observed variability of the age at disease onset.

A quantitative assessment of disease severity in large cohorts of SCA1, SCA2, and SCA3 patients showed that larger expansions are associated with a more severe ataxia in these genotypes while disease severity in SCA6 was mainly determined by age. Clinical observations in SCA7 and SCA17 families suggest that that there is a similar relationship between repeat length and disease severity. There is indirect evidence that longer repeats are also associated with more rapid disease progression, but prospective studies are lacking. Further, the repeat length partly determines which nonataxia symptoms occur in a particular SCA disorder. Thus, longer repeats are associated with peripheral neuropathy, brainstem oculomotor signs, and dystonia in SCA2. In SCA3, larger repeats are associated with spasticity and hyperreflexia. SCA7 patients with large expansion have visual loss preceding ataxia, while those with shorter expansion may have isolated ataxia without major visual deterioration.

While normal alleles are stable, expanded alleles are unstable and often change their length during transmission to the next generation. Instability of expanded alleles is amplified by the loss of non-CAG interruptions in the expanded alleles. In general, there is a tendency that abnormal alleles further expand during transmission to the next generation which results in anticipation, that is, earlier age of onset in the next generation. This tendency is particular strong during paternal transmission in SCA2 and SCA7.

Non-CAG interruptions do not only influence allele stability, but may also determine the clinical phenotype. In SCA2, uninterrupted alleles are associated with cerebellar ataxia, while the less common alleles carrying CAA interruption are found in patients with a parkinsonian phenotype.

Pathogenesis: That expanded polyglutamine tracts themselves exert powerful neurotoxic actions has been convincingly shown in transgenic models in which overexpression of expanded polglutamines in arbitrary proteins in neurons caused neurodegeneration. Several observations suggest that cleavage of the disease proteins and formation of smaller polyglutamine-containing protein fragments is a prerequisite for polyglutamine-mediated neurodegeneration. However, the enzymes mediating protein cleavage have not yet been fully identified. In most polyglutamine diseases, a nuclear localization of the disease protein is required for its deleterious action.

Elongated polyglutamines have a strong tendency to misfold and aggregate. According to current view, oligomeric intermediates originating from the aggregation process are responsible for the pathogenesis, while the light microscopically visible neuronal inclusions found in neurons of SCA brains are thought to be inert or even protective. Oligomeric intermediates exert their deleterious action by abnormally interacting with other cellular proteins. Potential interaction partners are transcription factors which themselves contain polyglutamine tracts. As a result, a general suppression of gene transcription has been found in models of polyglutamine diseases. The important role of transcriptional dysregulation in the pathogenesis of polyglutamine disorders is underlined by the discovery that SCA17 is caused by a CAG repeat expansion in the gene of an essential transcription factor, TATA-binding protein (TBP).

With the exception of SCA6 (α_{1A} voltage-dependent calcium channel subunit, CACNA1A) and SCA17 (TBP), the function of disease proteins of all SCAs of the polyglutamine group was completely unknown when the respective gene mutations were discovered. The physiological roles of these proteins which have been named ataxins are currently under intense investigation.

In SCA1, the polyglutamine expansion stabilizes ataxin-1 and leads to its accumulation. Ataxin-1 interacts in a polyglutamine-independent way with the mammalian transcription factor senseless/Gfi-1 which is expressed in cerebellar Purkinje neurons. Loss of Gfi-1 leads to degeneration of cerebellar Purkinje neurons suggesting that ataxin-1/Gfi-1 interaction contributes to the neurodegeneration in SCA1. Apart from transient interaction with a number of proteins including senseless/Gfi-1, ataxin-1 forms stable protein complexes with RNA-binding motif protein 17 (RBM17), a protein involved in RNA metabolism, and capicua, a transcription factor. Polyglutamine expansion favours the formation of complexes with RBM17 which contribute to neurodegeneration due to a gain of function mechanism, while formation of complexes with capicua are attenuated resulting in a loss of function. The observations lead away from simple models of polyglutamine toxicity and suggest opposing effects of the polyglutamine expansion on cellular function resulting in both gain and loss of function.

Ataxin-3, the disease protein of SCA3, binds polyubiquitin chains and acts as an ubiquitin protease. In addition, ataxin-3 has been shown to bind to DNA and form a transcriptional repressor complex. The transcriptional repressor function is lost in expanded ataxin-3. Overexpression of normal ataxin-3 prevents polyglutamine-induced neurodegeneration raising the question whether a loss of the physiological function of ataxin-3 amplifies the polyglutamine-mediated toxicity in SCA3. Thus, SCA3 pathogenesis like SCA1 has aspects of both, gain and loss of function.

SCA6 is caused by a CAG expansion in the CACNA1A gene that encodes the α_{1A} transmembrane subunit of the P/Q type voltage-sensitive calcium channel that is strongly expressed in cerebellar Purkinje neurons. It is therefore conceivable that the polyglutamine expansion which is located in the C-terminal part of the channel protein impairs the physiological function of these channels and that this contributes to the neurodegeneration in. However, electrophysiological studies in cells overexpressing the mutant channel subunit failed to provide a

consistent picture. More recently, it was found that that the deleterious action of the polyglutamine expansion depends on the cleavage and nuclear localization of the C-terminal part of the protein. This finding suggests that the mutant protein has pathogenic effects which are independent of its channel function.

Neuropathology: Given the diverse pathogenesis of the polyglutamine SCAs it is not surprising that autopsy findings vary. Even within one genotype, neuropathology is not uniform. SCA1, 2, and 7 are prototypes of a degeneration pattern that was previously designated as olivopontocerebellar atrophy with degeneration of the cerebellar cortex, pontine nuclei, and inferior olives. In SCA2 brains, there is almost always additional severe loss of dopaminergic neurons of the substantia nigra. In SCA3, there is degeneration of the cerebellar nuclei, brainstem, basal ganglia, and spinal cord, while the cerebellar cortex is widely spared. In contrast, the degeneration in SCA6 is largely confined to cerebellar Purkinje neurons without major involvement of other parts of the brains or spinal cord. In some polyglutamine SCAs, in particular SCA2, SCA3, and SCA7, degeneration in the central nervous system is accompanied by a peripheral neuropathy of axonal type.

An almost common morphological feature of polyglutamine disorders are neuronal nuclear inclusions formed by the respective elongated disease proteins. Such inclusions are prominent in SCA1, 3, 7, and 17, while they are less common or absent in SCA2 and SCA6. As these inclusions contain additional proteins, such as chaperones, proteasomal subunits and transcription factors it has been hypothesized that the inclusions contribute to the disease pathogenesis by depleting the cell from essential proteins. However, this hypothesis has not been supported by experimental evidence. Instead, it has been shown that the neurodegeneration can be dissociated from the formation of nuclear inclusions.

SCAs Due to Untranslated Repeat Mutations

Three SCAs are caused by repeat expansion mutations in untranslated parts of the affected genes. SCA8 is associated with a CTG expansion in the 3′ untranslated region of the ATXN8 gene. In contrast to all other known SCAs, penetrance of the mutation is incomplete, and expansions have been found in healthy individuals and in individuals with brain diseases other than ataxia. The normal SCA8 alleles have a length ranging from 15 to 37 CTG repeats, while expanded alleles are longer than 100 repeats. It was initially hypothesized that the SCA8 mutation exerts its effects through an RNA gain of function mechanism in which the transcript, in a mechanism resembling that in myotonic dystrophy, has toxic effects by sequestering RNA-binding proteins, or in which the transcript functions as an antisense and disrupts the expression of neighboring genes. More recently, it has been suggested that the ATXN8 gene is transcribed in a bidirectional manner resulting not only in a potentially toxic CUG-containing RNA, but also in a second transcript that is translated into a pure polyglutamine stretch. The SCA8 pathogenesis might thus involve toxic gain of function mechanisms at both the protein and RNA levels.

SCA10 is due to large unstable intronic pentanucleotide (ATTCT) expansions which may have a length up to 4500 repeats. Normal repeat length shows a range from 10 to 22 repeats.

SCA12 is caused by a CAG repeat expansion in the 5′ untranslated region of the PPP2R2B gene that encodes a brain-specific regulatory subunit of the protein phosphatase PP2A. Normal repeat size ranges from 7 to 32, the expanded repeat size from 55 to 93.

SCAs Due to Nonrepeat Mutations

SCA5, 11, 13, 14, 15, 27, and 16q22-linked ADCA are due to nonrepeat mutations, mainly missense mutations and deletions. Although the genes affected in these disorders have very diverse functions, all SCAs due to nonrepeat mutations have a number of features in common that distinguish them from the polyglutamine SCAs. SCAs due to nonrepeat mutations often have an early disease onset, that is, in adolescence or early adulthood. In addition, progression is much slower than in the polyglutamine SCAs. Many patients suffering from one of these disorders are mentally retarded. These features have led to the suggestion that the SCAs due to nonrepeat mutations are rather developmental than true neurodegenerative disorders.

An overview of the affected genes and mutations is given in **Table 1**. Among this group of disorders, 16q22-linked ADCA deserves special consideration. 16q-linked ADCA is frequent in Japan. The chromosomal region to which this disorder is linked overlaps with the SCA4 region, thereby raising the question whether both disorders are allelic. A strong argument against this assumption is the different clinical phenotype. 16q-linked ADCA is clinically characterized by progressive cerebellar ataxia. Correspondingly, imaging and autopsy studies show cerebellar degeneration. In contrast, the two SCA4 families described so far – one in Utah/USA and other in Germany – suffer from sensory ataxia without cerebellar involvement. In addition, the mutations present in the Japanese families were not detected in the German SCA4 family.

It is thought that the pathogenesis of the SCAs caused by point mutations is more closely related to the physiological function of the affected proteins than that of the SCAs which are due to repeat mutations. An example of this assumption is SCA5. SCA5 is caused by mutations of the SPTBN2 gene which is highly

Table 1 Molecular genetics of the SCA

Disorder	*Mutation*	*Gene product*
SCA1, 2, 3, 7	Translated CAG repeat	Ataxin-1, 2, 3, 7
SCA6	Translated CAG repeat	Voltage-gated calcium channel subunit
SCA17	Translated CAG repeat	TATA box-binding protein
SCA8	Untranslated/ translated CTG repeat (3′)	Ataxin-8
SCA10	Untranslated AATCT repeat (intron)	Ataxin-10
SCA12	Untranslated CAG repeat (5′)	Protein phosphatase 2
SCA4/16q-ADCA	Point mutation	Puratrophin-1
SCA5	Point mutation/deletion	β-III Spectrin
SCA11	Insertion/deletion	Tau tubulin kinase 2
SCA13	Point mutation	Potassium channel
SCA14	Point mutation/deletion	Protein kinase C-γ
SCA15/16	Deletion	Inositol-triphosphate receptor
SCA27	Point mutation	Fibroblast growth factor 14
SCA18–23, 25, 26, 28	Unknown	Unknown

expressed in cerebellar Purkinje neurons. SPTBN2 acts as a stabilizer of the glutamate transporter EAAT4. Mutations might thus result in abnormal glutamate signaling and excitotoxicity. On the other hand, point mutations of the PKCγ gene in SCA14 have been shown to lead to the formation of intracytoplasmic aggregates suggesting a disease mechanism resembling that in polyglutamine disorders. In general, the pathogenesis of the SCAs due to nonrepeat mutations is insufficiently studied so that statements about the mechanisms leading to these diseases at this point are speculative.

See also: Ataxia with Isolated Vitamin E Deficiency; SCA2; SCA3, Machado–Joseph Disease; SCA4; SCA5; SCA6; SCA7, Spinocerebellar Ataxia with Macular Dystrophy; SCA8; SCA11; SCA12; SCA13, 14, 15, and 16; SCA17; Senataxin.

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St. Vitus Dance

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Glossary

Chorea – Brief, random involuntary movements that tend to flow from body part to body part.
Psychogenic illness – Constellation of signs or symptoms without an organic basis.

Definition and History

St. Vitus dance is now believed to result from mass psychogenic illness/mass hysteria. Mass hysteria is a social illness, defined as 'a constellation of symptoms suggestive of organic illness, but without an identified cause in a group of people with shared beliefs about the cause of the

symptoms.' Mass hysteria is sudden in onset, preceded by the illness of an index patient in whom there has been a prominent response. The illness is propagated by proximity and along sight lines. Symptoms spread rapidly but involve few hard physical signs.

During the time of St. Vitus dance, bizarre dancing behavior developed in a group of people who shared a belief system that spiritual forces could provoke severe physical manifestations. Similar bizarre behavior developed in groups of people in Italy who thought they had been bitten by tarantulas (tarantism), and mass hysteria was the origin of witchcraft panics in Europe and New England. Modern episodes of mass hysteria are more likely to occur in the context of environmental concerns or heightened sensitivity to possible terrorist episodes or other criminal behaviors.

Epidemiology/Risk Factors

St. Vitus dance first affected the poor, though it did spread to affect members of all classes. Those who led a sedentary life (shoemakers, tailors) were thought to be preferentially affected, but even robust farmers were stricken. Although little can be gleaned from the descriptions of St. Vitus dance, other episodes of mass hysteria have been more common in women than in men.

Clinical Features and Diagnostic Criteria

> The effects of the Black Death had not yet subsided, and the graves of millions of its victims were scarcely closed, when a strange delusion arose in Germany, which took possession of the minds of men, and, in spite of the divinity of our nature, hurried away body and soul into the magic circle of hellish superstition.
>
> Hecker, 1888

St. Vitus dance is more an historical than a clinical syndrome. It has been variably known as the dancing mania, St. John's dance, and St. Guy's dance. Once they began, episodes of dancing mania spread across Europe over a period lasting more than 300 years.

Hecker dates the first cases to 1374, at Aix-La-Chapelle. The region had been visited by serious flooding, and there was unrest and lawlessness. In this context, men and women began to exhibit a strange ritual. They joined hands and formed circles, dancing deliriously for hours until falling to the ground, exhausted. When dancing, they seemed insensitive to the environment, though influenced by visions. The dancing was often followed by 'tympany' and flatulence, which was treated by bystanders who thumped or stepped on the dancers, or bound them tightly around the waist. Dancers took over houses of worship and inspired processions, prayer, and exorcisms. Although the affliction was largely confined to the poor at first, it did spread to other more privileged community members.

The connection to St. John the Baptist is believed to be related to a manner of his worship that involved jumping through flames or smoke as a means of securing protection from fevers or other disease. The connection to St. Vitus occurred after the malady spread to Strasburg in the early fifteenth century. Eager to control the affliction, the town council appointed superintendents to protect them and the townspeople from harm. Afflicted persons were brought to the chapels of St. Vitus, where they were attended to by the priests. A procession to the altar of St. Vitus frequently cured the sufferers of their torment.

Over time, the attacks became temporally attached to their patron saints, occurring around the time of feast days. Episodes of the dancing mania continued for hundreds of years, and their treatment was entirely the purview of the church. In many cases, musicians were enlisted to speed the course of the illness, since exhaustion seemed the first step to cure.

In the early sixteenth century, they drew the attention of Paracelsus, who divided St. Vitus dance into three subcategories: chorea imaginativa, chorea lasciva, and chorea naturalis. Chorea imaginativa arises from the imagination (dancing mania), chorea lasciva arises from sensual desires, and chorea naturalis arises from corporeal causes.

Differential Diagnosis

Despite the derivation of the word chorea from the Greek word for dance, choreic movements do not suggest an organized motor activity that would resemble dancing or jumping. Rather, the movements are brief and random, and tend to flow from one body part to another.

St. Vitus dance is of historical interest, though it can best be considered a mass functional or psychogenic illness. In this sense, functional/psychogenic chorea must be differentiated from organic choreas, including immune-mediated chorea (Sydenham's chorea, lupus chorea, antiphospholipid antibody syndrome), hereditary chorea (benign hereditary chorea, Huntington's disease, and Huntington-like illnesses), metabolic and hormonal chorea (hyperthyroidism, chorea gravidarum), drug-induced chorea (neuroleptic, sympathomimetic agents, oral contraceptives/hormonal treatments), and others. Like other psychogenic/functional movement disorders, psychogenic/functional chorea is often sudden in onset, variable and distractible, and it may be associated with other psychogenic/functional signs.

Diagnostic Work-up/Tests

Psychogenic/functional movement disorders are diagnosed clinically by their characteristic tempo, appearance, and associated symptoms. Neuroimaging studies, immune and metabolic studies, and genetic testing may be useful to distinguish these from organic causes.

Management

Paracelcus recommended treatment for his three types of St. Vitus dance. For the first type, chorea imaginativa, the sufferer was to make a wax image of himself, and concentrate all his blasphemies and sins into it, then burn the image. For chorea lasciva, Paracelsus recommended strict fasting and isolation followed by gradual return to society. The third type was to be treated with a number of potions applied internally in water or wine, and externally, as an ointment, with particular attention paid to the ticklish areas.

For individual victims of psychogenic/functional movement disorders, the course of treatment is not yet clear. In the absence of controlled clinical trials, various strategies are employed. These include cognitive behavioral therapy, pharmacological intervention, and various psychotherapies.

The management of modern outbreaks of mass hysteria is difficult. There are no pathognomonic signs of mass psychogenic illness, and expensive and prolonged investigation is the rule. Even when all organic causes of the symptoms are ruled out, there may be persistent beliefs that such a cause exists and has escaped detection or been 'covered up.' A detailed follow-up of a mass psychogenic illness in Tennessee suggested that the episode, in which 186 persons who had symptoms related to an 'abnormal smell' in a school, resulted in loss of 18 000 person-days of school, 178 emergency room visits, $93 000 in medical expenses, 200 person-hours, $9000 for toxicological studies, and 3000 person-hours of additional labor costs involving 12 government agencies, eight laboratories, and seven private consulting groups.

Prognosis

Although in most cases, St. Vitus dance was 'cured' by devotions to the saint or other interventions, there are reports of its sufferers sustaining permanent injury, even death while in its throes. Moreover, annual episodes surrounded the feast days of the patron saint in question.

There are little long-term prospective data to guide prognosis in today's victims of psychogenic/functional illness, but a monophasic illness seems more common. In outbreaks of mass psychogenic illness, recovery is the rule, though some victims may complain of chronic dysfunction.

See also: Chorea.

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Staircase (Skilled Reaching) Test

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Glossary

6-Hydroxydopamine (6-OHDA) – A neurotoxin that induces selective degeneration of catecholamine neurons, frequently used following injection into the vicinity of midbrain dopamine neurons to induce an animal model of Parkinson's disease.

Brain-derived neurotrophic factor (BDNF) – A member of the neurotrophin family trophic factors, that enhances survival of dopamine neurons both in vitro and in vivo.

Glial cell line-derived neurotrophic factor (GDNF) – An endogenous trophic molecule that enhances survival and fibre outgrowth of dopamine neurons both in vitro and in vivo.

Introduction

The staircase test was introduced by Montoya in 1990 to provide an objective and flexible alternative to a range of other tests used to assess forelimb use and motor skills in rats.

Very many studies of motor function involve the manipulation of systems, such as basal ganglia or forebrain dopamine pathways, in which bilateral lesions can yield animals that are akinetic, unmotivated and extremely ill, rendering them effectively untestable. This can be resolved by studying motor asymmetries in unilateral lesioned animals, but to be effective any test must be able to evaluate unilateral deficits and performance independently on the two sides of the body.

Hitherto, many tests involved observing rats or mice reaching to pick up food pellets in trays, tubes, and troughs either by direct observation or by video recording of performance for subsequent analysis. Such tests had clear face validity but suffered from several disadvantages: (1) they were time consuming and labor intensive; (2) they were scored by observer rating with all the attendant problems of potential experimenter bias; (3) even if skilled reaching is affected, rats are efficient at scooping up pellets with the open hand or tongue; and (4) rats with unilateral lesions are adept at finding strategies to use their unaffected limb, making rating of the affected limb problematic without use of further restraints such as casts or forelimb injections of local anesthetic. The alternative strategy has been to use operant paradigms with force transducers attached to lever press or lever release operanda. Such tests can be automated for objectivity and efficiency, but the need to restrict use of the unaffected limb, as opposed to simply measuring changes in preference or bias, was again problematic.

The Staircase Test

The staircase test emerged out of a variety of attempts to reconfigure lateralized reaching wells and tubes in a restricted cage so that the rat could only use one or the other limb in a particular location. The solution that emerged was to develop a platform within a narrow corridor, along which a rat (or mouse) can crawl, and reach down either side to pick up food pellets (**Figure 1**). However, the corridor is too narrow to allow the rat to turn around so it can only reach pellets from the left side using the left forepaw and from the right side using the right forepaw. A double staircase with a series of steps with a shallow well in each step and two food pellets placed in each well, then provided a linear series of distances the rat must reach to retrieve pellets and a corresponding graded level of difficulty. On each test, the mildly food-deprived rat is placed in the staircase apparatus for 15 min, at the end of which the number of pellets retrieved can be counted.

Two measures are typically recorded: *pellets retrieved*, the total number of pellets removed, which provides an index of the distance over which the animal can reach and coordinate an effective grasp and retrieval under proprioceptive feedback; and *maximum reach*, the furthest step with one or less pellets remaining, which provides an index of the maximum distance over which the animal can make a reaching attempt. In practice, the two indices yield very similar experimental outcomes, and for most purposes, simply recording the pellets retrieved provides a reliable and efficient metric. Nikkhah and colleagues have undertaken more detailed analyzes using color coded pellets on each step to differentiate more clearly retrieved from displaced pellets, but again for most purposes, the additional information acquired may not offset the cost in efficiency. Similarly, Whishaw has provided detailed and elegant video analysis of the precise motor choreography of reaching movements by rats, but this level of analysis is not required for most experimental neurobiological purposes.

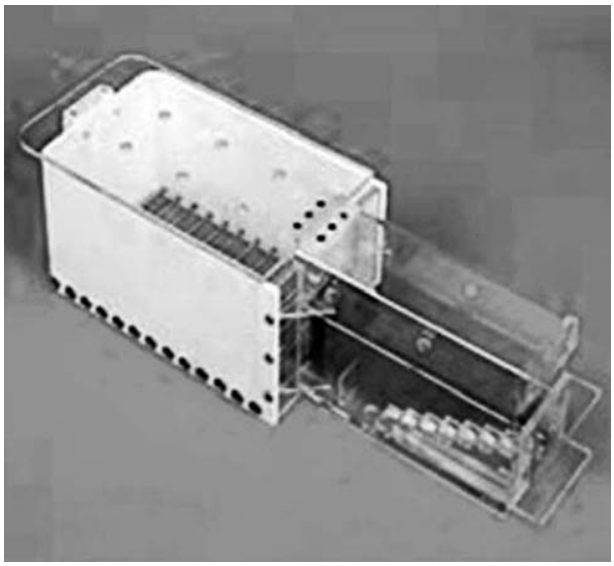

Figure 1 The staircase test apparatus.

Training is important to yield clear results. Early studies used only rather brief training preoperatively, whereas studies by Fricker–Gates have shown that more extensive training over 2–4 weeks to attain a stable baseline prior to experimental manipulation not only provides tighter variance and greater experimental power, but stabilizes ipsilateral performance and yields more selective impairments on the contralateral side. Conversely, studies that undertake task acquisition in animals that have already sustained unilateral lesions typically never acquire high levels of performance even with the supposedly intact ipsilateral limb.

Moreover, although most studies have been in the rat, the task can be readily adapted for other species, once allowance is made for species difference in patterns of behavior, and versions of the staircase test have been validated for the mouse and marmoset.

Key Results

The staircase was first validated with unilateral lesions of the motor cortex, but has been subsequently used most widely in experimental studies of basal ganglia function. Notably, both unilateral nigral and unilateral striatal lesions induce marked impairments of successful reaching with the contralateral paw in adult rats; however, profiles of recovery differ. When nigrostriatal lesions are made in neonatal rats they can develop normal reaching behavior. However, by the time the animals are weanlings, 3–4 weeks of age, even partial dopamine-depleting lesions produced sustained impairments in the staircase tests, while other tests such as stepping and cylinder can indicate partial recovery. Unilateral striatal lesions can be even more marked and long lasting. More recently, other experimental studies have adopted the staircase test to provide sensitive and efficient measurement of disturbed forelimb function relating to cortical damage, spinal trauma, and unilateral stroke, and the task has proved efficient for evaluation efficacy of symptomatic and neuroprotective drug treatments.

The staircase test has proved particularly informative in studies of cell transplantation. From the first studies, striatal grafts have been found to be effective in alleviating skilled reaching deficits in animals with excitotoxic lesions of the striatum, and indeed the staircase test has emerged as perhaps the most reliable and sensitive test of functional recovery in this lesion and graft model of Huntington's disease. Conversely, several authors have found that nigral grafts, which alleviate a range of simple motor asymmetries and akinetic deficits induced by nigrostriatal lesions, fail to yield recovery in the staircase test. Although, from the more diverse neuronal loss, the striatal lesion might be predicted to be the more difficult lesion to reconstruct, in this model the grafts are placed back into a homotopic site which allows for the extensive reformation of appropriate connections. By contrast, nigral grafts need to be placed ectopically in the striatum and although effective in replacing a dopaminergic striatal innervation do not restore nigrostriatal connectivity. Pharmaceutical studies provide compatible data, with beneficial effects in the staircase test of neuroprotective agents that reduce nigrostriatal degeneration (such as riluzole, melatonin, glial cell line-derived neurotrophic factor (GDNF), or brain-derived neurotrophic factor (BDNF)), but a failure of stimulant drugs (such as caffeine or apomorphine) to alter deficits in staircase performance, even when deficits in other simple motor tasks (such as rotation or reflexive stepping) are markedly reversed.

Such data suggest that the staircase apparatus provides an effective test of goal-directed skilled reaching, dependent upon the integrity of functional nigrostriatal and corticostriatal circuits, rather than on simple striatal activation per se.

See also: 6-OH Dopamine Rat Model; Basal Ganglia; Climbing Behavior; GDNF (including Nurturin); Handreach Task.

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Stem Cells

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Glossary

Huntington's disease – Huntington's disease is a neurodegenerative genetic disorder that results in abnormal movement.
Neural stem cells – Neural stem cells are self-renewing cells that generate the main cell types of the nervous system.
Parkinson's disease – Parkinson's disease is a chronic and progressive disease of the brain that impairs motor control, speech, and other functions.
Stem cells – Stem cells are cells that are characterized by the ability to renew themselves through cell division and have the ability to become specialized organ-cell types.

Introduction

The myriad of neurological pathologies that can affect the human brain from prenatal development and throughout lifespan along with the brain's limited self-repair capacity call for new therapeutic strategies. Our increasing knowledge about the fundamental biology and therapeutic potential of various stem cell types opened a new chapter in regenerative medicine. The initial work on rodent stem cells over the last two decades is now being successfully continued with stem cells of human origin and from different developmental stages. We have learned about key genes and cellular mechanisms that maintain the stem cell status or lead to differentiated progeny. We have also learned about the multiple roles of stem cells during development, disease, and aging. It is now well established that stem cells are not only a valuable tool for cell replacement but are equipped with important additional properties that may be harnessed for cell protection, detoxification, and gene therapy ('chaperone effects').

Stem cell biology is being recognized as a continuum of developmental processes that are tightly regulated, both temporally and spatially. Better understanding of these developmental events is considered to be a key strategy for the successful use of both endogenous and grafted stem cells for CNS repair and functional recovery. For instance, the generation of functional neurons and glial cells during brain development requires a concerted coordination of cell proliferation, migration, cell-type specification, and synaptic integration, all of which are also crucial for a successful stem cell therapy.

Stem Cell Prototypes

Stem cells give rise to organs and maintain tissue integrity and homeostasis in an adult organism. There are different types of stem cells, including embryonic and somatic (fetal or adult derived), from which new cells can be derived. To fulfill the criteria of a stem cell, as opposed to a 'progenitor' cell, a single clonal cell must have the following functional properties: (1) should be able to generate the cell types from the organ it was derived from and (2) should possess 'self-renewal,' that is, the ability to produce daughter cells with identical properties. The ability to populate a developing or injured region with appropriate cell types upon transplantation is another important stem cell feature that is well established with hematopoetic stem cells and awaits standardization in other organ systems, including the brain. In the following sections, we introduce two prototypical stem cells, the embryonic stem cells (ESCs) and neural stem cells (NSCs), and discuss their potential for neural repair.

Embryonic Stem Cells

ESCs are derived from the inner cell mass of blastocysts of different species, including human. They can be totipotent (be able to generate all cell types in an organism except the placenta), pluripotent (the ability to yield mature cell types from all different germ layers), or multipotent (be able to give rise to all cells within an organ). Work performed with mouse ESCs has provided proof-of-principle that pluripotent cell lines can be harnessed for developmental biological studies as well as for new therapeutics. Since significant species differences exist between

mouse and human ESCs (hESCs) regarding signaling pathways and molecular regulation of pluripotency, it is pivotal to fully characterize and define the molecular mechanisms in human ESCs. Currently, our understanding of human ESCs cells is increasing and knowledge is being accumulated on improved cell culture conditions, long-term propagation, controlled differentiation, and transplantation into animal models of human disease.

The list of various cell types differentiated from human ESCs (e.g., neurons, cardiomyocytes, hepatocytes) is continuously increasing. Pluripotent ESCs can be stepwise differentiated in the culture dish by recapitulating aspects of in vivo development and the use of relevant epigenetic factors. Importantly, the acquisition of a particular developmental stage of a cell is best characterized by considering morphological, immunophenotypic, and functional criteria. The unlimited access to specific functional human cells is expected to play an important role not only in therapeutic cell replacement but also for disease modeling and drug screening.

Neural Stem Cells

In contrast to pluripotent hESCs, somatic stem cells are believed to be multipotent, thereby capable of generating the major cell types limited to the tissue of origin. Typically, NSCs are capable of producing neurons, astrocytes, and oligodendrocytes. Somatic/tissue-specific stem cells are the building blocks of organs during development and survive in specialized microenvironments ('stem cell niche'), contributing to new cells throughout life. NSCs (1) are multipotent (the ability to yield mature cells in all three fundamental neural lineages throughout the nervous system: neurons; astrocytes; and oligodendrocytes), (2) have the ability to populate a developing region and/or repopulate an ablated or degenerated region of the CNS with appropriate cell types, and (3) undergo 'self-renewal,' that is, the ability to produce daughter cells with identical properties. NSCs are highly abundant during embryogenesis, with a sharp decline shortly after birth. In the adult nervous system, NSCs are confined to the subgranular zone (SGZ) in the dentate gyrus of the hippocampus and the subventricular zone (SVZ) lining the lateral ventricles. The newly born neurons in hippocampus have been suggested to improve memory and play a role in mood behavior such as stress and depression. Neuroblasts born in the SVZ migrate along the rostral migratory stream (RMS) to the olfactory bulbs, where they differentiate into periglomelular and granule neurons. Isolation of cells from brain regions such as amygdala, substantia nigra, and cortex has included cells with stem cell characteristics in vitro. Morphologically, NSCs share properties with both astrocytes and radial glia. The main characteristic is a long process that extends radially. Although no definitive marker has been suggested for neural stem cells, a substantial amount of work shows that they are positive for nestin, an intermediary filament protein, and glial fibrillary acidic protein (GFAP), used traditionally to identify astrocytes.

NSCs or progenitor cells with a more restricted developmental potential can be generated from hESCs or directly isolated from the developing CNS as well as from neurogenic regions of the adult brain. Historically, the first established NSCs lines exploited the knowledge accumulated on tumor viruses and immortalization. These cell lines have been invaluable in expanding our experience on basic stem cell biology and neural repair. Some of these multipotent cell lines, such as the C17.2 NSC line, are still widely used. However, NSCs that have not been genetically modified can also be propagated in vitro for extended periods of time, using high concentrations of mitogenic factors such as basis fibroblast growth factor (bFGF) and epidermal growth factor (EGF). Neural stem/progenitor cells have been cultured as monolayers on coated substrates or as free-floating spherical aggregated, termed neurospheres.

Stem Cell Repertoire

Chaperone Effects

Initially, stem cells were considered as exclusive tools for cell replacement. However, there are multiple evidence now for robust additional biological properties ('chaperone effects') of stem cells that may be exploited therapeutically. Chaperone effects of stem cells include the natural delivery of neurotrophic, cytoprotective, and antiinflammatory molecules (e.g., GDNF, BDNF, NT-3) in order to rescue dysfunctional cells. This concept of stem cell-based chaperone effects was first demonstrated in the brain of aged and parkinsonian mice and later confirmed and extended to other organ systems and various diseases (e.g., bone marrow-derived mesenchymal stem cells or embryonic stem cells for cardiac disease, umbilical cord cells in stroke).

Environmental Cues

Increasingly, the microenvironments within the CNS are providing insight into the molecular milieu regulating stem cell biology. A specialized microenvironment in the neurogenic regions is responsible for the continued self-renewal and differentiation of the stem cell pool. For example, these regions have a higher density of blood vessels releasing factors, such as vascular endothelial growth factor (VEGF) and brain-derived neurotrophic factor (BDNF), contributing to increased proliferation and neurogenesis. Different levels of growth factors can have fundamentally different effects on proliferation and differentiation. For example, low levels of insulin-like

growth factor-1 (IGF-1) promote neurogenesis, whereas higher levels increase proliferation and oligodendrogenesis. Established protocols for the isolation of neural stem cells include the growth factors epidermal growth factor (EGF) and bFGF that sustain self-renewal of NSCs. Injection of these factors intracranially into mice have shown to regulate both proliferation and differentiation in vivo. Neurotrophins such as BDNF in collaboration with retinoic acid and Wnt signaling regulate neurogenesis; with ciliary neurotrophic factor (CNTF)/leukaemia inhibitory factor (LIF) or bone morphogenic proteins (BMPs), induce gliogenesis. It is also know that the cellular milieu contributes to fate determination and cortical development, specifically through the effects of resident astrocytes in both the subventricular zone (SVZ) and hippocampus. Physical exercise and enriched environment have been shown to promote neurogenesis in the SGZ. The effects from physical activity are partly mediated by IGF-1, VEGF, BDNF, and endogenous opioids. The characterization of the stem cell microenvironment will provide the molecular and cellular scaffold upon which stem cell therapy, both endogenous and exogenous, can be built.

Stem Cells as Vectors for Gene Therapy

Brain lesions can be focal and restricted to a certain region or widely distributed in the parenchyma. Ideally, both lesion types would be targeted with a specific and efficient delivery of therapeutic molecules and drugs. In fact, efficient delivery is still a major hurdle in gene therapy. The finding that endogenous and grafted NSCs display an extensive migratory potential and tropism toward brain lesions founded the idea that these cells may be used as therapeutic vectors. Proof-of-principle experiments in animal models of lysosomal storage diseases (example for a widely distributed brain lesions) and brain tumors (example for a focal lesion) have shown that genetically modified NSCs are powerful therapeutics to cross-correct hereditary enzymatic deficiencies or to dramatically reduce a tumor mass. Thus, NSCs hold great promise for both cell and gene therapy.

Stem Cell-based CNS Repair

It is manifest that stem cells can be used to replace neuronal, astrocytic, and oligodendroglial cells lost because of various brain diseases. However, it is important to note that a successful use of stem cells is probably dependent on many factors, including the nature and degree of injury, disease history and age of the patient, primarily affected cell types, type of stem cell chosen for transplantation, and the site of grafting. A deeper insight into these parameters is important to tailor patient-specific treatment paradigms in a clinical context.

Stem cells have been explored in a number of rodent and primate models of human neurological diseases. These studies showed successful survival, differentiation, and synaptic integration of grafted stem cells which led to functional restoration and amelioration of symptoms. In the following, we highlight some examples of stem cell-based CNS repair and discuss the challenges that remain to be addressed prior to clinical application.

Parkinson's Disease

Parkinson's disease (PD) is characterized by a progressive deterioration and loss of nigrostriatal dopaminergic neurons in the substantia nigra. The consequence of this cell death in the ventral midbrain is a deficient dopamine neurotransmission in the target region, the striatum. Clinically, the PD presents with clinical symptoms such as tremor, rigidity, and bradykinesia. Patients transplanted with fetal mesencephalic grafts in the early 1990s have demonstrated that an ectopic transplantation of dopamine-producing cells into the striatum can restore motor function and ameliorate clinical symptoms. Because of the limited availability of fetal tissue, stem cells are expected to provide unlimited numbers of transplantable dopamine neurons.

Several studies using rodent and primate models of PD have demonstrated successful integration and functional improvement after the grafting of dopaminergic neurons derived from both ESCs and NSCs. In primate models, monkey embryonic stem cells have been transplanted and animals evaluated for behavioral improvements. As with the rodent models, functional improvements occur. Furthermore, these behavior assessments can be corroborated with functional neuroimaging (**Figure 1**).

The considerable progress in stem cell-based treatment of PD in animals still faces many challenges before clinical translation. Human ESCs differentiate to dopaminergic neurons under various protocols, yet the creation of a purified and homogenous population of dopaminergic neurons is challenging and needs improvement. Animal models for future investigation should increasingly include primates in order to refine the mechanics and logistics of transplantation. Patients in whom stem cell therapy will be the most effective with the least side effects should be defined. The effects of posttransplantation training and rehabilitation need to be better understood. It appears that these contribute to improved functional outcome in experimental animal models. The clinical experience with fetal grafts suggests that the patient's disease history is an important parameter and that cell therapy will fail to be the method of choice for every parkinsonian patient, and therefore, patient selection will be pivotal to clinical improvements after graft

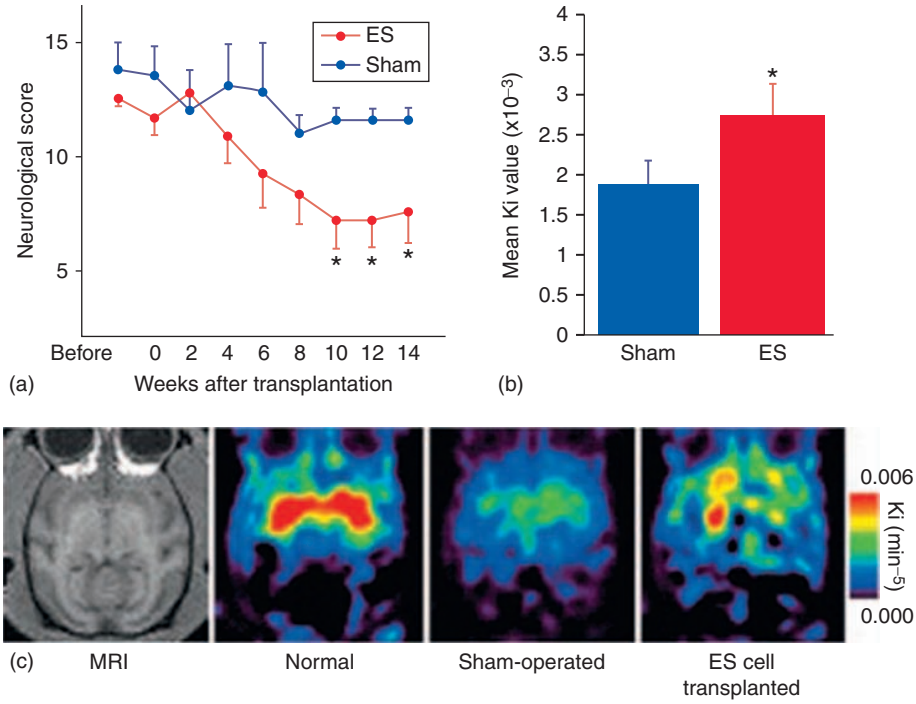

Figure 1 Function of ES cell-derived neurospheres in MPTP-treated monkeys. Behavioral scores (a) and PET study (b, c) of ES cell-transplanted ($n = 6$) and sham-operated animals ($n = 4$). (b) Mean K_i values from entire putamen. (c) Increased ^{19}F-fluorodopa uptake in the putamen of ES cell-transplanted animals. All values are mean ± SD. $P < 0.05$. Reproduced from Takagi Y, Takahashi J, Saiki H, et al. (2005) Dopaminergic neurons generated from monkey embryonic stem cells function in a Parkinson primate model. *The Journal of Clinical Investigation* 115: 102–109.

placement. Finally, the adverse effects such as dyskinesias observed in some patients after transplantation of fetal grafts need careful consideration, and further, the safety of hESCs needs to be established prior to clinical transplantation.

Huntington's Disease

Huntington's disease (HD) is a progressive neurodegenerative disease resulting in cognitive and motor impairments and death. Neuronal dysfunction and degeneration contribute to progressive physiological, motor, cognitive, and emotional disturbances characteristic of HD. The mechanism of the disease is not fully understood, but a number of factors have been identified. A mutation in the Huntingtin gene causes the production of an abnormal form of the protein huntingtin, which in turn produces cellular and anatomical changes in the brain. There is no cure for HD, although there are treatments to relieve some of its symptoms. Research into the treatment of HD has centered on cell therapy strategies to protect vulnerable neuronal cell populations or to replace dysfunctional or dying cells that include therapy with the potential for self-repair through the manipulation of endogenous stem cells and/or neurogenesis, the use of stem cell transplantation as a cell replacement strategy, and the administration of neurotrophic factors to protect susceptible neuronal populations. These approaches have shown some promising results in animal models of HD.

Stem cell therapy in adult patients with HD has received an increasing attention for its potential to alleviate pathological neurodegeneration by replacing lost neuronal and/or glial populations, by triggering endogenous repair mechanisms, or by protecting existing cells primarily through trophic support. Stem cell transplantation is a promising field in cell therapy for HD, as stem cells are relatively easy to obtain compared with primary fetal tissue and have the potential to be manipulated to eliminate possible problems of host rejection. Transplanted ESCs have been shown to differentiate into neurons in the HD-affected striatum and appear to migrate to nearby cortical regions where they have been found to express markers of immature neurons.

Recent work in stem cell therapy has been conducted in animal models of HD. However, protocols and procedures developed from trials of hESCs transplantation in patients with HD will lay the groundwork to move stem cell therapy into the clinic. One of the first challenges to stem cell therapy in HD is to determine which source of stem cells is most efficacious, and many sources have been examined. In addition to hESCs, stem cells derived from mesenchymal cells in adults have been investigated

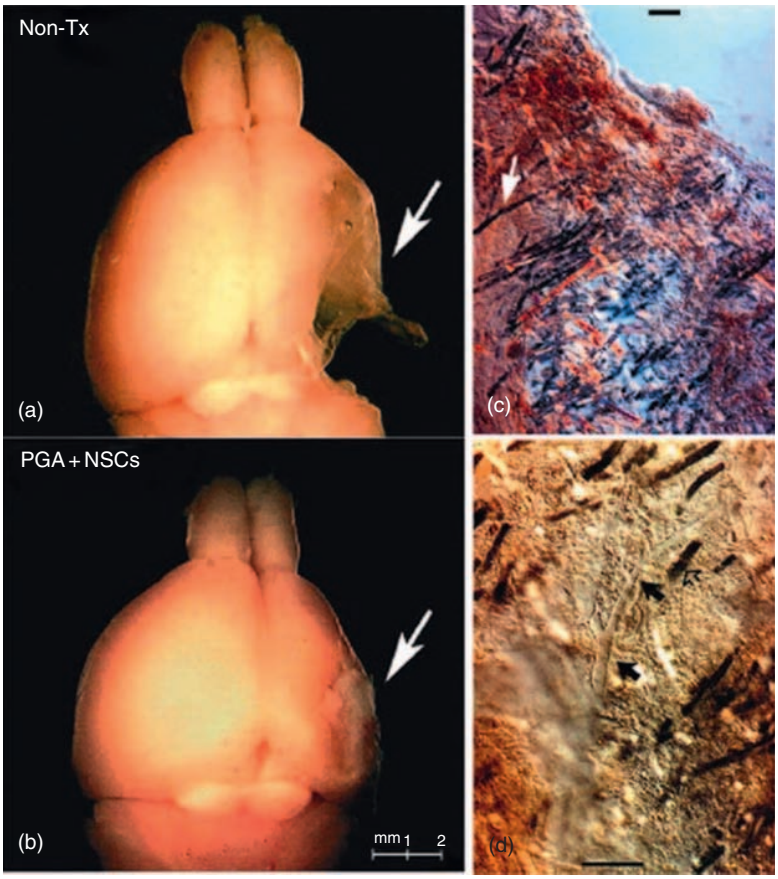

Figure 2 Implantation of NSC–PGA complexes into a region of cavity formation following extensive HI brain injury and necrosis. (a) Brain of an untransplanted (non-Tx) mouse subjected to right HI injury with extensive infarction and cavitation of the ipsilateral right cortex, striatum, thalamus, and hippocampus (arrow). (b) Contrasting with (a), the brain of a similarly injured mouse implanted with an NSC–PGA complex (PGA + NSCs), generated in vitro as described in (a), into the infarction cavity seven days after the induction of HI (arrow; $n = 60$). At maturity (age-matched to the animal pictured in (a)), the NSC–scaffold complex appears, in this whole mount, to have filled the cavity (arrow) and become incorporated into the infarcted cerebrum. (c, d) Higher magnification of representative coronal sections through that region, in which parenchyma appears to have filled in spaces between the dissolving black polymer fibers (white arrow in (c)) and even to support neovascularization by host tissues, as seen in (d). A blood vessel is indicated by the closed black arrow in (d); open arrow in (d) points to degrading black polymer fiber. The neural composition of that parenchyma is examined by immunocytochemistry in **Figures 4** and **5**; degrees of monocyte invasion and glial scarring are examined in Fig. 6. Scale bars: (c, d) 100 μm. Reproduced from Park KI, Teng YD, Snyder EY (2002) The injured brain interacts reciprocally with neural stem cells supported by scaffolds to reconstitute lost tissue. *Nature Biotechnology* 20: 1111–1117.

as a readily available source of stem cells in HD. Although few neurons have been formed from mesenchyme-derived stem cell grafts, transplantation of these grafts has elicited some behavioral recovery.

The differentiation of stem cells or treatment with growth factors in vitro prior to transplantation may facilitate fate determination while decreasing the risk of tumor formation posed by stem cells. One such protocol in which mouse embryonic cells directed toward a GABAergic fate retain their neuronal identity after transplantation into a rodent lesion model of HD has proved successful. Therefore, stem cell therapy for HD has the potential to alleviate cognitive and motor deficits in degenerative disease through the replacement of degenerating cells and the restoration or preservation of proper network function.

Endogenous Stem Cell Recruitment for CNS Repair

The alternative or compliment to stem cell transplantation would be the manipulation of endogenous stem cells for therapeutic purposes. The advantages would include using the patient's own cells, not needing an invasive procedure, and obviating the concern over the immunogenicity of transplanted cells. It appears that adult neurogenesis is restricted to the olfactory bulb and dentate gyrus of the hippocampus, yet it is possible that some NSCs exist along the entire adult neuraxis.

Exploiting endogenous NSCs would require successful coordination of cell proliferation, differentiation, migration, and integration, and it does appear that some

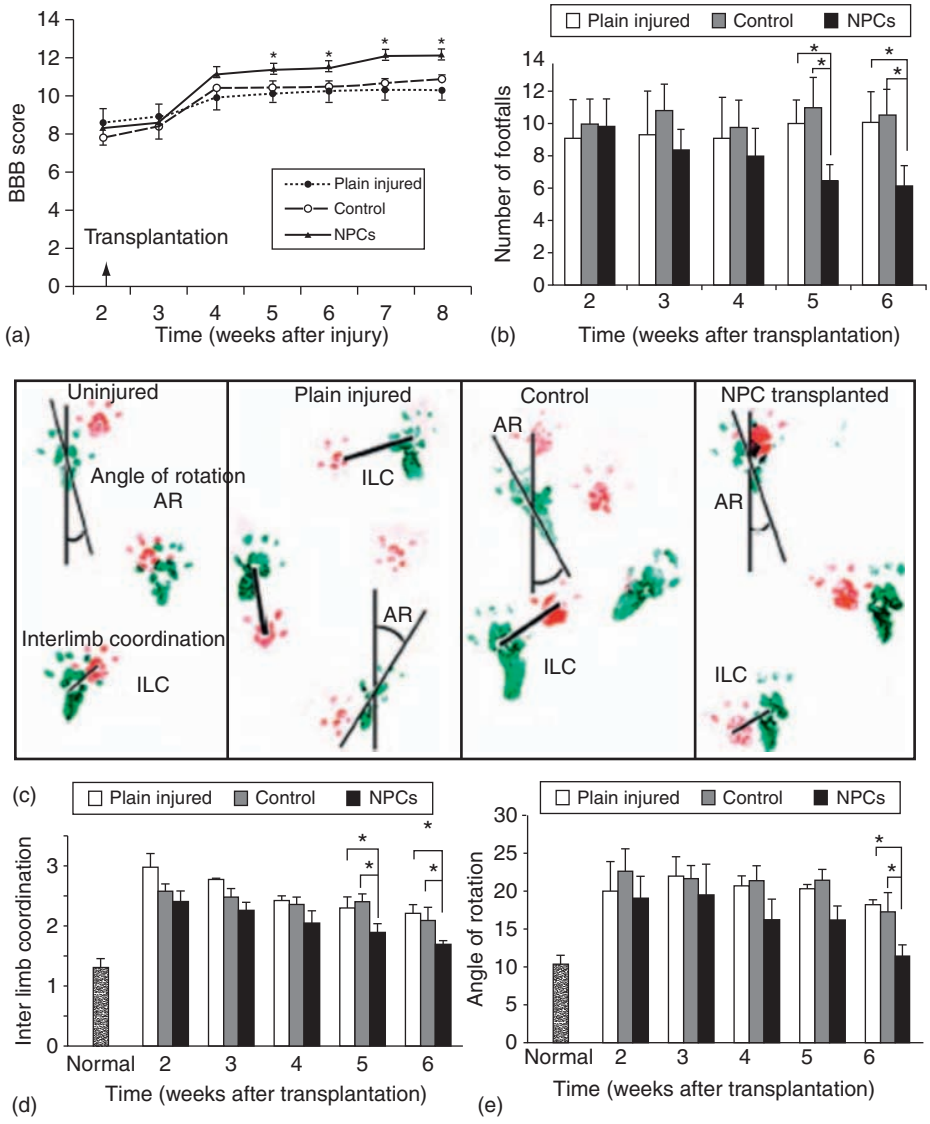

Figure 3 Subacute transplantation of YFP-NPCs resulted in a significant locomotor recovery compared with injured rats in the control group. (a) BBS rating scale showed a significant improvement in the locomotor BBS score in transplanted rats at 3 weeks after transplantation compared with the plain injured and control groups ($n = 5$ for plain injured group and $n = 8$ for other groups). (b) Using grid-walk analysis, transplanted rats also showed fewer errors in hindlimb placements at 5 and 6 weeks after transplantation compared with the plain injured and control groups ($n = 5$ for plain injured group and $n = 8$ for other groups). (c) Representative footprints of normal, plain injured, control, and grafted rats ($n = 5$ for plain injured group and $n = 8$ for other groups) shows improvement in interlimb coordination as well as angle of rotation in the transplanted group compared with the plain injured and control groups. (d, e) Footprint analysis revealed that transplantation with adult NPCs significantly improved interlimb coordination and reduced the hindlimb angle of rotation at 5 and 6 weeks after transplantation. The data show the mean ± SM. $^*p < 0.05$. Reproduced from Karimi-Abdolrezaee S, Eftekharpour E, Wang J, et al. (2006) Delayed transplantation of adult neural precursor cells promotes remyelination and functional neurological recovery after spinal cord injury. *Journal of Neuroscience* 26: 3377–3389.

instructive signals remain in the adult CNS. However, most CNS regions are not permissive for neurogenesis under normal in vivo conditions, yet some studies suggest that endogenous NSCs are primed to respond to environmental signals that exist primarily during pathological states. Accordingly, one approach to accentuate endogenous stem cell proliferation is with the administration of growth factors. Intraventricular infusion of transforming growth factor α (TGF-α) into rodents with lesions of the substantia nigra dopaminergic neurons has led to functional improvements, putatively through recruitment of endogenous stem cells. Other likely bioactive molecules with potential to evoke a proliferative response, in regions of the brain with multipotent cells, are neurotrophins. Physiologically, neurotrophins are involved in cell cycle regulation, cell survival, and differentiation and are

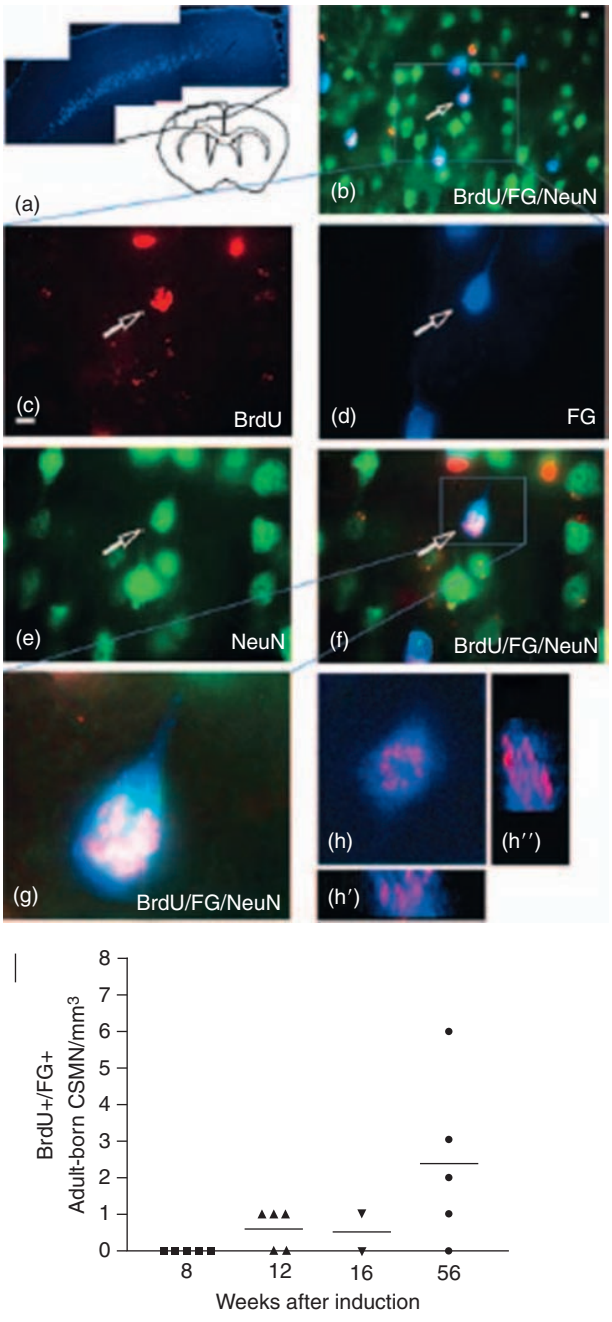

Figure 4 A subset of newborn layer V cortical neurons extends axons to the cervical spinal cord. (a) Both newborn and original layer V CSMN were retrogradely labeled by FG (blue). (b) Field expanded in C–F showing a BrdUrd+/NeuN+/FG+ triple-labeled adult-born neuron (arrow). (Bar, 10 μm.) (c–e) Individual images show that this BrdUrd+ nucleus (c, red) is located within this neuron, which is retrogradely labeled with FG from the cervical spinal cord (d, blue) and express NeuN (e, green). (Bar, 10 μm.) (f) Overlay showing BrdUrd+/FG_/NeuN+ neuron colocalization. (g) Higher-magnification overly of the same neuron from (c) to (f). (h) A separate example of an adult-born neuron with a projection to the spinal cord. Laser-scanning confocal images were combined to produce 3D reconstructions of newborn neurons. Viewing a BrdUrd+/FG+ newborn beuron along its *x*(*H*′), *y*(*H*′′), and *z* axes (*H*) unequivocally demonstrates the colocalization of BrdUrd and FG. (i) Quantification of BrdUrd+/FG+ adult-born CSMN extending spinal projections from 12 to 56 weeks after induction of original CSMN apotosis. Each point indicates the number of adult-bron BrdUrd+/FG+ neurons per mm^3 in an individual animal; each bar indicates the mean. Reproduced from Chen J, Magavi SS, Macklis JD, et al. (2004) Neurogenesis of corticospinal motor neurons extending spinal projection in adult mice. *PNAS* 46: 16357–16362.

critical during normal development. Growth factor infusion can also promote proliferation of SVZ-derived progenitor cells that gave rise to hippocampal CA1 pyramidal neurons in rodent stroke models, with improvements in spatial orientation. Whether the neurogenic response creates neurons with long-term viability remains to be shown. Another candidate with efficacy in stroke models is erythropoietin (EPO), which has been shown to induce neurogenesis and functional improvement in rats. Furthermore, endogenous neural precursors can differentiate into new neurons that extend long-distance projections to the spinal cord, in the adult rodent. Targeted apoptosis of corticospinal motor neurons was induced and it was demonstrated that adult-born corticospinal motor neurons were generated extending from the motor cortex to the spinal cord (**Figure 4**).

The horizon for neural repair includes continued investigation into whether the diseased CNS can be treated with growth and differentiation factors to induce neural repair. As more is learned about the molecular signals and environmental cues, endogenous stem cells may prove to be a compliment or even replacement to transplantation of exogenous stem cells.

Other Stem Cells

The use of embryonic or somatic stem cells for brain repair is currently in the focus of rigorous scientific investigation. Other stem cells have also been suggested as sources for cell therapy. For instance, some groups have found that mesenchymal stem cells (MSCs) can differentiate into astrocytes and neurons *in vitro* and *in vivo*, and may have the advantage over ESCs or NSCs of being a highly accessible source for the patient's own stem cells. However, there is ongoing controversy about the plasticity and developmental potential of MSCs. Some groups suggested that the findings made with MSCs may be cell culture artifacts rather than being true differentiation into unexpected cell types. Therefore, it is crucial to assay the differentiation of any stem cell into a particular cell type by combining morphological, immunophenotypic, and functional criteria. Currently, MSCs do not appear as a realistic alternative to the use of ESCs or NSCs for neural repair.

Conclusion

Stem cell biology represents a strong foundation for neural repair. So far, gained experimental evidence suggests that this technology may be applicable to treat patients in the future. Since hESCs can be multiplied indefinitely and have the potential to give rise to a variety of functional human cells, it is conceivable to believe that stem cells will play an important role in disease modeling and drug testing. Moreover, since stem cells mimic aspects of normal development, these cells may be used to study early steps of human development that would not be accessible to experimentation otherwise.

We have highlighted current problems in the rapidly progressing stem cell field which involve safety issues, standardization of the protocols used, development of rigorous assays for characterization, and accumulation of experimental data in primate models of human disease. Realistic candidate diseases and patients that may benefit from stem cell therapy need to be defined before any clinical application. Since clinicians and stem cell biologists share a strong common interest to understand and treat human disease, stem cells have the true potential to transform modern medicine.

See also: Huntington's Disease; Parkinson's Disease: Definition, Diagnosis, and Management; Transplantation.

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Stepping (Forelimb Akinesia) Test

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Glossary

Adjusting step – A catch-up step by the legs to maintain center of gravity and stable balance in response to being pushed over-ground. This movement is impaired in animal models of Parkinson's disease.

Akinesia – A loss or severe reduction in the ability to self-initiate walking movements.

Bracing – A leg-skid reaction to being pushed over-ground that reflects impaired capacity to make catch-up steps, but helps to maintain stable equilibrium and center of gravity when the legs cannot step adequately.
Catalepsy – Loss of spontaneous movement characterized by muscle tension in the flexor and extensor muscles without loss of the capacity to engage in bracing reactions or labyrinthine righting reactions to maintain static stable balance.
Catch-up step – A leg step to adjust to an imposed shift of weight. The step helps to maintain center of gravity and stable balance in response to being pushed over-ground. This motor response is impaired in animal models of Parkinson's disease.
Dopamine – A neurotransmitter that is progressively lost in the brains of patients with Parkinson's disease.
Parkinson's disease – A neurological disorder characterized by a progressive loss of dopamine cells in the substantia nigra of the midbrain, and by severe motor symptoms that include difficulty in initiating stepping and related movements for walking.

Introduction

Progressive degeneration of dopamine (DA) neurons in the substantia nigra, in Parkinson's disease, leads to impaired capacity to initiate movement (akinesia). Patients with this disorder often freeze when trying to walk. They also do not respond quickly enough and effectively when pushed off balance, and must be caught by the examiner to prevent falling. These parkinsonian symptoms also appear in patients with schizophrenia who have been treated with high doses of traditional antipsychotic agents that block the DA synaptic transmission. To explore brain events associated with akinesia and postural instability, and to develop new treatments, it is imperative to be able to model these motor symptoms in animal models. Parkinsonian signs can be observed and quantified in rats that have been given a neurotoxin that kills DA cells or DA antagonist drugs.

Rat Tests to Assess Stepping Deficits

The effects of severe bilateral loss of DA neurons or drugs that completely interfere with DA synaptic transmission in rats are marked. Spontaneous movement is lost. The animal cannot initiate stepping, and when pushed forward or sideways on a smooth surface, it will brace against the movement or will drag its limbs. If the rat's hindlegs are lifted off the ground, it is unable to initiate stepping with the forelegs. In contrast, normal rats can walk on their forelegs without any problem, and respond to being pushed in this wheelbarrow-like fashion with excellent reactive stepping, each step precisely adjusted in size to maintain center of gravity.

If the DA deficiency is limited to one hemisphere, stepping can be assessed in each foreleg independently by lifting not only the hindlegs but also each foreleg, one at a time. In this case, the animal can self-initiate walking when the weight is supported by the ipsilateral foreleg, but not when its weight is supported only by the foreleg contralateral to the DA deficiency. When pushed by the experimenter on a smooth surface, the contralateral foreleg may brace or drag instead of making adjusting (catch-up) steps to maintain center of gravity. The number of catch-up steps made over a set distance is reduced as a result.

This test may be comparable to the push–pull exam used to observe postural instability in Parkinson patients, who fail to step adequately or quickly enough to maintain center of gravity. In rats, if the surface is sticky (e.g., sandpaper), and the animal's center of gravity is slowly relocated by the experimenter, the contralateral limb does not drag or brace, but instead will lag behind substantially and make an adjusting step only when the extent of the imposed weight shift is abnormally large. That is, the distance (step size) covered by the contralateral foreleg during the weight shift will be longer than normal in this case. This effect may be analogous to the patient with Parkinson's disease who does not respond adequately to being pushed or pulled by force, and must be caught by the examiner to prevent falling.

The anti-Parkinson drug levodopa can partially reverse stepping deficits in rats if the DA depletion is not complete, but the occurrence of dyskinesia makes assessment difficult. However, if levodopa is combined with an anticholinergic drug, both self-initiated and experimenter-imposed stepping reactions are improved markedly.

Summary and Conclusion

Normal rats can walk on their forelegs when their hindlimbs are lifted off the ground. Rats with neurotoxin-induced bilateral DA deficiency cannot walk. When pushed forward or laterally they drag their forelegs. If the DA deficiency is unilateral, each foreleg can be evaluated independently by lifting both hindlegs plus one of the forelegs. When the contralateral (impaired) foreleg bears the weight, it cannot initiate stepping or react appropriately to an imposed shift of weight with a normal size catch-up step to maintain center of gravity. These unilateral deficits can be quantified easily in rats, and contribute to the reduced use of the impaired foreleg and increased use of the nonimpaired foreleg, during spontaneous vertical–lateral exploration of the walls of a cylindrical enclosure, proportional to the extent of DA cell loss.

See also: Basal Ganglia; Basal Ganglia, Functional Organization; Bradykinesia; Cylinder Test (Paw Reach Test); Foot Print Analysis; Freezing of Gait; Gait Disturbances in Parkinsonism; Gait Ignition Failure; Kinesia Paradoxica; Motor Impersistence; Neuroleptics and Movement Disorders.

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Relevant Websites

www.schallertlab.orgh – Schallertlab.

Stereology

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Glossary

Density ratio – When the value obtained is related to the ROI, it is said to be a density ratio (number per unit area, etc.). By definition, this is a fraction and the result could be due to changes in either (or both) the numerator or denominator. Failure to recognize this can lead to the investigator falling into the ''Reference Trap'' where an erroneous conclusion is made about which parameter changed. This can be avoided by determining total values instead of relying on density ratios.

Probe – A probe is a sampling device (line, circle, box, etc.) that interacts with the tissue being examined to generate a numerical value. This is not the physical insertion of this device into the tissue but the projection of tissue being sampled upon the probe (accomplished by a computer overlay on the microscope image). For counting cells, the optical disector probe places a two-dimensional counting frame upon the microscopic image to sample cells as they are encountered while the probe moves through the tissue.

Region of interest – The a priori definition of what is to be sampled, also abbreviated ROI. When this is not readily defined by natural boundaries, it should be clearly defined by whatever reliable anatomical references exist to ensure reproducibility of the data.

Systematic random sampling – To be statistically valid, cells should be counted at random. However, to make random sampling more efficient, systematic random sampling (SRS) randomizes the initial start site, and then subsequently moves the sampling field at a systematic defined distance through the tissue. This type of sampling is most powerful when applied in a nested sampling scheme, also known as a fractionated sampling scheme, where all levels of specimen examination (sectioning, staining, placement under the microscope, and focus depth) are initially randomized.

Definition and History

Stereology is the process of sampling and counting material using specific protocols to obtain an estimate of a quantitative parameter, such as number, length, volume, etc. Obtaining accurate estimates is a critical component of producing a study outcome with statistical validity. By using appropriate sampling procedures and applying counting or measuring protocols (known as probes), stereology makes it possible to avoid potential artifacts and errors that could significantly skew results. When appropriately applied, stereology can allow for reliable detection of differences only slightly greater than interanimal variation, that is, on the order of 15–20% differences between mean values. As changes of physiologically relevant ranges within tissue are often far below a fold difference, stereology provides a powerful analytical tool for in vivo histological studies. Stereology can often be applied to in vitro studies to improve sampling validity for quantitative parameters. The concepts related to stereological sampling have their roots in the mathematics of geometric probability that extend back to the Golden Age of Greece. While it has been applied to physical sciences and geology since the nineteenth century, the use of stereology in the biological sciences only began in the last half of the twentieth century. A major advance came in the mid-1980s when a number of papers established that it was possible to design conceptual probes to independently sample tissue, rather than relying upon geometric models of tissue structures themselves. This new design-based stereology has almost completely replaced the use of the older geometric model-based stereology in most biological research applications.

For studies of movement disorders, stereology can readily be applied to document pathological changes or loss of cells or innervation in experimental injury models. Careful quantitative outcomes from these studies can provide far more information than qualitative or semi-quantitative descriptions alone. Furthermore, they can be used in conjunction with quantitative values obtained from protein, molecular, or behavioral studies to explore relationships and potential correlations. Stereology is especially important for intervention studies where it becomes necessary to evaluate if the experimental manipulation can produce improvement in cell survival or outgrowth beyond the extent of spontaneous recovery. The quantitative resolution that stereology provides may permit conclusions to be drawn from such studies. As a result of the required comprehensive sampling necessary for a stereological study, the outcome measures can be known to apply to the entire structure with assurance. For example, the traditional approach of examining only sections through the middle of the substantia nigra for comparison has, at its core basis, validity only for the middle of that nucleus. If there were organizational or parametric changes that displaced or altered nuclear arrangement, these may bias the assumption that the centers were equivalent samples. All of these considerations are avoided by stereological sampling where sections through the entire structure provide the basis for the quantitative estimate. For cases where only a subset of the structure is the focus of study, such as the dorsolateral quadrant of the striatum for example, the region of interest can be defined to include just that region, provided sufficient objective landmarks can be used to make such a definition.

Modern design-based stereology has as its foundation the principle that any object within the tissue should have an equal probability of being counted. This is in contrast to the traditional histological studies that simply counted cells observed in the microscope field without allowance for the spatial organization of these cells with respect to the histological section in which they were embedded. Cells and fibers in tissue are distributed in three-dimensional space and any given section through the tissue will capture only parts of the cell. This reality can produce a number of artifacts, for which it is difficult to calculate a correction. Rather than attempting to correct for these problems, design-based stereology uses a probe that is designed (hence the name) to approach the object so that it will be encountered for measuring with equal probability in three-dimensions. These probes are not physical items inserted into the tissue, but rather frames that are superimposed upon the histological image. With the use of computer imaging, these can be seamlessly blended with the microscopic image for counting. In the case of counting cells, the optical disector probe places a box of known size within the tissue and cells are counted according to how they interact with this box. The optical disector probe avoids the problem of sampling large cells with higher probability, as would be the case if cells are counted in a single focal plane. For measuring length, it is possible to generate a sphere of known size and count the intersections of fibers with the sphere, a probe commonly known as 'spaceballs.'

While the probes themselves are powerful tools for avoiding the artifacts created by generating a tissue section, the nested sampling design in which they are applied to the tissue prevents the investigator from being led astray by changes in tissue parameters. The classical approach to evaluating changes in, for example, cell number was to express the results as a number per field or area or section. Of course, all of these are density ratios, meaning that the comparison between conditions is valid only if the parameter to which the number is related (field, area, section, etc.) does not differ between groups. However, pathological or experimental changes can often produce overall changes in tissue volume and the use of density measurements can produce erroneous conclusions, a problem known as the reference trap. Thus, stereological probes must be applied to tissue with appropriate systematic random sampling so that the entire

structure being examined is thoroughly sampled with statistical validity. The most efficient sampling design is a nested one where the fraction of sampling density is used to calculate the estimate of the total parameter. Such designs are known as fractionated sampling (i.e., a known fraction, such as 1/50th, of the structure was sampled) and they are named together with the probes they use (i.e., optical fractionator). Fractionated sampling schemes are not sensitive to volume changes and are thus the approach of choice for generating accurate estimates.

The statistical validity of the study is dependent upon the robustness of the estimate for each individual in the study. To ensure that each estimate was produced with sufficient rigor, it is necessary to assess the variance due to sampling for each individual in the study. Simply stated, this is a question of how much does one need to count to get a good estimate. The measure of this is assessed by calculating the coefficient of error (CE). The sampling density should be sufficient to produce a low CE value, in general, below 15% (0.15). If the value is too high, then the sampling should be redone at a higher density (more sections and/or more sites per section). However, it must be kept in mind that the CE is also a reflection of the heterogeneity of cell distribution and clustering, and that, with some tissue, it may not be possible to obtain such a low value, no matter how dense the sampling is.

While stereology is a powerful tool, there are some common pitfalls that the user must consider and potential artifacts that must be recognized. The following points are recommended as best practices for using stereology:

1. The entire structure to be quantified must be included in the available sections. If only a portion of the structure is sampled, the estimate produced is only relevant to that portion and any assumption that the data can be extrapolated to the entire structure will require validation.
2. As any portion of the section must be available for sampling, the specimen preparation must be uniformly suitable. Too many sample sites that are unavailable for counting due to preparation artifacts will erode the robustness of the estimator.
3. Most probes in design-based stereology rely on three-dimensional sampling through the tissue. Therefore, tissue section thickness must be thick enough (typically $>20\ \mu m$) to be useful.
4. It is necessary to validate that staining extends throughout the depth of the tissue section. The presence of a region in the section center devoid of staining will lead to an underestimation of an unknown extent.
5. The structure to be sampled (the region of interest) must be objectively designated as much as possible. Some structures have clear boundaries (e.g., the edge of the corpus callosum), however, many internal CNS structures blend into adjacent structures at their margins. Establishing a clear definition of structure margins (likely based upon cytoarchitecture) will assure reproducibility between investigators. Fortunately, fractionated sampling, such as obtained by using the optical fractionator procedure, does not require a firm bounding edge for estimation (as no area–volume calculations are needed), so this sampling is ideal for structures such as the substantia nigra.
6. Once a sampling scheme is decided upon, evaluate the coefficient of error (CE) values for each individual in the study. If the tissue is homogeneous, it should be possible to reduce this below 15% (0.15). If too high, increase sampling density to produce a reliable estimate. Ideally, this should be worked out early in the study to determine the optimal sampling. Each group in the study (i.e., experimental group versus control group) can be independently adjusted for optimal sampling. However, all individuals within a group should be sampled with the same scheme.

See also: 6-OH Dopamine Rat Model; Alzheimer's Disease and Parkinsonism; Caspases and Neuronal Cell Death; Confocal Microscopy; Dopamine Transporter: Aging and Parkinson's Disease; Dyskinesias: Animal Models; Glial Cell Activation in PD; Glial Cytoplasmic Inclusions; Huntington's Disease; Locus Coeruleus and Norepinephrine; MPTP; Multiple System Atrophy: Animal Models; Neurofibrillary Tangles; Neuroimaging, Parkinson's Disease; Neuronal Ceroid Lipofuscinosis; Neuroprotection in Movement Disorders; Parkinson's Disease: Animal Models; Stereology; Substantia Nigra; Transplantation.

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Stiff Person Syndrome and Variants

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Glossary

Central motor conduction time (CMCT) – The CMCT is a measure of corticospinal tract function, normally assessed by stimulating the motor cortex transcranially using a magnetic stimulator, which produces a motor cortical evoked potential (MEP) in contralateral muscle. The CMCT is estimated by subtracting the peripheral motor conduction time from the MEP latency.

Continuous motor unit activity (CMUA) – Involuntary sustained EMG activity distinguishable from other forms of repetitive EMG discharge and diagnostic of SPS.

Glutamic acid decarboxylase (GAD) – Enzyme and rate-limiting step in the synthesis of GABA.

GAD65 – The synaptic vesicle associated 65 kDa isoform of GAD.

H-reflex (or Hoffmann reflex) – A muscle reflex generated by the electrical stimulation of muscle afferent nerves (Ia fibers) analogous to the mechanically induced spinal stretch reflex.

Intracortical facilitation (ICF) – Paired pulse paradigm using transcranial magnetic stimulation (TMS), with an interstimulus interval of 6–15 ms, to test motor cortical excitability.

Long interval intracortical inhibition (LICI) – Paired pulse paradigm using TMS, with an interstimulus interval of 50–200 ms, to test cortical excitability.

Progressive encephalopathy with rigidity and myoclonus (PERM) – Variant of stiff-person syndrome.

Short interval intracortical inhibition (SICI) – Paired pulse paradigm using TMS, with an interstimulus interval of 2–5 ms, to test motor cortical excitability.

Stiff-limb syndrome (SLS) – Variant of stiff-person syndrome.

Witebsky postulates – A series of criteria originally developed by the German–American immunologist Ernst Witebsky to determine whether a condition could be considered autoimmune. These postulates require that

1. an autoimmune reaction is identified either by the presence of auto-antibodies or a cell-mediated immune response (typically by transfer of pathogenic antibody or pathogenic T cells into experimental animals);
2. the corresponding auto-antigen is known; and that
3. an analogous response causes a similar disease in experimental animals.

There should also be circumstantial clinical evidence to support a diagnosis of autoimmune disease (e.g., response to immunotherapy).

Definition and History

Stiff-person syndrome (SPS) was first described in 1956 by Moersch and Woltman, who reported a series of 14 patients (10 male and 4 female) collected over 32 years with fluctuating rigidity, spasms, and gait disturbance, but without evidence of extrapyramidal or pyramidal disease. Their first case was a 49-year-old man who farmed in Iowa and first presented to the Mayo Clinic in 1924, and consequently, the original report described the condition as 'stiff-man syndrome.' With increasing recognition of the syndrome, it has become apparent that the sexes can be affected equally, and therefore, the condition is now generally referred to either as SPS or Moersch–Woltman syndrome.

SPS is a rare, insidiously progressive autoimmune disease of the central nervous system, characterized by axial and appendicular rigidity, with superimposed stimulus-sensitive spasms. Antiglutamic acid decarboxylase (anti-GAD) antibodies, and more particularly, antibodies to the GAD65 isoform are present in serum or cerebrospinal fluid (CSF) of 60–80% of patients with SPS. Paraneoplastic SPS accounts for about 5% of cases and can be associated with antiamphiphysin antibodies (thymoma, bronchogenic adenocarcinoma, and breast carcinoma), anti-Ri (ANNA-2) antibodies (bronchogenic adenocarcinoma), and antigephyrin antibodies (undifferentiated mediastinal carcinoma), in addition to anti-GAD antibodies (breast carcinoma, multiple myeloma, thymoma, and renal cell carcinoma). However, paraneoplastic antibodies are not always detected. Postinfectious SPS and drug-induced SPS have also been described. The latter has only been reported with oral retinoids (e.g., isoretinoin, etretinate) and resolves following treatment cessation.

Prototypic SPS is considered to be part of a spectrum of related disorders, including stiff-limb syndrome (SLS), Jerking SPS, and progressive encephalomyelitis with rigidity and myoclonus (PERM), that share clinical, laboratory, electrodiagnostic, and histopathological features.

Some patients can present initially with SLS and progress over a period of years to classical SPS and PERM.

The annual incidence of SPS and its variants is about one per million in the European population. There is no consensus in the literature as to the distribution of SPS between the sexes; in some series, it appears to affect males more than females (~2:1), whereas in other series the reverse is true (~1:3). Typically, the condition first presents in the fourth to sixth decade.

Clinical Features and Diagnostic Criteria

The core features of classical SPS are stiffness and rigidity, in axial and proximal limb muscles, with superimposed stimulus-sensitive axial and appendicular spasms, but without evidence of brainstem, pyramidal, extrapyramidal or lower motor neurone signs, sphincter disturbance, sensory disturbance, or cognitive impairment (for diagnostic criteria see **Box 1**). Spasms can be provoked by stimuli, including voluntary movement, emotional triggers, and unexpected somaesthetic or auditory stimuli; are associated with intense pain; and can sometimes persist for days (*status spasticus*). Spasms can affect facial muscles and larynx causing stridor, and occasionally can be so severe in the limbs that they cause fractures. Continuous muscle contractions can cause board-like rigidity in the abdominal muscles, and cocontraction of abdominal and paraspinal muscles results in an abnormal axial posture, typically lumbar hyperlordosis. The gait is usually deliberate and slow and examination often reveals an exaggerated startle and head retraction (or glabellar) reflex, which fails to habituate. Paroxysmal dysautonomia, in the form of hyperpyrexia, diaphoresis, tachypnoea, tachycardia, pupil abnormalities, and arterial hypertension, can also occur.

Ocular abnormalities, including autoimmune retinopathy and scleritis, have been described in SPS. Motility disorders, including horizontal diplopia and nystagmus, and vertical diplopia and downbeat nystagmus, have also been described, but only in ataxic SPS or coexistent myasthenia gravis.

SPS is often mistaken for a psychogenic disorder, and historically, before Moersch and Woltman original report, all cases were considered thus. However, it is also recognized that psychiatric disorders, including anxiety, depression, alcohol abuse, agoraphobia, paroxysmal fear, task-specific phobia (fear and avoidance of situations because of motor symptoms of SPS), and phobic anxiety without avoidance, are frequent amongst patients with SPS. The absence of premorbid or inherent psychiatric disease would suggest that such disorders develop in SPS either as a consequence of the condition (and delayed diagnosis or misdiagnosis) or as a manifestation of the condition.

Box 1 Diagnostic criteria

Core diagnostic criteria

A. Positives

Stiffness and rigidity in axial muscles
Abnormal axial posture (90% lumbar hyperlordosis)
Stimulus-sensitive spasms (stimuli include voluntary movement, emotional upset, unexpected somaesthetic or auditory stimuli, e.g., see **Figure 1**)
EMG evidence of CMUA in at least one axial muscle (see **Box 2** and **Figure 1**)

B. Negatives

Absent brainstem, pyramidal, extrapyramidal and lower motor neurone signs
No sphincter disturbance
No sensory disturbance
Absence of chronic pain syndrome
No cognitive impairment (except seizure-related)

Supplementary diagnostic criteria

Stiffness and rigidity in proximal limb muscles
Resolution of rigidity and stiffness with IV benzodiazepines
EMG evidence of abnormal exteroceptive reflexes (see **Box 3**)
Serum anti-GAD65 antibodies > 20 nmol l^{-1} (60-90% of classical SPS patients)
CSF protein >0.6 g l^{-1} and/or WBC>5 and/or OCBs (60% of classical SPS)
CSF anti-GAD antibodies
Non-habituating startle response
Non-habituating head retraction reflex (i.e., glabellar reflex)

Associated clinical features

Ocular signs (see text)
Paroxysmal dysautonomia (hyperpyrexia, diaphoresis, tachypnoea, tachycardia, pupillomotor, hypertension)
Paroxysmal fear

Box 2 Electrodiagnostic criteria

Diagnostic features	Notes
CMUA	In at least one axial muscle (see **Figure 1**)
Cutaneomuscular (exteroceptive) reflexes	Widespread, non-habituating, low threshold responses to stimulation of tibial nerve, with simultaneous co-contraction of antagonists
Additional features	
Nonhabituating acoustic startle reflex	EMG recorded from axial and leg muscles
Increased cortical excitability	Silent period reduced by 20% compared to controls, increased ICF, and reduced SICI and LICI
Spasmodic reflex (propriospinal) myoclonus	Sequence of 1–3 synchronous myoclonic EMG bursts in trunk muscles 60–70 ms after median nerve stimulation
Blink reflex	R2 EMG component of blink reflex does not suppress after conditioning stimulus, whereas in controls R2 component suppresses for up to 1 s
Head retraction reflex	Stimulation of trigeminal nerve produces 12.5–20 ms response and 44–70 ms response in trapezius, which does not habituate

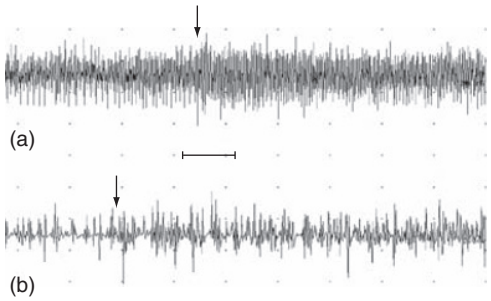

Figure 1 (a) Unrectified EMG recorded with a needle electrode from a lumbar paraspinal muscle in a patient with SPS showing continuous motor unit activity (CMUA) at rest. Recordings were made while the patient was lying prone and motionless on an examination couch. The arrow indicates the time at which an auditory stimulus was delivered. Note that the background firing frequency of the multiunit recording increases following the auditory stimulus and remains elevated (timebase is 20 s per division and amplitude is 2 mV per division). (b) The same recording as illustrated in (a) but displayed on an expanded timebase (10 s per division).

Pathophysiology

Impaired γ-amino butyric acid (GABA)ergic and glycinergic synaptic transmission is central to the pathophysiology of SPS. This functional impairment is thought be the result of reduced presynaptic transmitter synthesis, immunological destruction of inhibitory interneurones, or reduced postsynaptic receptor number. Both magnetic resonance spectroscopic studies and 11C-flumazenil positron emission tomography (PET) have shown either reduced GABA levels or reduced GABA binding (either representing receptor downregulation or neuronal attrition) in sensorimotor and limbic cortex of patients with SPS. Electrophysiological studies in SPS have shown that both GABAergic (vibration-induced inhibition of H-reflex) and glycinergic (early reciprocal inhibition and nonreciprocal (Ib) inhibition) inhibition is impaired within the spinal cord. However, in the same studies the GABAergic pathways mediating the presynaptic component of reciprocal inhibition, and recurrent (Renshaw) inhibition were normal, arguing against an indiscriminate autoimmune process involving only spinal inhibitory interneurones. One explanation for these findings is that stiffness and rigidity, much like spasticity, is determined by an imbalance in the strength of descending input, as a consequence of changes in the brainstem or intracortical inhibition.

Histological findings at postmortem have been variable. Initial reports failed to identify any abnormalities. However, more recent reports have described selective loss of GABAergic neurones within the cerebellum and the spinal cord, or a more aggressive inflammatory picture of perivascular lymphocytic infiltration and gliosis within spinal cord, brainstem, basal ganglia, and cerebral cortex. An autopsy in one patient, who presented initially with SPS but died several years later of PERM, showed both GABAergic neuronal attrition and evidence of perivascular lymphocytic infiltration and gliosis, suggesting perhaps that the spectrum of pathological findings is a reflection of the spectrum of disease severity and duration.

The evidence that SPS (and its variants) is an autoimmune disease, as defined by the Witebsky postulates, is manifold:

1. *Antibodies (including paraneoplastic antibodies) against a number of components of GABAergic and glycinergic synaptic function* (*see* **Figure 2**) *are found in the serum and CSF of 80–90% of patients with SPS.* Antibodies target the synthesis of GABA by anti-GAD65, trafficking of GABA receptors by GABARAP (GABA receptor associated protein), anchoring of GABA receptors by gephyrin and synaptic vesicle, and receptor recycling by amphiphysin.
2. *Only antibodies in CSF and serum from patients with SPS inhibit GABAergic function in vitro.* Electrophysiological studies have shown that CSF or serum anti-GAD65 antibodies from SPS (or ataxic) patients reversibly inhibit GABAergic transmission in rat cerebellar slices, whereas anti-GAD65 antibodies from patients with polyendocrine syndrome or type I diabetes mellitus do not.
3. *Serum antibodies from SPS patients can reproduce the clinical features of SPS in rats in vivo.* In rats, intraperitoneal injection of the purified IgG fraction of plasma from a patient with paraneoplastic SPS (breast carcinoma

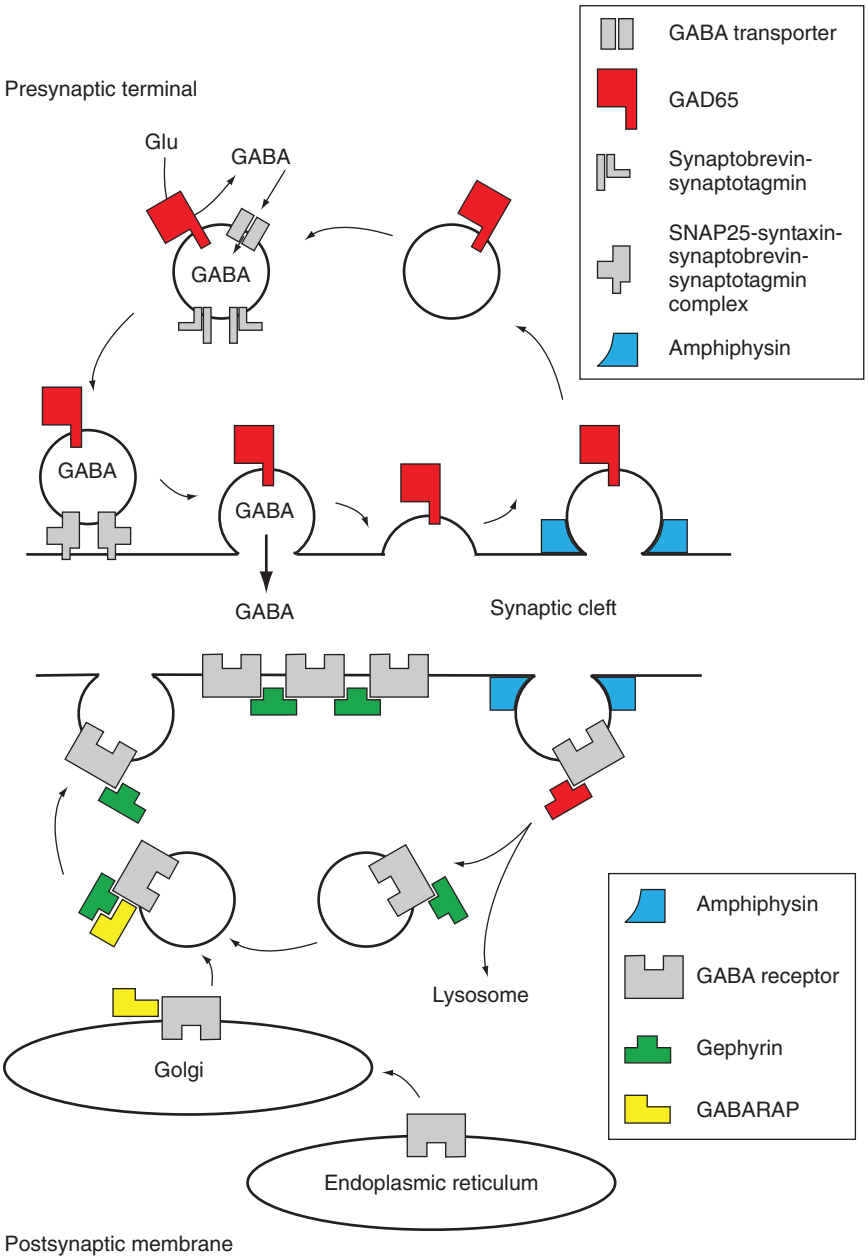

Figure 2 Auto-antibodies target cytosolic proteins in SPS. Most auto-antibodies in SPS target cytosolic proteins responsible for membrane trafficking at synapses and GABAergic synaptic function (except anti-Ri which targets an unidentified neuronal nuclear antigen). Protein targets are illustrated in colour in this simplified diagram of a GABAergic synapse, including presynaptic terminal, synaptic cleft, and postsynaptic membrane. GAD65 (glutamic acid decarboxylase) is the rate-limiting step in the synthesis of GABA from glutamate. Amphiphysin interacts with dynamin and cytoskeletal proteins during endocytosis to close-off the vesicle, and is therefore involved in synaptic vesicle formation and receptor recycling. Gephyrin anchors GABA (and glycine) receptors to the cytoskeleton, both for receptor trafficking and membrane stabilization. GABARAP (GABA receptor associated protein) binds to GABA receptors and is involved in receptor trafficking.

and antiamphiphysin antibodies) causes behavioral and electrophysiological changes consistent with SPS.

4. *Other antineuronal antibodies are found in SPS.* These include anti-ICA105 antibodies, anti-17β-hydroxysteroid dehydrogenase type 4 antibodies, and anti-Ri (ANNA2) antibodies in paraneoplastic SPS, which target a nuclear antigen within neurones.
5. *SPS is associated with other autoimmune diseases (and the presence of other tissue specific auto-antibodies).* For example, type I diabetes mellitus, Grave's disease, Hashimoto's thyroiditis, and pernicious anemia.
6. *SPS is associated with human lymphocyte antigen (HLA)-DQB1*0201 and HLA-DRB1*0301.*
7. *SPS responds to treatment with immuno-modulatory agents.*

The observation that GAD65 reactive CD4 positive T helper cells are present in SPS would also seem to support the hypothesis that SPS is a B-cell mediated disease. The molecular homology of peptide sequences from coxsackie virus, CMV, West Nile virus, and GAD65 might point to an environmental trigger for autoimmunity in SPS, and the description of postinfectious cases of SPS would appear to support this. However, disease severity in SPS is not correlated with anti-GAD titres, and although there is transmission of maternal anti-GAD antibodies to the fetus, unlike myasthenia gravis, neonates do not show evidence of SPS.

Whether anti-GAD65 antibodies (or any of the other SPS associated auto-antibodies described to date) directly cause SPS, are markers of autoimmunity, or are an epiphenomenon of neuro-degeneration, as seen in Batten disease (juvenile neuronal ceroid lipofuscinosis), is unclear. One well-rehearsed argument is that SPS autoantibodies must be an epiphenomenon, because they target intracellular proteins (see **Figure 2**), which are inaccessible to antibodies because of the barrier presented by the plasma membrane. GAD65, which is a synaptic vesicle associated protein, is a potential exception to this (see **Figure 3(a)**). However, only the membrane anchoring component is exposed during exocytosis, and not the enzymatic unit, which is largely cytosolic.

There is now increasing evidence that some antibodies can penetrate the cell membrane. Particularly polyreactive anti-DNA antibodies containing positively charged lysine and arginine-rich polypeptide sequences, as seen in systemic lupus erythematosus (SLE). These antibodies

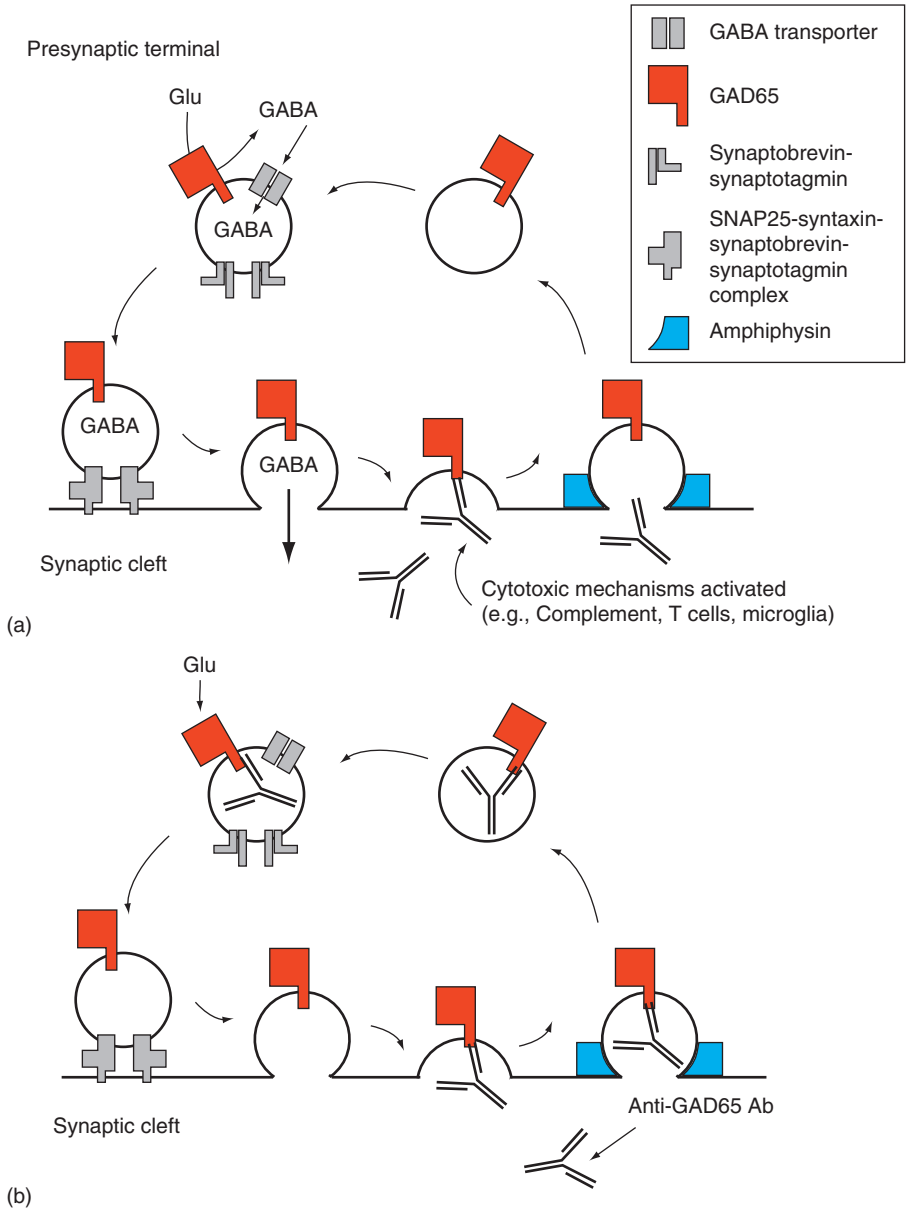

Figure 3 (Continued)

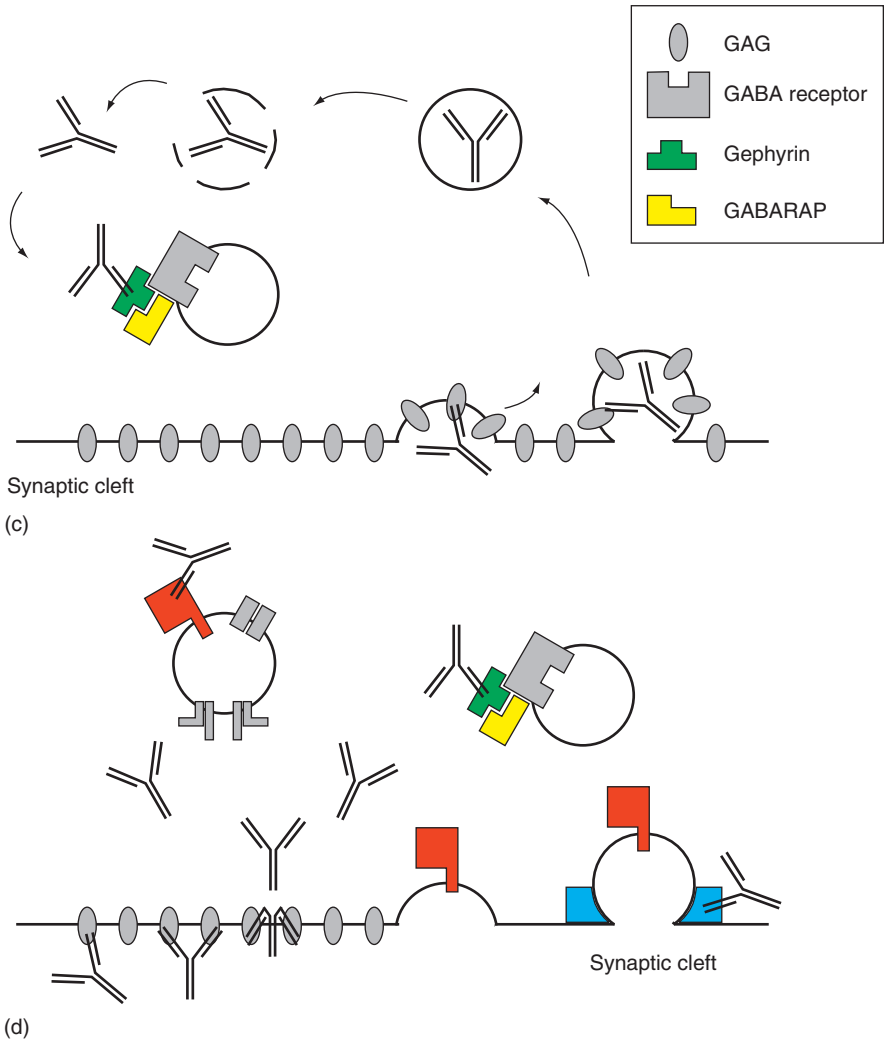

Figure 3 (a) Putative mechanisms by which auto-antibodies targeting cytosolic proteins inhibit GABAergic synaptic transmission in SPS. GAD65 is a vesicle associated protein. During exocytosis the membrane anchoring element is exposed to the extracellular milieu, presenting a potential target for antibody-mediated cytotoxic mechanisms. (b) Alternatively, antibody binds to GAD65 during exocytosis and is then incorporated into synaptic vesicles following endocytosis, where it inhibits GAD65 and prevents vesicle recycling. However, GAD65 antibodies bind to the enzymatic subunit, which is entirely cytosolic, and is not exposed during exocytosis. (c) SPS associated auto-antibodies bind to specific glycosaminoglycans (GAGs) and are endocytosed via energy-dependent mechanisms. The vesicle membrane is lysed by unknown mechanisms once the vesicle is intracellular (d). SPS associated auto-antibodies bind to specific glycosaminoglycans (GAGs), undergo conformational changes that result in amphiphatic alpha-helical structure that facilitates their insertion into the lipid bilayer and translocation into the cytosol.

bind strongly to specific glyosamino-glycans (GAGs) and enter the cell either by energy-dependent endocytotic mechanisms (**Figure 3(c)**), or by energy-independent conformational changes that result in amphiphatic alpha-helical structures that facilitate their insertion into the lipid bilayer (see **Figure 3(d)**).

Investigation

Box 3 contains a list of potential differential diagnoses of SPS and its variants, most of which can be excluded either by a thorough history and examination, or by routine laboratory or radiological investigations. If SPS is suspected, serum should be screened for anti-GAD antibodies (specifically anti-GAD65 antibodies), anti-GABARAP antibodies (if available), and paraneoplastic antibodies (anti-Ri, anti-amphiphysin, anti-gephyrin), and other tissue-specific auto-antibodies (e.g., antigastric parietal cell antibodies, antithyroid microsomal antibodies). Serum anti-GAD65 antibody titres are typically high (>20 nmol l^{-1}). Electromyography should demonstrate evidence of CMUA in at least one axial muscle (see **Figure 1**), with normal motor unit morphology (see **Figure 4**), which resolves with

Box 3 Differential diagnosis of axial and appendicular rigidity with continuous involuntary anterior horn cell activity and spasms

SPS (axial rigidity with CMUA ± spasms)
Trauma (Cervical spinal cord injury)
Cervical syringomyelia
Subacute necrotizing myelopathy
Inflammatory myelopathy (Atypical SPS)
Intrinsic spinal cord neoplasm (Cervical spinal cord astrocytoma)
Spinal cord infarction/ischaemia (Anterior spinal artery territory)
Acute/chronic/relapsing tetanus (Chronic toxin production in deep wounds)
Encephalomyelitis lethargica
Strychnine poisoning
Hyperekplexia (e.g., described in GLRA1 mutations)
Generalized dystonia (e.g., DYT1 causing stiff-child syndrome)

SLS/focal SPS (focal rigidity with CMUA ± spasms)
Neuroborreliosis
Acute poliomyelitis
Tetanus ascendans (See above)
Neuromyotonia/Isaac's syndrome (Easily differentiated on EMG)
Focal dystonia

Jerking SPS (rigidity + myoclonus)
MSAp
SCA-2

PERM (encephalopathy + rigidity + myoclonus)
Subacute sclerosing panencephalitis
Encephalitis lethargica
Drugs (e.g., neuroleptic malignant syndrome)
Serotonin syndrome
Opiate toxicity
Corticobasal degeneration
Creutzfeldt–Jakob disease
SCA3/Machado–Joseph disease (Single patient with 73 CAG repeats in the MJD gene)
Leigh syndrome

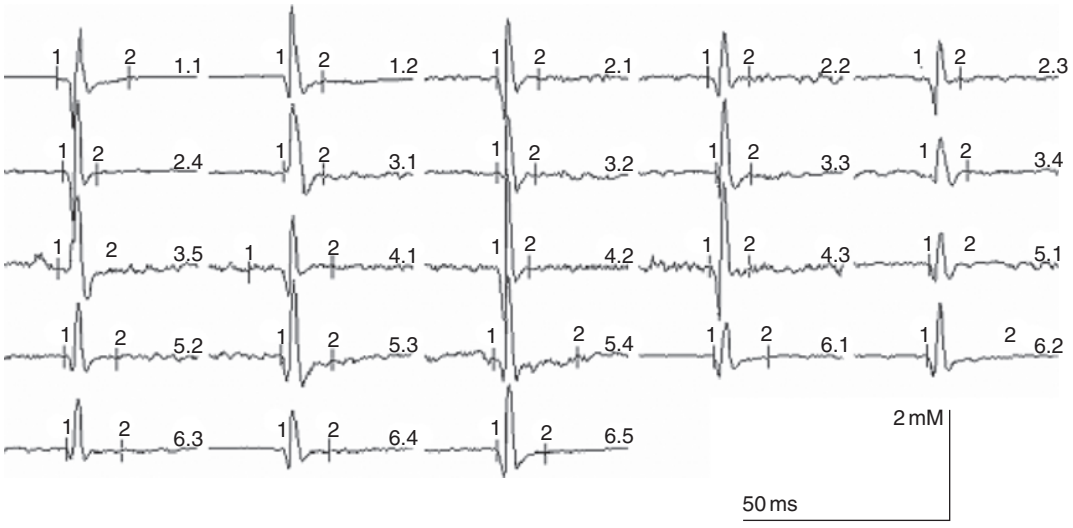

Figure 4 Averaged motor unit action potentials, generated using the Multimap™ program, from the recording illustrated in **Figure 1**. Note the normal duration, amplitude, and shape of the averaged motor unit potentials (Timebase 50 ms and amplitude 2 mV as indicated by horizontal and vertical bars).

intravenous benzodiazepines, and abnormal exteroceptive reflexes (see **Box 2**). CSF is abnormal in up to 60% of classical SPS (either protein $> 0.6\ g\ l^{-1}$ and/or WBC > 5 and/or oligoclonal bands (OCBs) and/or CSF anti-GAD antibodies). Magnetic resonance imaging of the neuraxis is normal in SPS.

If paraneoplastic antibodies or tumour markers are positive (or conversely if auto-antibodies, anti-GAD65 and paraneoplastic antibodies are all negative), further investigations should include CT chest, abdomen, and pelvis, mammography and PET, since treatment of an associated malignancy can either stabilize or reverse the features of SPS. In PERM, the risk of underlying malignancy is ~20%, and therefore, all patients should be screened, irrespective of the serology.

Management and Prognosis

Rigidity and spasms usually respond to GABA agonists such as benzodiazepines, baclofen, and tiagabine, and pain crises are usually managed with intravenous or subcutaneous opiates. Patients in whom rigidity and spasms are, or become, resistant to benzodiazepines can benefit from treatment with levetiracetam, intravenous propofol infusion, or intrathecal baclofen. Botox is a useful adjunct for treating severe rigidity as is muscle afferent block. Patients who continue to progress despite adequate symptomatic therapy, or who fail to respond symptomatically from the outset should be considered for disease-modifying therapy with immunomodulatory or immunosuppressive agents. Steroids, cyclophosphamide, and plasma exchange have all been used with varying success. However, the only disease-modifying therapy with prospective, randomized, controlled trial evidence is regular treatment with intravenous immunoglobulins. More recently, the specific B-cell depleting monoclonal antibody rituximab has been used successfully in a number of cases and is part of an ongoing trial in the USA.

Patients with prototypic SPS generally progress and then stabilize over a period of months to years. However, 10% will require prolonged admission to intensive care at some stage during the disease, and sudden death has been reported in as many as 10% of patients with prototypic SPS, typically because of unexplained metabolic acidosis or autonomic crises. The prognosis in SPS variants is more variable.

SPS Variants

Stiff-Leg (Limb) Syndrome (SLS) or Focal SPS

At least 30% of patients with SPS present initially with asymmetrical or unilateral rigidity and spasms in the arm or leg. However, there is a distinct entity first described as stiff-leg syndrome, but known either as SLS or focal SPS, in which stiffness and spasms are typically limited to the legs. Lumbar hyperlordosis is not a presenting feature, and progression to classical SPS is slow and only occurs in 75% of patients. Symptoms usually start in one leg before progressing to both legs after an interval of 6 months to 4 years, but in ~15% of cases SLS initially appears in the arm. Interestingly, unlike other variants of SPS, ~40% of patients have a preceding illness. Symptoms can resolve after 12 months, but typically persist for several years, and sometimes for as many as 20 years. In about 54% of patients with SLS, there is a relapsing-remitting course. Symptoms or signs of brainstem involvement, which are often transient, appear after 2 years in ~40% of patients. Sphincter involvement, including frequency, urgency, and urge incontinence, is present in 54% of patients after ~5 years. Unlike prototypic SPS with axial rigidity, the prognosis in terms of disability in SLS is poor, and about 50% of patients are wheelchair dependent after an average interval of 3.5 years.

SLS is twice as common in females and the age range at presentation is 18–71. Only three cases of paraneoplastic SLS has been described: in association with bronchogenic small cell carcinoma, breast carcinoma (and anti-GAD antibodies), and myeloma (and anti-GAD antibodies). Symptomatic therapy with diazepam and baclofen, while providing some relief from spasms, is ineffective at reducing stiffness and disability in ~75% of patients with SLS.

Alternative causes of focal stiffness and rigidity, with or without spasms (see **Box 3**), can easily be excluded by appropriate investigations. In SLS electrophysiological investigations are the most sensitive diagnostically and demonstrate core features of SPS (see **Box 2**). However, in 20% of patients, there is also evidence of denervation; in 75% there is an abnormal interference pattern on electromyogram (EMG) of the affected limb; and 13% have abnormal central motor conduction times (CMCTs). There is also asymptomatic evidence of CMUA in paraspinal and abdominal muscles in 30% of SLS patients. Of the 24 cases described in the literature, 11 (46%) had anti-GAD antibodies in CSF or serum, and 16 (70%) had auto-antibodies of some description. When the CSF is examined, in about 40% of SLS patients, there is a raised protein ($>0.6\ g\ l^{-1}$); in 10% there is pleocytosis (WBC $> 5\ \mu l^{-1}$); and in 20% there are unmatched oligoclonal bands. Histological examination of postmortem tissue from a single patient with paraneoplastic SLS was normal.

Jerking SPS

In the earliest descriptions of jerking SPS, patients had a protracted history of progressive appendicular and axial rigidity with spasms, identical to classical SPS,

before developing nocturnal myoclonus. The term 'jerking stiff-man syndrome' had not emerged until 1980, with the description by Leigh et al., and the condition is now generally referred to as jerking SPS. Patients initially present with the diagnostic features of SPS (see **Box 1**) and in the cases described there is progression over 2.5–14 years, with increasing appendicular and axial rigidity and spasms, before the onset of reflex reticular myoclonus. Although according to strict criteria there should only be clinical features of SPS and myoclonus, seizures, downbeat nystagmus, hyperreflexia, ankle clonus, and ataxia have been described in a minority of cases. Such features usually herald a more widespread encephalopathic process, involving cerebellum, brainstem, and cerebral cortex, akin to PERM.

In the patients from whom information is available, CSF parameters were normal (CSF was not tested for oligoclonal bands or anti-GAD antibodies), but postmortem histology confirmed clinical suspicions of a more widespread encephalopathic process. An autopsy in one patient, who died of chronic obstructive pulmonary disease, showed evidence of Purkinje cell loss within the cerebellum and neuronal loss within the lateral nuclei of the ventral horn of spinal cord, thalamus, and lateral *substantia nigra*. In a second patient, who died of central apnoea, there was widespread perivascular lymphocytic infiltration in the spinal cord, brainstem, thalamus, hippocampus, and amygdala, with a dense polyclonal mononuclear infiltrate within the ventral horm of the cervical and lumbar cord with preservation of axons and myelin.

Progressive Encephalomyelitis with Rigidity and Myoclonus (PERM)

PERM was first described by Campbell and Garland in 1956, as 'subacute myoclonic spinal neuronitis,' but the term progressive encephalomyelitis with rigidity was only introduced 20 years later with the description of two further patients, one of whom had myoclonus. PERM is typically a subacute or chronic polioencephalomyelitis predominantly involving spinal cord and brainstem, but occasionally including the limbic system and cerebral cortex. Patients display core features of SPS (see **Box 1**), but with brainstem myoclonus affecting all limbs. They also have evidence of more diffuse brainstem and cerebellar involvement (e.g., oculomotor abnormalities, nystagmus, vertigo, dysarthria, dysphagia, pathological startle response, ataxia, etc.), and in two-thirds of patients, there are upper motoneurone signs. Two-thirds of patients will also have evidence of autonomic disturbance, which is typically manifest during spasms as pyrexia and diaphoresis. In at least 10% of cases, there are clinical signs of a more diffuse cortical disturbance (e.g., cognitive impairment, seizures). As with SPS, psychological abnormalities are evident, including paroxysmal fear. Less commonly, there are signs of lower motoneurone disease and sphincter disturbance. Of the 49 cases reported in the literature to date, 60% were female, the age range at presentation was 13–81 years with a mean of 49 years, and the duration of disease ranged from 10 days to 8 years.

Serum anti-GAD antibodies are positive in 75% of patients with PERM and up to 90% of patients with PERM have CSF abnormalities (protein > 0.6 g dl^{-1}, pleocytosis, OCBs or CSF anti-GAD antibodies or CSF paraneoplastic antineuronal antibodies). Radiological investigations in PERM are usually normal. Electrophysiology shows the typical features of SPS (see **Box 2**). At autopsy there is histological evidence of widespread perivascular lymphocytic cuffing with neuronal loss and gliosis, particularly in the medial part of the ventral horn, Clarke's column, and brainstem, but also within areas of cerebral cortex and cerebellum.

The prognosis is generally poor with 25% of patients requiring prolonged intensive care treatment. PERM is the cause of death in as many as 40% of patients, and in 10% of patients with PERM, death is sudden, typically as a result of metabolic acidosis or dysautonomia. In 20% of patients with PERM, there is underlying malignancy and associated paraneoplastic antibodies (e.g., anti-Ri, antiamphiphysin, antigephyrin). Typically, paraneoplastic PERM has a poor response to treatment with both symptomatic and immunomodulatory agents, and there is gradual deterioration and death within 1–6 months. However, stabilization and recovery can occur if the underlying malignancy is identified and treated early. In a very small number of cases, PERM is preceded by a viral prodrome, and therefore presumably postinfectious. In such cases, there is spontaneous resolution of symptoms and signs within a month of initial presentation.

Ataxic SPS

Cerebellar ataxia is an almost universal feature of both jerking SPS and PERM, and has been reported in at least 11 patients with prototypic SPS. In ataxic SPS, signs of ataxia can precede, succeed, or present simultaneously with signs of SPS. The interval between ataxia and SPS can be months or years. When cerebellar ataxia associated with anti-GAD antibodies develops without features of SPS, it is known as cerebellar ataxia with polyendocrine autoimmunity (CAPA). Occasionally, ataxia can present with a 'stroke-like' onset.

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Striatal Hand

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Glossary

Botulinum toxin – A biological toxin that is used therapeutically to decrease the release of acetylcholine from the neuromuscular junction. It can be useful in treating various forms of dystonia and is of particular use in treating striatal hand.
Parkinsonism – A descriptive term for neurological conditions characterized by different combinations of tremor, rigidity, bradykinesia (slowness), and gait/posture impairments. The prototype of parkinsonism is Parkinson's disease, but other conditions in this category include multiple system atrophy, corticobasal degeneration, and progressive supranuclear palsy.
Striatal hand – A specific postural and functional abnormality in the upper extremities of patients with basal ganglia disorders, in particular Parkinson's disease and neurodegenerative disorders predominated by parkinsonism or dystonia.

Definition and Clinical Features

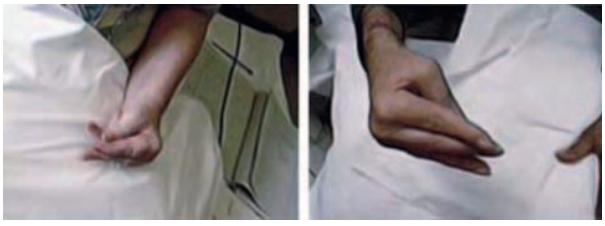
The term striatal hand refers to specific postural and functional abnormalities in the upper extremities of patients with basal ganglia disorders, in particular Parkinson's disease (PD). Striatal hand also occurs in multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), neurodegeneration of the brain with iron accumulation, and dystonia-complex regional pain syndrome (D-CRPS). Striatal hand is usually characterized by a flexion of the metacarpophalangeal (MCP) joints, extension of the proximal interphalangeal joints, and often a milder degree of flexion at the distal interphalangeal joints. Wrist flexion and ulnar hand deviation are common. In many patients with PD, a typical posture with extension of the index finger, flexion of the third, fourth, and fifth MCP joints, and thumb adduction is observed and the term, "clenched fist" has been used to describe the more marked and fixed forms of this abnormality (**Figures 1** and **2**).

The side of striatal deformity is usually ipsilateral to the side of initial bradyinesia or rigidity but bilateral manifestation occurs in many patients. Striatal hand typically occurs as a late complication in PD, but in some patients, it may be seen at early stages. Similar to the abnormal postures that may occur in the feet, neck, and trunk in parkinsonian syndromes, abnormal hand postures are often wrongly attributed to causes such as rheumatoid arthritis or Dupuytren's contracture, particularly when they occur in the absence of marked parkinsonism. Patients often present to primary care physicians, rheumatologists, or orthopedic surgeons, thus delaying diagnosis and treatment.

Loss of function, pain, and disfigurement are the major associated problems. Pain may be intense and is often exacerbated by passive stretching. Difficulties with hand hygiene often occur, caused by the nails digging into the palm or by excessive flexion at the MCP joints and leading to skin maceration and palmar infections. The hand deformity often progresses rapidly over weeks to months, and once the "clenched fist" posture develops, it is usually irreversible due to contractures.

Pathophysiology

The underlying pathophysiology of these deformities is not well understood, but animal models demonstrate an involvement of the basal ganglia. It is believed that striatal dopamine deficiency is the primary chemical alternation leading to striatal hand deformities. In this way, the phenomenon is similar to the transient dystonias that develop in PD patients before treatment with dopaminergic drugs is begun or as a problem that occurs late in the disease when patients experience motor fluctuations in medication responses and develop painful dystonia when their dopaminergic medications are not working (OFF dystonia). However, no factors are currently known to predict which patients will develop fixed striatal postural abnormalities. A correlation with the degree of rigidity in the affected limb has been suggested. Reduced numbers of sarcomeres have been demonstrated in rigid limbs, which are believed to be precipitated by prolonged immobilization of the muscles with short lengths during sustained contraction and by secondary alterations in soft tissue plasticity and viscoelasticity, leading to atrophy and fibrosis. This process produces further reduction in muscle compliance and exacerbates muscle hypertonicity. Although it is not clear if these further changes are part of the primary postural abnormality or a secondary phenomenon, they may ultimately result in a combination of muscle contraction and contractures.

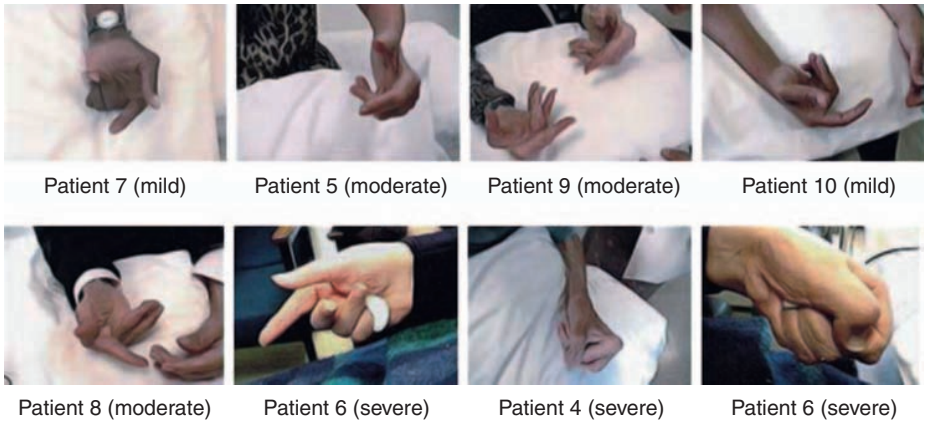


Patient 1 (moderate) Patient 3 (mild)

Figure 1 Hand deformities in two patients with CBD. Reproduced from Cordivari C, Misra VP, Catania S, and Lees AJ (2001) Treatment of dystonic clenched fist with botulinum toxin. *Movement Disorders* 16: 907–913, with permission from Wiley-Liss.

Epidemiology and Risk Factors

Hand deformities in PD patients were first described in the nineteenth century but no epidemiological studies have systematically investigated their prevalence in patients with parkinsonian disorders. A study from a tertiary referral center reported postural abnormalities of the hand in 8.4% of 202 consecutive patients with parkinsonian syndromes. Striatal limb (including foot) deformities were present in 12.8% of PD patients, 26.3% of MSA patients, and 5.3% of PSP patients. The study was retrospective and did not grade severity. In an earlier series of 86 patients with parkinsonism, some deformity of the hands was reported in 40% overall and in 24% of PD patients. Not all studies report high prevalences, and one study reported a low frequency in a PD clinic without giving details on the patient population. It is likely that the definition of the deformities and the search methods have a considerable impact on detection rates. Subtle postural changes may not be recognized, and prospective epidemiological studies are needed to determine the accurate prevalence and impact of striatal deformities in patients with parkinsonism.



Patient 7 (mild) Patient 5 (moderate) Patient 9 (moderate) Patient 10 (mild)

Patient 8 (moderate) Patient 6 (severe) Patient 4 (severe) Patient 6 (severe)

Figure 2 Hand deformity in seven patients with PD. Reproduced from Cordivari C, Misra VP, Catania S, and Lees AJ (2001) Treatment of dystonic clenched fist with botulinum toxin. *Movement Disorders* 16: 907–913, with permission from Wiley-Liss.

Most studies show that female PD patients are more commonly affected by striatal hand than male patients. In one study, the mean duration of PD before the development of clenched fist was 12 years (range 7–30). Patients with striatal deformity tend to be younger and to have an earlier age of onset of parkinsonism. The reasons for this occurrence are unknown, but it has been speculated that the higher rate of dystonia in young-onset PD, including those due to monogenic forms including *Parkin* mutations, may be related to the neuroplasticity of younger brains in response neurodegeneration and resultant abnormal neurophysiologic processing, expressed as dystonia.

Ergot-derived dopamine agonists have been implicated in the development of soft tissue changes, but in one study, no differences in agonist treatment were found between patients with and without striatal hand. Mean Unified Parkinson's Disease Rating Scale (UPDRS) scores, indicating more severe parkinsonism, were higher in patients with striatal limb deformities.

Management

Drug treatment for these deformities is usually unsatisfactory although in some cases response to dopaminergic drugs including L-dopa and anticholinergics has been observed. Improvement following subthalamic stimulation or thalamotoy has been reported in rare cases, and orthopedic procedures, including Z-lengthening and capsulotomy have been performed. Recent reports point towards botulinum toxin injections as the most promising treatment approach. Experience with this modality was reported in CBD and has more recently been reported in patients with PD and D-CRPS. Muscle relaxation, pain relief, and improved palmar hygiene are most commonly observed following botulinum injections, although the literature does not yet permit conclusions on percentages of responders or degrees of improvement. Functional improvement is more commonly observed in PD than in CBD, where additional underlying problems such as apraxia and cognitive dysfunction often preclude practical use of the affected hand. However, even in these patients, improved pain and palmar hygiene can have an impact on the quality of life. As with other indications for botulinum toxin, the duration of response is usually around 3–6 months, and repeated injections on a regular basis are therefore needed.

Because of the complexity of muscle involvement, botulinum toxin injections are best performed under EMG guidance, using the amount of EMG activity from affected muscles recorded at rest and in response to passive stretch, to guide the choice of muscles and the dose of botulinum toxin injected. EMG is presumed to allow a distinction between muscle contraction (increased EMG activity at rest and with passive stretch) and contractures (no or very little activity). The degree of improvement appears to be related to the severity of associated contractures, and the absence of EMG activity at rest has been found to be a negative prognostic factor and to correlate with poor response to botulinum toxin. The muscles for injection most commonly found to result in an improvement in typical striatal hand are the lumbricals, flexor digitorum superficialis, and the short adductors of the thumb. However, each case must be considered separately, and the muscles to be injected must be chosen clinically depending on the posture.

In PD, functional improvement is particularly observed when treatment is started soon after the appearance of the deformity. A study showed that in these patients, EMG showed prominent ongoing muscle activity, suggesting a significant element of abnormal muscle contraction rather than contractures. This observation suggests that early treatment with botulinum toxin may prevent contractures. Even when muscle contractures have developed, botulinum toxin may help maintain muscle length, reduce painful spasms, and possibly prevent progression to severe clenched fist.

Physiotherapy is recommended in clinical practice, although its role in this condition has not been investigated in studies. Further research is needed to define causes, treatments, and outcomes in striatal hand.

See also: Botulinum Toxin; Complex Regional Pain Syndrome; Dystonia; Electromyography (EMG).

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Relevant Websites

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Striatonigral Degeneration

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Glossary

α-Synuclein – One in a family of structurally related proteins that are prominently expressed in the central nervous system. Aggregated α-synuclein proteins form brain lesions that are hallmarks of some neurodegenerative diseases (synucleinopathies), such as PD, Lewy body dementia, and multiple system atrophy.
Anterocollis – Anterior flexion of the neck.
Dysarthria – Speech that is characteristically slurred, slow, and difficult to produce and to understand. There may be problems controlling the pitch, loudness, rhythm, and voice qualities of speech.
Dystonia – Involuntary movements and prolonged muscle contraction, resulting in twisting body motions, tremor, and abnormal posture.
Glial cytoplasmic inclusions – Intracytoplasmic predominantly oligodendroglial argyrophilic inclusions that exhibit modest tau and strong alpha-synuclein immunoreactivity.
Impotence – The consistent inability to sustain an erection sufficient for sexual intercourse or the inability to achieve ejaculation, or both.
Incontinence – The inability to keep urine in the bladder.
Orthostatic hypotension – Temporary lowering of blood pressure due usually to standing up suddenly (by 30 mmHg systolic or 15 mmHg diastolic).
Parkinsonism – A group of neurodegenerative disorders characterized by tremor, rigidity, akinesia or bradykinesia and postural instability.
Tau inclusion bodies – Protein involved in fibrillogenesis found in neurons and glia of various neurodegenerative disorders (tauopathies), such as FTD Complex, Pick's Disease, CBG and PSP.

Definition and History

The term striatonigral degeneration (SND) was first introduced in 1964 to characterize a new syndrome of parkinsonism associated with other signs of neurological dysfunction (e.g., cerebellar tremor, ataxia, chorea, pyramidal signs, syncope, and incontinence). The term, SND, was specifically chosen as it captured the concept of primary neuronal degeneration of small nerve cells in the anatomical areas that were thought to be involved (i.e., putamen, substantia nigra, globus pallidus, caudate and subthalamic nucleus). The term olivopontocerebellar atrophy (OPCA) was coined decades earlier in 1900 by Dejerine and Thomas to describe two sporadic cases of parkinsonism associated with progressive cerebellar degeneration. On pathology, they found loss of neurons in the pontine and inferior olivary nuclei and cerebellar cortex. In 1960, Shy and Drager published a clinicopathological study of patients presenting with idiopathic orthostatic hypotension, bladder dysfunction, and syncope, associated with neurodegeneration of the intermediolateral cell column of the spinal cord, medulla, pons, midbrain, cerebellum, and basal ganglia. In 1969, Grahm and Oppenheimer conceptually unified these three disorders, SND, OPCA, and Shy-Drager syndrome, stating, "...What we wish to avoid is the multiplication of names for 'disease entities,' which in fact are merely the expression of neuronal atrophy in a variety of overlapping combinations. We, therefore, propose to use the term multiple system atrophy (MSA) to cover the whole group." Thus, MSA represents a spectrum of related clinical syndromes characterized by varying degrees of parkinsonism, cerebellar dysfunction, and autonomic insufficiency. SND represents a form of MSA identified by predominant involvement of the extrapyramidal and pyramidal systems.

Pathogenesis/Pathophysiology

The pathogenesis of SND is unknown. In a neuropathological review of 33 patients with pure SND, macroscopic findings include severe atrophy and a brownish discoloration of the putamina from iron deposition. The substantia nigra was depigmented from loss of dopaminergic neurons. Microscopically, the putamina contain dark brown-pigmented granules mainly in the glial and neuronal cytoplasm. These glial cytoplasmic inclusions (GCIs or Papp-Lantos inclusions) have recently been recognized as a unique cellular pathological marker for MSA. They surround the nuclei of oligodendroglia with crescent or flame-shaped morphology. GCIs exhibit modest τ- and strong α-synuclein immunoreactivity. Since α-synuclein is such an important constituent of GCIs, MSA is now classified as α-synucleinopathy. There is selective degeneration of Met-enkephalin-containing neurons in the putamen and ventrolateral portion of the globus pallidus

externa, but preservation of these in the caudate nucleus. There are no consistently identified abnormalities of the remaining basal ganglia, cerebellum, pons, and medulla oblongata. Lewy bodies are rarely found, and this finding, in addition to the severe degeneration of the putamina, is a characteristic that differentiates SND from idiopathic Parkinson's disease (PD). In addition, some have found marked loss of tyrosine hydroxylase-immunoreactive neurons in the A1 and A2 regions of the medulla oblongata, suggesting that medullary involvement may play a role in the diminished vasomotor control characteristic of SND.

Epidemiology/Risk Factors

Given that the absolute diagnosis of SND requires neuropathological confirmation, there have been very few studies reporting the incidence or prevalence of SND. However, based on previous autopsy studies, it is estimated that 4–8% of patients with clinical parkinsonism have SND, with a mean duration of disease of 4.5 years. There are rare familial associations. MSA has a prevalence of about 4.4 per 100 000 in the United Kingdom, and is known to affect both sexes equally. In one meta-analysis of pathological proven cases of MSA, the mean age of onset was 54.2 years with a median survival of 6.2 years.

Clinical Features and Diagnostic Criteria

SND is clinically difficult to distinguish from PD, but the prototypical signs of SND are parkinsonism, severe neck flexion (anterocollis), and extrapyramidal features, such as spasticity brisk reflexes and Babinski sign. These two disease entities share many of the same features, and the diagnosis can be particularly challenging in the early stages of disease or when patients present with atypical PD. In fact, ~25% of patients initially diagnosed with PD are found to have parkinsonism as part of another disorder, and clinicopathological studies have shown significant inaccuracy in diagnosing these disorders in vivo. Patients with both SND and PD have parkinsonism, characterized by tremor, rigidity, akinesia or bradykinesia, and postural instability. Also, patients with both diseases typically develop at least some degree of autonomic failure, such as constipation, impotence, orthostatic hypotension, and urinary symptoms. Urinary symptoms may include urgency, frequency, nocturia, incomplete bladder emptying, and incontinence. However, in patients with SND, dysautonomia is a prominent feature, and symptomatic autonomic failure tends to present early in the disease course. One study showed that symptomatic orthostatic hypotension occurring within the first year of disease predicted MSA in 75% of pathologically confirmed cases. Another distinguishing feature is that patients with SND respond very little, if at all, to levodopa. Conversely, patients with idiopathic PD typically maintain this response throughout the disease course. Many patients with SND have no tremor, whereas the presence of an asymmetric resting tremor is quite specific for idiopathic PD. Patients with SND also seem to have more rigidity/hypokinesia as their initial symptom compared to patients with PD (84% versus 27%, respectively). Other suggestive symptoms and signs of SND include early slowness of gait with or without falls, severe dysarthria with marked hypophonia, dysphagia, respiratory stridor, dystonia, and myoclonus. Patients with SND also tend to have a more rapid progression of disease compared to PD, and may become wheelchair bound sooner.

Although these clinical findings can be helpful in identifying probable SND, there are no specific diagnostic criteria for SND. However, in 1998, a consensus committee developed diagnostic criteria for MSA based on four clinical domains: autonomic and urinary dysfunction, parkinsonism, cerebellar dysfunction, and corticospinal tract dysfunction (**Table 1**). Based on this, the recommended current nomenclature is MSA-P, where parkinsonism is prominent, and MSA-C where cerebellar dysfunction is prominent. Most cases of SND fall into the MSA-P category, and the added features of anterocollis and pyramidal tract abnormalities typify this subgroup within MSA-P. Using the four clinical domains as listed in **Table 1**, possible MSA is defined as one criterion plus two features from other separate domains. When the criterion is parkinsonism, a poor levodopa response counts as one feature (hence only one additional feature is required). For probably MSA, one needs to fulfill the criterion for autonomic failure/urinary dysfunction plus have poorly levodopa responsive parkinsonism or cerebellar dysfunction. A definite diagnosis of MSA requires neuropathological confirmation showing the characteristic distribution of GCIs and degenerative changes. The exclusion criteria include symptomatic onset under the age of 30, family history of a similar disorder, systemic diseases, laboratory evidence or other identifiable causes for the features listed in **Table 1**, and hallucinations unrelated to medication. The exclusion criteria based on physical examination include DSM criteria for dementia, prominent slowing of vertical saccades or vertical supranuclear gaze palsy and evidence of focal cortical dysfunction. While these guidelines have not yet been validated, these criteria provide an extremely useful tool for diagnostic consistency.

Differential Diagnosis

As with many neurodegenerative diseases, time is the most useful tool for the accurate diagnosis of SND.

Table 1 Consensus criteria for the diagnosis of MSA

Clinical domain	*Features*	*Criteria*
Autonomic and urinary dysfunction	Orthostatic hypotension (by 20 mmHg systolic or 10 mmHg diastolic); urinary incontinence of incomplete bladder emptying	Orthostatic fall in blood pressure (by 30 mmHg systolic or 15 mmHg diastolic) and/or urinary incontinence (persistent, involuntary partial or total bladder emptying, accompanied by erectile dysfunction in men)[a]
Parkinsonism	Bradykinesias, rigidity, postural instability and tremor	1 of 3 (rigidity, postural instability, and tremor) and bradykinesia
Cerebellar dysfunction	Gait ataxia; ataxic dysarthria; limb ataxia; sustained gaze-evoked nystagmus	Gait ataxia plus at least one other feature
Corticospinal tract dysfunction	Extensor plantar responses with hyperreflexia	No corticospinal tract features are used in defining the diagnosis of MSA[b]

[a]Note the different figures for orthostatic hypotension depending on whether it is used as a feature or a criterion.
[b]This criterion is ambiguously worded. One possible interpretation is that, while corticospinal tract dysfunction can be used as a *feature* (characteristic of the disease), it cannot be used as a *criterion* (defining feature or composite of features required for diagnosis) in defining the diagnosis of MSA. The other interpretation is that corticospinal tract dysfunction cannot be used at all in consensus diagnostic criteria, in which case there is no point mentioning it.

A patient's initial presentation merely represents one cross-section of time in a disease that is continually evolving and progressing. Therefore, it is important to bear in mind the broad differential diagnosis for SND when evaluating a patient, especially as many of these diseases have overlapping symptomatology.

SND is known to be difficult to clinically distinguish from PD. In one study, SND was misdiagnosed as idiopathic PD in 31% of cases. Some features that might help differentiate SND from PD include significant dysautonomia, minimal or lack of response to levodopa, presence of pyramidal or cerebellar signs, and no resting tremor. Patients with SND may also develop cranial or cervical dystonia, most frequently seen as or anterocollis. While early autonomic dysfunction is an important distinguishing feature of SND, these symptoms are also reported with diffuse Lewy body disease (DLB) and PD. SND can also easily be confused with PSP, especially early in the course of the disease. Early postural instability can be a feature of both diseases; however, recurrent falls within the first year have been shown to be a strong predictor of PSP (68% of pathologically confirmed cases). PSP is also more frequently characterized by prominent supranuclear vertical ophthalmoparesis. If postural instability is associated with urinary incontinence and dementia, normal pressure hydrocephalus should also be considered. Early postural instability can also be seen in PD, called 'postural instability gait disorder (PIGD),' and this tends to have a worse prognosis than tremor-predominant PD. Patients with SND may have a tremor with a jerky quality, indicating the coexistence of myoclonus, however this can also be seen in corticobasal degeneration (CBD). CBD is more frequently distinguished from SND by the presence of cortical dysfunction (i.e., apraxia and cortical sensory loss), and in time, the combination of apraxia, dystonia, rigidity, akinesia and myoclonus can make the affected limb/s functionally useless. Significant cognitive disability is rare in SND, and should lead one to consider CBD or PSP.

Diagnostic Work-up/Tests

The diagnosis of SND is a clinical one, but ancillary testing can prove useful in supporting a diagnosis, as well as excluding other conditions. In patients with SND, there have been some reported characteristic findings on brain MRI. These include putaminal atrophy and abnormal putaminal hypointensity on T_2-weighted imaging with hyperintensity on the lateral edge (which can also be seen on proton density images). These findings correlate with neuronal loss, iron deposition, microgliosis, and astrocytosis in the putamen. When present, these findings can be helpful; however, negative MRI results do not rule out the diagnosis of SND. PET scanning using 18F-fluorodeoxyglucose has been shown to reveal decreased glucose metabolism in the caudate and putamen in patients with SND. Using proton magnetic resonance spectroscopy (MRS), patients with SND have a significantly reduced *N*-acetylaspartate/creatine ratio and choline/creatine ratio in the putamen and globus pallidus, compared to the preserved ratios in patients with PD. Again, whether these findings can truly distinguish SND from other forms of parkinsonism is unknown.

Sphincter electromyographic (EMG) studies can reveal external anal sphincter denervation showing changes suggesting chronic reinnervation, with markedly

prolonged motor units. Tilt table testing can be used to evaluate postural hypotension. Other useful supportive studies include swallow studies for dysphagia, urodynamic studies for urinary problems, and sleep studies for respiratory stridor.

Management

There is no straightforward treatment for SND, and management will depend on each patient's constellation of symptoms. While many patients with SND may not respond to levodopa, there is a wide range of therapeutic effects and each individual response will vary. Therefore, it is reasonable to start with a trial of carbidopa/levodopa, knowing that patients with SND may require larger doses of this medication compared to patients with PD. Dopamine agonists are generally thought to be less effective than levodopa. While oral agents such as baclofen and benzodiazepines (e.g., valium, klonopin) can be used for spasticity and anterocollis, botulinum toxin injections may be the most beneficial. Autonomic dysfunction is difficult to treat. Symptomatic orthostatic hypotension can be managed with sodium and fluid replacement. Fludrocortisone, a mineralocorticoid, and midodrine, an α-adrenergic agonist, may be helpful. Urinary frequency can be treated with anticholinergics such as oxybutynin. Sildenafil citrate and similar medications have been used for the treatment of erectile dysfunction; however, this has been known to worsen orthostatic hypotension.

Prognosis

SND is a progressive, unrelenting neurodegenerative disease. One study examined the disease progression and survival of 230 patients with MSA, and found that the median time from initial symptom to combined motor and autonomic dysfunction was 2 years. Median intervals from onset to aid-required walking, confinement to a wheel chair, a bedridden state, and death were 3, 5, 8, and 9 years, respectively. Patients with MSA-P had a more rapid functional deterioration than MSA-C patients, but showed similar survival. There was no gender difference in survival.

See also: Alpha-synuclein; Autonomic Dysfunction; Corticobasal Degeneration; Dementia with Lewy Bodies; Dystonia; Levodopa; Multiple System Atrophy; Parkinson's Disease: Genetics; Progressive Supranuclear Palsy; Substantia Nigra; Tremor.

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Subacute Sclerosing Panencephalitis

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Definition and History

Subacute sclerosing panencephalitis (SSPE) is a persistent chronic measles virus (MV) encephalitis that causes widespread demyelination of the central nervous system (CNS). It was first clinically described in 1993 by J.R. Dawson as 'subacute inclusion encephalitis' since type A inclusion (suggesting viral etiology) were seen in the brain biopsies. Later, in the next decade, the Belgain neuropathologist van Bogaert described 'subacute sclerosing leukoencephalitis' in a case of deep lethargy.

Pathogenesis/Pathophysiology

There are several factors influencing the chronic infections of mutant MV in the brain. The earlier in life the host is exposed to the MV, the greater the possibility of developing SSPE due to the immaturity of the immune system.

There are genetic factors predisposing to MV chronic infection such as polymorphism of interleukin-2, interleukin-4, or interferon receptor factor-1 involving the cellular response. A weak or less robust cellular immunity may allow the MV to persist for years, while the humoral response is insufficient to clear the organism.

The virus itself is less pathogenic due to several mutations accumulated intracellularly; the protein M gene (matrix) of the wild-type MV that causes SSPE has been identified as the main hypermutated gene, while the hemagglutinin and nucleocapsid genes remain highly preserved. The mutated virus is rendered less cytophatic than its nonmutated progenitor, which leads to a level of tolerance to the infection and a more protracted course over the years. After primary entry through the CD46 neuronal receptor, the virus spreads trans-synaptically probably using Neurokinin-1 as its anchor.

Epidemiology/Risk Factors

The epidemiology of SSPE is inversely linked to the extent of measles vaccination coverage. In the developed world, the prevalence has declined steadily since the introduction of the MV vaccine in the 1960s. Prevalence figures in the United States in 1963 were 0.61 per million as against the current 4–5 cases per year. Twenty-one cases per million are still reported in India, 11 per million in Japan, and 0.06 per million in Canada. Overall, 4–11 cases of SSPE are expected for every 100 000 cases of clinically diagnosed measles. The incidence changes dramatically with age at the time of primary infection and vaccination status.

The prevalence is higher in males, while females have longer latency periods with a later age of onset of symptoms. There is a higher risk of SSPE in Hispanics and Asians and less prevalence in blacks. Other risk factors are rural dwelling, poverty, overcrowding, poor schooling of parents, older mothers, fewer cultural events, and higher order of birth. The MV vaccination has been largely ruled out as risk factor for SSPE and is considered to be the best currently available preventive measure against it.

Clinical Features and Diagnostic Criteria

The onset usually occurs 6 years after the primary infection; early onset is associated with a fulminant course and early death. The mean age at presentation is 8 years and is manifested as poor school performance, behavioral changes, and personality changes. Twenty percent of patients are diagnosed in this stage. Abnormal movements, usually myoclonus and seizures, occur followed by prominent pyramidal tract signs and dementia leading to a vegetative state and death.

Adult onset SSPE is initially manifested by ocular complaints that precede the behavioral changes and abnormal movement up to 2–5 years. The mean age of onset is 20.9 ± 4.9 years. Although it has a higher incidence of spontaneous remissions, survival is shorter.

The clinical stages that have been proposed under a wide consensus include

Stage I: Personality changes and behavioral disturbances
Stage II: Myoclonus, seizures, and severe intellectual deterioration
Stage III: Rigidity and progressive deterioration
Stage IV: Coma leading to death.

The disability can be graded by the Neurological Disability Index created specifically for this pathology. Diagnosis is primarily clinical and supported by the immunological evidence of intrathecal anti-MV response as well as ancillary findings such as EEG and MRI (see **Table 1**).

Differential Diagnosis

Generally, any patient with rapidly evolving dementia, myoclonus, and seizures should be considered for the

Table 1 Subacute sclerosing panencephalitis diagnostic criteria

Major	Elevated CSF measles antibody titers
	Typical or atypical clinical history:
	Typical: Acute (rapidly) progressive, subacute progressive, chronic progressive, chronic relapsing/remitting
	Atypical: Seizures, prolonged stage I, unusual age (infancy/adult)
Minor	Typical EEG (PC)
	CSF IgG increased
	Brain biopsy (See in text)
	Specials: Molecular diagnostic test to identify MV mutated genome

Usually two majors plus one minor required, the more atypical, the more criteria 5 and/or 6 are needed.

diagnosis of SSPE. Other conditions that may mimic SSPE include acute disseminated encephalomyelitis, tumors, multiple sclerosis, metabolic white matter disease, chronic Rasmussen's encephalitis, Unverricht–Lundborg disease, Lafora disease, juvenile ceroid lipofuscinosis, myoclonic epilepsy with ragged fibers, and neuraminidase deficiency.

Diagnostic Work-up/Tests

Serology

Increase IgG against MV is seen with a 1:40 to 1:1280 ratio in serum and 1:5 to 1:40 ratio in cerebrospinal fluid (CSF). The ELISA technique in CSF for MV IgG has a sensitivity of 100%, specificity 93.3% and positive predictive value of 100% in a patient with a clinical picture suggestive of SSPE.

EEG

Periodic complexes (PCs) are described as stereotyped, bilaterally synchronous, and symmetrical 100–1000 mV, 1–3 Hz waves, sometimes intermingled with spikes or sharp waves. Duration ranges from 1 to 3 s and the interval between complexes varies 2–20 s. These PCs may occur during sleep, and in early stages, can be elicited by external stimuli.

Magnetic Resonance Imaging (MRI)

Hyperintense lesions on T2 sequences are observed early in the disease, mostly in the cortex; they tend to have asymmetric distribution with posterior predilection. As the disease progresses, the lesions disappear and new lesions occur symmetrically in the periventricular white matter with mild cortical atrophy; latter involvement of deeper structures and brain stem marked with progressive atrophy is evidenced. These changes do not correlate to clinical stages.

Pathology

Major changes are observed in the cortex and the white matter with predominance of the posterior parts of the brain and medial thalamus with relative cerebellar sparing. Edema corresponds to early phases, followed by neuronal loss, demyelination, perivascular lymphocytic infiltration, spongiosis, and gliosis in addition to acidophilic hyaline nuclear and cytoplasmic inclusions suggestive of viral nucleocapsids.

Management

Certain trials have shown a benefit in 30–40% of the patients, depending on the study design. The benefit is determined by either slower progression or stabilization of the disease course or increased survival or – less commonly – clinical improvement. The benefit offered, although relatively modest, is significantly better than the 5% of spontaneous remission reported in the literature.

The most common therapy used is the combination of intrathecal interferon-α (INF-α) and oral inosiplex beneficial in around 35% of patients; no clear advantage of this treatment has been obtained in comparison with inosiplex monotherapy. Complications are mainly associated with the intrathecal reservoir used for the INF administration. High-dose ribavirin has shown some benefits with rare side effects. Amantadine and intravenous immunoglobulin have been used but lack sufficient evidence to recommend their use.

The patients who respond to treatment have later relapses that might warrant life-long treatment. Once a therapeutic option has failed, another one should be probably considered.

Prognosis

SSPE is relentlessly progressive with a fatal outcome in 95% of the patients. Spontaneous remissions occur in 5% of cases with higher remissions in the adult onset form. The median survival is 1.8 years with 5% dying in the first 3 months and only 20% alive after 4 years. The impact of treatment on prognosis is still uncertain due to poor follow-up after relapses.

See also: Akinetic-Rigid Syndrome; Bradykinesia; Myoclonus; Rigidity.

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Substantia Nigra

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Glossary

Dopamine – Major neurotransmitter used by many neurons in the central nervous system. It mediates its effects through activation of two major families of receptors called D1 and D2 receptor families. It plays an important role in motor control, reward-related behavior, and cognition. Dopaminergic neurons in the substantia nigra pars compacta degenerate in Parkinson's disease.
Drug addiction – Pathological condition by which progressive drug use results in the development of drug-seeking behavior, constant cravings with obtaining the drug, experiencing tolerance to the substance of abuse, withdrawal symptoms and decreased motivation for normal life activities.
Nigrostriatal pathway – Major bundle of axons that originate from dopaminergic neurons in the substantia nigra and terminate in the striatum. This pathway degenerates in Parkinson's disease.
Parkinson's disease – Second most common neurodegenerative disease after Alzheimer's disease characterized by the severe loss of dopaminergic neurons in the substantia nigra. The main symptoms are slowness of movements, muscular rigidity, rest tremor, and postural instability. Some patients also suffer of nonmotor symptoms such as depression and cognitive deficits.
Reward – Incentive given for the accomplishment of a task. The rewards used in animals to perform tasks often include food or liquid.
Visual saccades – Fast, simultaneous movements of both eyes in the same direction. Used as a mechanism for fixation and rapid eye movement. The relationships between the substantia nigra pars reticulata and the superior colliculus play an important role in the regulation of saccadic eye movements.

Definition and History

The substantia nigra (SN) is a brain structure that was first recognized by Vicq d'Azir in 1786, as a large cell mass located dorsal to the cerebral peduncle at the basis of the mesencephalon. It is made up of two major neuronal populations that can be differentiated by their neurotransmitter content, connectivity, and function. The substantia nigra pars compacta (SNc) in a cell-rich zone that comprises densely aggregated pigmented neurons along the dorsal part of the structure, while neurons of the substantia nigra pars reticulata (SNr) are less abundant, more diffusely distributed along the ventral part of the structure and do not contain pigmentation (**Figure 1**).

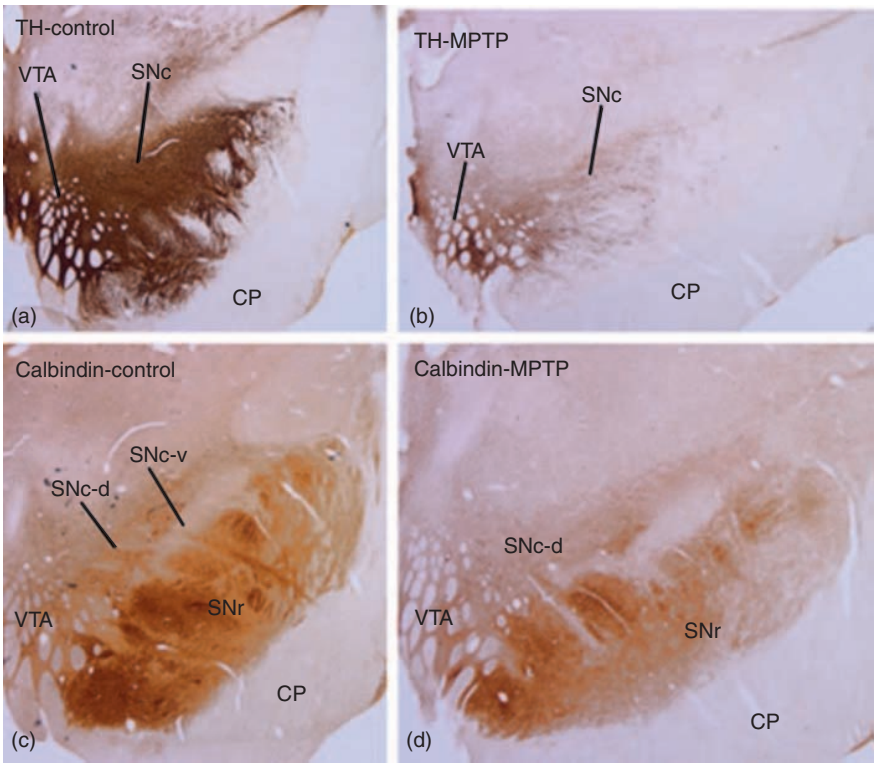

Figure 1 Transverse section of control (a and b) and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated (c and d) rhesus monkey brains immunostained for tyrosine hydroxylase (TH) or calbindin D28K showing the localization of the dorsal and ventral tiers of the SNc (SNc-d and SNc-v) and the VTA. The SNr is also labeled on these micrographs. CP, cerebral peduncle.

Together, these two neuronal groups are integrative components of the basal ganglia circuitry; the SNc being the main source of dopamine to the striatum (often referred to as the nigrostriatal pathway), while the SNr is one of the main output nuclei of the basal ganglia. In the following account, the functional and anatomical characteristics of each of these neuronal groups will be discussed in more detail and their respective role in the normal and pathological basal ganglia circuitry will be highlighted.

The SNc and Other Ventral Midbrain Dopaminergic Cell Groups

General Organization and Neurochemical Phenotypes

The SNc is a key component of the ventral midbrain dopaminergic cell groups originally recognized by Dahlstrom and Fuxe in 1964 using histofluorescence method to visualize catecholamines. Two other major components of this region include the medially located ventral tegmental area (VTA) and the more caudal retrorubral field (RRF). According to the nomenclature of catecholaminergic cell groups introduced in the mid-1960s, these structures correspond to the A8 (RRF), A9 (SNc), and A10 (VTA) regions.

The SNc is made up predominantly or large densely packed dopaminergic neurons that form a clearly distinguishable structure in humans because of their high content in neuromelanin, a byproduct of dopamine autooxidation. The content in neuromelanin in SNc neurons is much higher in humans than in any other primate species and is age-dependent, increasing significantly until about 60 year old, and then gradually declining due to the progressive loss of midbrain dopaminergic neurons. It has been suggested that the accumulation of neuromelanin and other byproducts of dopamine oxidation may contribute to the loss of SNc neurons in Parkinson's disease (PD) (see below).

In humans, SNc neurons are divided into three major groups, the dorsal α group, often referred to as the dorsal tier group (SNc-d), the densocellular β group, and the ventral γ group made up of cell columns that extend their dendrites dorsoventrally into the SNr up to the dorsal surface of the cerebral peduncle (**Figure 1**). These two groups are commonly recognized as the ventral tier neurons (SNc-v). There is strong evidence that dendrites of SNc-v neurons release dopamine into the SNr, thereby providing a source of local dopamine into the SN. One of the main neurochemical features that differentiate dorsal from ventral SNc neurons is the expression of

the calcium binding protein, calbindin D28K, which is more heavily expressed in SNc-d and VTA neurons than SNc-v cells (**Figure 1**). It has been hypothesized that this differential expression of calbindin confers to SNc-d and VTA neurons some neuroprotective properties in PD. Other neurochemical features that differentiate SNc-d/VTA neurons from SNc-v cells include the relatively high level of D2 dopamine receptors and higher expression of dopamine transporter (DAT) in the SNc-v group. Finally, VTA dopaminergic neurons co-express neuropeptides such as neurotensin and cholecystokinin, known to play important role in the regulation of dopamine release and function in the midbrain and striatum. Although the SNc is largely made up of dopaminergic neurons with very few, if any GABAergic interneurons, the VTA comprises a significant population of GABAergic cells that act as interneurons and provide extrinsic projections to the prefrontal cortex.

Efferent and Afferent Connections

Midbrain dopaminergic cell groups are the main sources of dopamine to cortical and subcortical telencephalic structures. In general, SNc neurons are recognized as the main sources of dopamine to the dorsal striatum (caudate nucleus and putamen), known as the nigrostriatal pathway, whereas the VTA contributes dopamine innervation to the ventral striatum (nucleus accumbens and olfactory tubercle) and cerebral cortex, known as the mesostriatal and mesocortical systems, respectively (**Figure 2**). The VTA and medial SNc neurons are also the main sources of dopamine innervation to the hippocampus and amygdala. It is noteworthy that the dopamine innervation of the cerebral cortex in rodents is confined to the prefrontal cortex, while in primates, it extends beyond prefrontal regions to include neocortical areas involved in sensorimotor processing. In addition to the striatum, extrastriatal basal ganglia nuclei, including the globus pallidus, the subthalamic nucleus (STN) and the SNr, also receive SNc dopaminergic inputs, which represent additional routes through which dopamine may influence basal ganglia functions (**Figure 2**). Dopaminergic inputs to the thalamus have also been demonstrated in primates, but the exact sources of this system remain unclear.

The main sources of inputs to ventral midbrain dopaminergic neurons include glutamatergic and cholinergic neurons in the brainstem pedunculopontine tegmental nucleus (PPN) as well as GABAergic neurons in the ventral striatum, ventral pallidum, and SNr. Additional, more modest, sources of afferents to the ventral midbrain include the prefrontal cortex, central amygdala, and superior colliculus that use glutamate, GABAergic inputs from the lateral habenula and ascending monoaminergic inputs from the raphe (serotonin) and the locus coeruleus (noradrenaline) (**Figure 2**).

Degeneration of Dopaminergic Cell Groups in PD

Midbrain dopaminergic neurons in the SNc and their corresponding axonal projections to the caudate nucleus and putamen (i.e., the nigrostriatal pathway) are severely affected in PD, while VTA neurons that project to the ventral striatum are relatively less damaged in this disease (**Figure 1**).

Dopamine plays a critical role in regulating striatal activity through stimulation of two main receptor subtypes (D1 or D2), which have opposite effects on striatal neurons. Because these receptors are largely segregated into two major populations of striatal projection neurons, their decreased activation in parkinsonism results in complex changes in the functional circuitry of the basal ganglia that are thought to underlie the main pathophysiological features of PD.

Dopaminergic neurons in the VTA and the related mesostriatal and mesocortical systems play an important

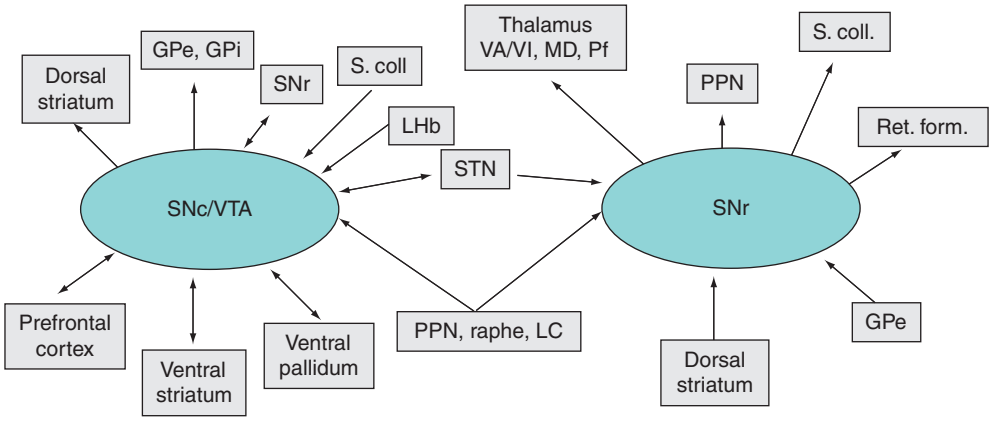

Figure 2 Diagram that summarizes the afferent and efferent connections of the SNc/VTA and SNr. For the sake of simplicity, some minor connections have been omitted. GPe, external globus pallidus; GPi, internal globus pallidus; LC, locus coeruleus; LHb, lateral habenula; MD, mediodorsal nucleus; Pf, parafascicular nucleus; PPN, pedunculopontine nucleus; Ret. Form., reticular formation; SNr, substantia nigra pars reticulata; S. coll., superior colliculus; VA/VL, ventral anterior/ventral lateral nucleus.

role in regulating limbic functions related to reward and motivational behaviors. These systems are the key mediators of neurochemical and pathophysiological changes in neural circuits that underlie addiction to drugs of abuse.

Physiological Roles of Dopaminergic Neurons

In addition to their obvious role in motor control, midbrain dopaminergic neurons are also involved in complex cognitive and limbic functions. Based on the seminal work achieved by Wolfram Schultz and colleagues in nonhuman primates, it is now well established that midbrain dopamine neurons play important roles in learning, cognition, and reward-related behaviors. Although these neurons do not respond to movements per se, they encode the rewarding aspects of environmental stimuli showing short phasic increases of activity in response to unconditioned stimuli such as food reward or following sensory conditioned reward-predicting stimuli. They also code for the discrepancy between the prediction and occurrence of reward, thereby providing a critical 'prediction error' signal to the striatum and the cerebral cortex, which constitutes a powerful teaching signal for behavior and learning. Because of these important physiological properties, pathological changes of dopamine neurons activity underlie the complex symptomatology of various neurological and psychiatric disturbances such as seen in PD, schizophrenia, attention deficit hyperactivity disorder, and drug addiction.

The SNr: An Output Structure of the Basal Ganglia

In contrast to the SNc, SNr neurons are much less abundant, more diffusely distributed and use GABA as neurotransmitter. They are located ventral to SNc neurons and give rise to thalamic and brainstem GABAergic outflow from the basal ganglia (**Figures 1** and **2**). The dorsal striatum is, by far, the most massive source of GABAergic inputs to these neurons, which also receive GABAergic influences from the external globus pallidus (GPe) and glutamatergic inputs from the STN. Other minor inputs to these neurons originate from the brainstem PPN (acetylcholine/glutamate), the raphe (serotonin), and the locus coeruleus (noradrenaline). In turn, the SNr provides significant GABAergic projections to the ventral motor and mediodorsal thalamus, the PPN, the superior colliculus, and the reticular formation. The SNr projection to the superior colliculus is an important regulator of saccadic eye movements (**Figure 2**).

Conclusions

The SN is a key structure in the central nervous system recognized for its important functions in motor, cognitive, and limbic behaviors. A deeper understanding of the etiology and the mechanisms that underlie the degeneration of SNc dopaminergic neurons in PD and the functional abnormalities of VTA neurons in drug addiction remain major challenges that face the scientific community for years to come.

Acknowledgments

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See also: Basal Ganglia; Basal Ganglia, Functional Organization; Direct Pathway; Dopamine; Indirect Pathway.

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Subthalamic Nucleus

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Glossary

Hemiballismus – Disorder caused by stroke or lesioning of the subthalamic nucleus on one side of the brain. Hemiballismus is clinically described as unilateral, large amplitude, involuntary proximal limb movements.

Parkinson's disease (PD) – Neurodegenerative disease first described by James Parkinson in 1817. PD is clinically described by bradykinesia, rest tremor, and rigidity.

Subthalamic nucleus deep brain stimulation (STN DBS) – The first case report of subthalamic nucleus deep brain stimulation was published in 1994 by A.L. Benabid. Deep brain stimulation is a high-frequency continuous electrical stimulation to the subthalamic nucleus through a surgically implanted device, which has been shown to improve motor symptoms in PD.

Definition and History

The subthalamic nucleus (STN) is part of the basal ganglia circuitry and one of the main regulators of motor function. The STN was first described by Jules Bernard Luys in 1865. It is also known as corpus luysi or Luys' body.

Anatomy

The STN is derived from the proliferative epithelium of the marginal layer of the subthalamus and is initially seen as part of the intermediate layer around 33–35 days of gestational age. The nucleus assumes its characteristic lens-shaped appearance between 48 and 51 days. The STN has approximately 560 000 cells in humans and the volume of the STN is 240 mm^3. It is located in the most caudal part of the diencephalon. The dimensions of the almond-shaped STN are approximately 10 mm *rostrocaudal*, 10.5 mm *mediolateral*, and 7 mm *dorsoventral*.

The STN is a relatively small, densely populated, biconcave lens-shaped nucleus located between the zona incerta (ZI) *dorsally* and the substantia nigra pars reticulata (SNr) *ventrally* in the upper midbrain. The posterior limb of the internal capsule is *anterior and lateral*. The medial lemniscus is *posterior*. The red nucleus and the third cranial nerve are *medial*.

More specifically, the *borders* of the STN can be described in much greater detail:

Dorsal

Dorsally, the STN is limited by a portion of the fasiciculus lenticularis (H_2) and the ZI, which separate this nucleus from the ventral thalamus. Pallido-thalamic projections originate from the globus pallidus, internal segment (GPi), which contain γ-aminobutyric acid (GABA), and initially constitute two separate bundles: fasciculus lenticularis (H_2) and the ansa lenticularis. These fibers merge in the Fields of Forel (H) and then ascend as a single bundle in the thalamic fasciculus (H_1) into the rostral part of the ventral lateral thalamus (see **Figure 1**).

Anterior and Lateral

The STN *anterior and lateral* borders are surrounded by the dense bundles of myelinated fibers of the posterior limb of the internal capsule which descend as the striae pedunculi interni (Str.pd.i) into the cerebral peduncle inferiorly.

Medial

Rostromedially, the STN borders the fields of Forel (H) and the thalamic fasciculus (H_1), which separates this nucleus from the mamillo-thalamic tract (T.mth) and the posterior aspect of the mamillary body also known as the nucleus postmammillaris hypothalami (Pm.h).

Caudally and medially, the STN borders the zona incerta (ZI) and the FasciculusQ (Sano), which separates the nucleus from the red nucleus dorsally and the third cranial nerve (III) ventrally.

Posterior

Posteriorly, the STN borders the zona incerta (ZI), which separates the nucleus from the radiations of the medial lemniscus also known as (Ra.prl) or Radiatio praeleminscalis and just posterior to those radiations is the medial lemniscus. The red nucleus also continues to rest *posterior and medial* to the STN.

The STN is subdivided into somatic motor, oculomotor, limbic, and associative *territories*.

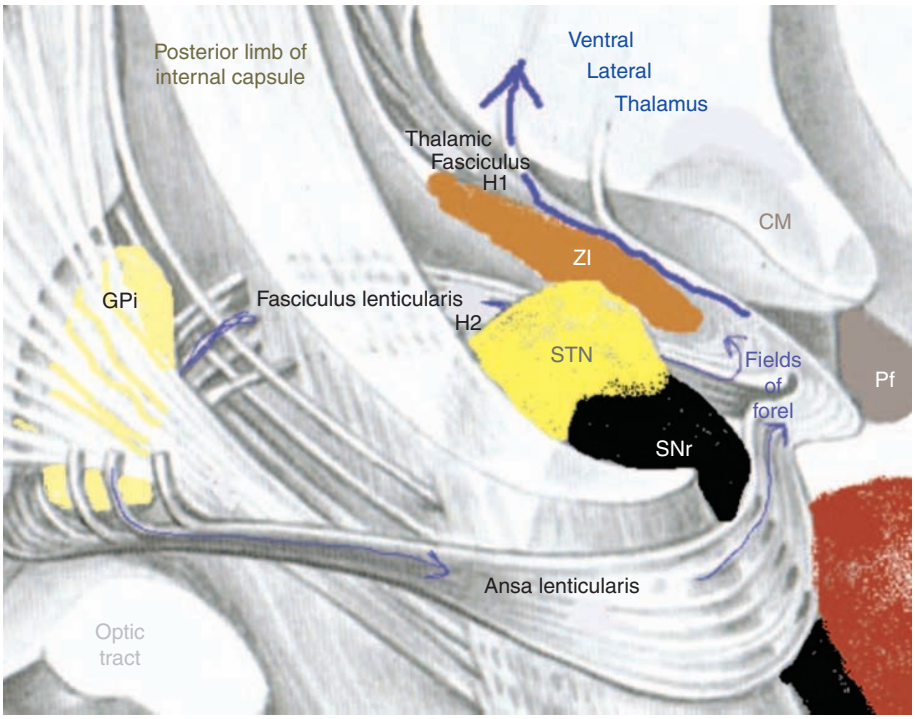

Figure 1

Somatomotor

The somatomotor territory is the largest territory of the STN, occupying two-thirds of the STN in the *dorsolateral* quadrant of the STN. Deep brain stimulation (DBS) electrodes should be placed in this region for maximal efficacy. Using microelectrode recordings in human clinical studies during surgery for DBS, this sensorimotor region is routinely mapped and identified when the contralateral body is manipulated to trigger firing of neurons that respond to either active, passive, or tremor movements. These neurons are called kinesthetic cells.

Associative

The associative territory and limbic territory share the other one-third of the STN. The associative territory is located in the *ventromedial* quadrant of the rostral STN. This territory receives input from the prefrontal cortex and frontal eye fields and projects to the SNr, which is involved in oculomotor control and cognitive aspects of motor behavior.

Limbic

The limbic territory is located in the *medial* tip of the rostral STN. This territory receives input from the medial prefrontal cortex and the anterior cingulate cortex. The limbic territory projects to the ventral and medial pallidum, which controls motivational and emotional aspects of motor behavior.

The *somatotopical* organization of the STN has been well documented. There is a distinct topographical representation of the leg, arm, and face. The leg area is located in the upper dorsal one-third and centro-*medial* portion. The face is located in the dorsal two-thirds and central portion. The arm is located in the dorsal two-thirds but in the *lateral* region of the STN (see **Figure 2**).

The *vascular supply* to the STN includes perforating branches of the anterior choroidal artery (pedunculosubthalamic arteries), posterior communicating artery, and the posteriormedial choroidal artery (lateral mesencephalosubthalamic arteries). When Cooper ligated the anterior choroidal artery to treat Parkinson's disease (PD) in 1953, the antiparkinsonian effects might have been in part related to the infarction of the STN.

STN Afferents

The STN receives inputs from *excitatory* glutamatergic projections from the cerebral primary motor cortex, parafascicular nucleus (Pf), and centromedian nucleus (CM) of the thalamus. *Inhibitory* GABA projections come from the globus pallidus, external segment (GPe). Dopaminergic projections come from the substantia nigra compacta (SNc). Cholinergic and serotonergic projections are from the pedunculopontine nucleus (PPN) and dorsal raphe nucleus (DRN) respectively.

STN Efferent Targets

STN neurons are glutamatergic projection neurons and they provide *excitatory* input to the GPe and GPi, and SNr.

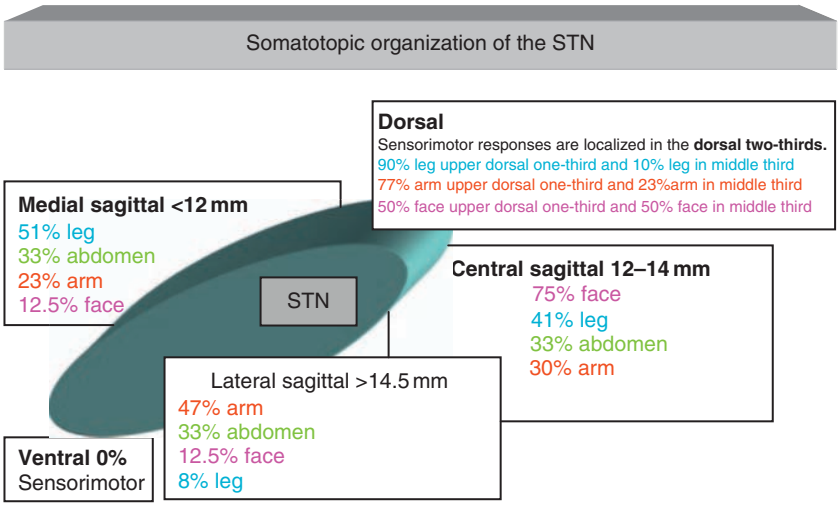

Figure 2

This makes the STN the only glutamatergic nucleus in the basal ganglia.

Physiology

The STN is a commonly used target for DBS in PD. Over 60 000 DBS cases have been performed worldwide using STN, Vim, and GPi as the physiological targets. Microelectrode recording (MER) is often used and this allows for physiological confirmation of the STN target and its borders. Under normal physiological conditions, the STN exhibits a regular pattern of discharges with intervals of bursting activity. In the parkinsonian state, the STN has a characteristic irregular spontaneous discharge pattern at a mean rate of 20–50 Hz. During MER of the STN, the cells should be assessed for the presence of movement-related activity by examining the contralateral extremities. The limbs should be moved rapidly with shoulder, elbow, wrist, hip, knee, and ankle abduction, adduction, internal and external rotation, flexion, extension, dorsi-flexion and plantar-flexion. Movement-related activity is found if the cells exhibit reproducible modulation of the cell discharge during passive movement. Movement-related activity confirms localization within the motor area of the STN located primarily in the *dorsolateral* portion of the nucleus.

Pathology

Surgical lesions of the STN in normal primates and mainly hemorrhagic lesions of the STN in humans are associated with contralateral hemiballismus and it therefore comes as no surprise that in PD patients, surgical lesions of the STN may also be associated with hemiballism. Hemiballism is characterized by irregular, coarse, violent movements of the proximal muscles of the limbs. It may be caused by a reduced glutamatergic excitatory drive of subthalamopallidal fibers, resulting in a reduced inhibitory activity of the pallidothalamic pathway, leading in turn to disinhibition of thalamocortical projections. This is partly supported by electrophysiological recordings in patients with hemiballism, where GPi firing rates were low (about 30 Hz) compared with those in PD and even levodopa (LD)-treated PD patients. However, altered firing patterns in these pathways as a result of STN lesions may play a more important role.

Deep Brain Stimulation

Levodopa remains the gold standard for the treatment of PD; however, long-term use of levodopa is associated with motor complications, including dyskinesias. There has been a new interest in functional neurosurgery such as DBS to alleviate the symptoms of PD. High-frequency STN stimulation improves motor function in PD patients. The precise mechanism(s) by which this occurs remains controversial.

The STN is targeted for DBS, using stereotactic coordinates and direct visualization using magnetic resonance imaging (MRI) with either T_2 or inversion recovery coronal and axial images. Using the standard 1.5 T MRI, the STN itself is generally not easily visualized and indirect localization can be used based on visualization of the red nucleus and its relationship to the STN. The STN is typically located approximately 11–12 mm lateral from

the midline, 2–4 mm posterior to the midcommisural point (MCP), and 4 mm below the anterior and posterior commissural (AC-PC) plane. The STN is obliquely oriented along the three anatomical axes. It is approximately 55° oblique to the frontal plane and 35° oblique to the sagittal plane and 20° oblique to the horizontal plane. The optimal approach to this almond-shaped nucleus is 60° from the AC-PC plane with a slight lateral to medial approach that will result in a longer trajectory through the STN.

Using MER, a typical trajectory through the brain will encounter the following structures: Caudate with insertional activity at less than 1–6 Hz, and then the anterior thalamus with low density spontaneously firing neurons followed by an electrically quiet ZI and fields of Forel (H_1) and (H_2). Just before entering into the dorsal border of the STN, there will be a sudden increase in background activity and border cells may be present. The STN will have lots of activity with high-frequency cells (20–50 Hz) with short pauses. As described earlier, the STN may have movement-responsive cells if the trajectory is in the dorsolateral quadrant of the STN representing the sensorimotor region. When the cell activity decreases, the base of the STN is reached and finally the SNr is approached with increasing background activity and higher frequency (50–120 Hz) regular firing rates.

After the STN is localized, a permanent DBS lead, which is a quadripolar electrode, is implanted and secured and connected to an internal pulse generator neurostimulator. This is a silver vanadium oxide battery housed in a titanium case, which allows for the programming of the deep brain stimulator.

Stimulating the STN in a parkinsonian patient induces improvements in contralateral tremor, rigidity, and bradykinesia. Occasionally, stimulation effects may be seen when stimulating near the border of the STN. These stimulation-induced effects may include contralateral muscle contractions, dysarthria, or conjugated gaze deviation if the *lateral* border is stimulated due to the spread to the internal capsule. Stimulation of the *medial* border may cause unilateral eye deviation from spread to the third cranial nerve (III). Contralateral paresthesias are demonstrated when the *posterior* border of the STN is stimulated (see **Figure 3**). Bilateral DBS of the STN can have behavioral and cognitive consequences such as personality changes, disinhibition, cognitive decline, acute depression, decline in verbal and working memory, impairments in executive functioning, attention, and verbal and visual learning. This is most probably due to interference with the basal ganglia-thalamocortical associative and limbic circuits. Hypersexuality, anxiety disorders, hallucinations, and suicide have also been reported.

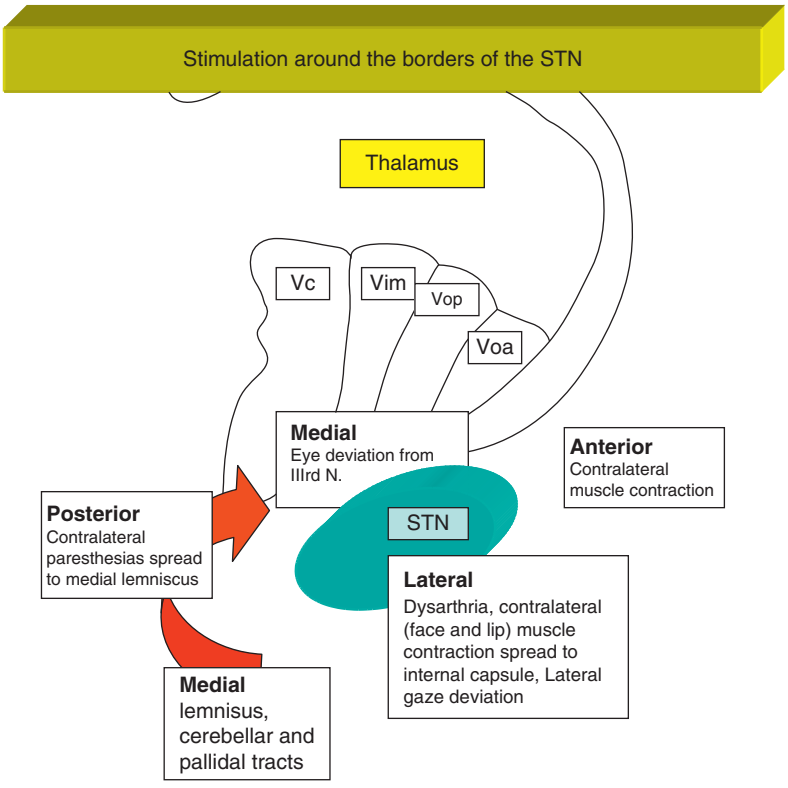

Figure 3

Conclusion

The STN is a critical component of the basal ganglia controlling not only motor function, but also cognition and affective behavior. Besides the treatment for PD, the STN is also being investigated at this time for the treatment of dystonia, tremor, and epilepsy.

See also: Basal Ganglia; Basal Ganglia, Functional Organization; Deep Brain stimulation; Hemiballismus; Parkinson's Disease: Definition, Diagnosis, and Management.

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Supranuclear Eye Movement Control

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Glossary

Oral dyskinesia – Abnormal, involuntary, aimless, repetitive movements affecting the tongue, lips, and jaw.

Oral stereotypies – Repetitive, aimless, patterned movements of the tongue, lips, and jaw.

Oromandibular dystonia – Sustained muscle contractions resulting in twisting repetitive movements and abnormal postures, producing lip retraction and grimacing, tongue rolling and thrusting, jaw closure with trismus, jaw opening or lateral deviation, and jaw jerks, sometimes generating teeth grinding noise (wakeful bruxism) and tremor.

Tardive dyskinesia – Term encompassing a variety of abnormal, involuntary movements following chronic exposure to dopamine receptor-blocking agents (e.g., antipsychotic drugs, antiemetic agents such as metoclopramide), commonly involving the lower facial musculature to justify the label "orobuccolinguomasticatory syndrome".

The cranial nerves control the eye muscles. There are six extraocular muscles innervated by cranial nerve 3, 4, and 6. The nuclei for these cranial nerves are located in the brainstem. The complex and precise array of eye movements that secure clear vision results from the interaction of a number of neural systems. Their combined output plays on the ocular motor nuclei in the brainstem. Thus the term supranuclear is appropriate to designate these systems. Input for the supranuclear control of eye

movements comes from the saccadic, the smooth pursuit, the vestibular, the optikokinetic, and the vergence systems. While the cranial nerves control eye muscles, the supranuclear areas control eye movements. The goal of the supranuclear control centers and the nuclei of the muscles is to provide the ocular motor system with the ability to attain a target and to maintain a target upon the fovea of the retina. The supranuclear system of eye movements is divided into the systems that perform saccades, smooth pursuit, and vergence, all of which work in concert to maintain an image of regard on the fovea. Additionally, the involuntary reflexes of the vestibular oculomotor system and optokinetic nystagmus are under the control of supranuclear centers.

Saccades are a fast eye movement to move the fovea rapidly to a target sensed in the peripheral visual field. A pulse of innervation provides a velocity command followed by a tonic pulse step discharge to maintain foveal fixation. These forces work against the viscous forces within the orbital tissues. Saccades can be either visually guided or volitional, controlled from the frontal eye fields (FEFs), and the parietal eye fields (PEFs). The PEF process visually guided saccades and the FEF process both volitional and visually guided saccades. Information is dispatched to the superior colliculus (SC) and then to the brainstem structures responsible for analyzing eye movement control. There is an ongoing balance between the pause and burst cells to allow eye movements to occur. An additional pathway through the caudate to the substantia nigra pars reticulata (SNPR) projects to the superior colliculus; discharges during fixation and subsequent pauses thus disinhibit SC burst neurons during voluntary and visually guided saccades.

From the FEF and the SC, fibers project to the contralateral paramedian reticular formation (PPRF) and the mesencephalon in the region of the rostral interstitial medial longitudinal fasciculus (riMLF). Horizontal saccades are generated from the contralateral FEF and SC, while vertical saccades originating in the riMLF require simultaneous action in both FEFs and SCs. The balance between the excitatory burst neurons and the inhibitory burst neurons allow saccades to occur. The abducens nucleus in the pons controls horizontal eye movements innervating the ipsilateral lateral rectus through cranial nerve 6, and via the medial longitudinal fasciculus, the MLF, the contralteral medial rectus subnucleus of cranial nerve 3 in the midbrain. Vertical gaze control originates in the riMLF requiring output to the nuclei of cranial nerves 3 and 4. Burst neurons subserving vertical and horizontal gaze are modulated by omnipause cells in the midline caudal pons.

Smooth pursuit is a slow eye movement, the purpose of which is to maintain an image of regard on the fovea once a saccade finds the object. Area V5 and V5a in the temporal occipital junction are involved to maintain smooth pursuit. Control is believed to be for ipsilateral smooth pursuit. Lesions in the area decrease the speed of smooth pursuit and the accuracy of saccades in the contralteral visual field. Fibers from V5 and V5a project to the ipsilateral pons, dorsal cerebellar vermis, and the cerebellar flocculus. The flocculus contributes to smooth pursuit and to vestibular involuntary eye movements.

The eye movement system of humans allows the eyes to move in opposite directions at the same time: convergence and divergence. The purpose of vergence eye movements is to maintain the image of regard on the fovea and to maintain stereopsis at near. Image disparity stimulates the vergence system. The exact supranuclear location of the vergence system is poorly identified. Vergence burst, vergence tonic, and vergence burst-tonic cells are located in the midbrain reticular formation, sending information to the medial and lateral rectus motor systems. Areas that may be involved in vergence include the posterior temporal, prestriate, and dorsal prefrontal cortex. The vergence system is also activated in the near triad of miosis, accommodation, and convergence, an involuntary reflex that can be volitionally suppressed or diminished following a variety of entities that inhibit cortical activity. Head trauma and processes that result in meningeal irritation can diminish the near triad.

The vestibuloocular reflex (VOR) is an involuntary reflex under the command of the semicircular canals. The purpose is to maintain an image on the fovea as the head rotates in the opposite direction. Otolith receptors are activated for both horizontal and vertical movements and are involved in a tilt reaction stimulated by gravity. Via the vestibular nerve signals are transmitted to the vestibular nucleus from which information is processed via several routes. For horizontal movements, information is directed to the area of the abducens nucleus and MLF. Primary and second order neurons work through additional ascending tracts, lateral to the MLF, transmitting vertical and torsional commands through the MLF and brachium conjunctivum to the nuclei of cranial nerve 3 and 4. There is a signal for the initial movement, an eye velocity position signal, and a tonic contraction signal to maintain target position. Signal coding occurs in the neural integrator, for saccades, pursuit, and optokinetic movements. For horizontal movements, the neural integrator is located in the medial vestibular and adjacent nucleus prepositus hypoglossi; for vertical and torsional movements, the integrator is located in the interstitial nucleus of Cajal of the rostral midbrain and vestibular nucleus. Visual input coordinates with VOR for low-frequency eye movements, balancing eye speed to head speed. Clinically, the VOR can be tested in a cooperative patient with distant fixation and rotation of the head in the vertical and horizontal plane. In the unconscious patient, the VOR can be driven through the use of the caloric response, with both warm and cold water infused into the ear.

Optikokinetic eye movements balance eye and head movements at low-frequency rotations. To maintain eye speed, the same as head speed at low frequency, the VOR activates and maintains fixation. The optikokinetic aids the VOR in keeping the eyes still during low-frequency stimulation. Optikokinetic slow phases occur reflexively by scenes that stimulate a large portion of retina. A slow phase to maintain fixation, similar to smooth pursuit, and an opposed quick phase represent optikokinetic nystagmus (OKN) The OKN is involuntary, but can be suppressed voluntarily with poor fixation or volitionally. Angular and translational eye movements are balanced by the involuntary vestibulo-ocular reflex and the optikokinetic system. The reflex is best observed when a large object subtending about 40° of the visual field is moved with a background scene moving in the opposite direction. The motion processing area of cerebral cortex is activated in all conjugate tracking mechanisms, the OKN, and the smooth pursuit system.

See also: Eye Movement Abnormalities in Movement Disorders.

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Surgery for Movement Disorders, Overview, Including History

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Glossary

Deep Brain Stimulation (DBS) – A surgical procedure that is very effective in *treating Parkinson's disease*. The surgery includes the implantation of permanent electrodes in various parts of the brain through which continuous pulses of electricity are given through an implanted pacemaker to control the symptoms of Parkinson's disease.

Dopamine – A neurotransmitter (neural messenger) that is involved in numerous processes, including movement and mood regulation.

Dyskinesia – Abnormal muscle movements. May appear as a side effect of long-term drug treatment in Parkinson's disease and may worsen in response to stress.

Dystonia – Involuntary movements and prolonged muscle contraction, resulting in twisting body motions, tremor, and abnormal posture. These movements may involve the entire body or only an isolated area. Symptoms may even be 'task specific,' such as writer's cramp.

Parkinson's disease – Parkinson's disease (PD; paralysis agitans) is a *neurodegenerative disease*. The disease produces a progressive movement disorder characterized by tremor, rigidity (increased tone or stiffness in the muscles), *akinesia* (lack of spontaneous movement), and *bradykinesia* (slowness of movement), failing balance, and walking problems.

The history of neurosurgical procedures for movement disorders dates to the early twentieth century. The first surgeries involved cortical resections to treat chorea. A number of procedures predominantly directed at lesioning the corticospinal system to treat the tremor associated with Parkinson's disease (PD) followed. Beginning in the early 1940s, the realization that the basal ganglia were involved in the pathogenesis of movement disorders led to the exploration of various structures including the subthalamic area, the globus pallidus, and the thalamus to treat PD and dystonia. Until effective medications in the form of levodopa were available, neurosurgery played an important role in the treatment of PD. With the introduction of dopamine replacement and the realization of its striking clinical benefit in the 1960s, the role of neurosurgery for PD diminished considerably. There are now, however, a large number of Parkinson's patients who continue to be disabled by fluctuations in their motor function and who suffer adverse effects despite optimal medication therapy. With the introduction of deep brain stimulation (DBS) and the realization of its increased level of safety and efficacy, there has been a rediscovery of neurosurgery for movement disorders.

There have currently been ~40 000 patients with PD and other movement disorders treated with DBS. Stimulation is directed at treating motor fluctuations and the levodopa responsive components of PD. DBS can also be effective in treating levodopa induced dyskinesias through both a direct reduction in the propensity of dyskinesias and also because the procedures can be associated with a diminution in the requirement for drug. The use of DBS is now well established at most major neurosurgical centers. The mechanism of action is still not fully elucidated but is thought to be related to the neutralization or suppression of the pathological activity along the basal ganglia circuits.

A number of other experimental approaches to treat PD, including cellular transplantation and gene therapy, are in clinical trials. The outcomes of these experimental therapies will be available in the near future. The ongoing challenges for movement disorder surgery include how to treat the nondopaminergic, medication unresponsive components of PD such as cognitive dysfunction, psychiatric dysfunction, particularly depression, autonomic dysfunction, speech, and gait and posture problems. The second important challenge is that so far we have no means of slowing down or stopping the progression of the illness.

See also: Deep Brain stimulation; Dyskinesias; Dystonia; Motor Fluctuations; Pallidotomy for Parkinson's Disease; Parkinson's Disease: Definition, Diagnosis, and Management; Thalamotomy.

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Relevant Websites

http://www.ninds.nih.gov/disorders/deep_brain_stimulation/deep_brain_stimulation.htm

http://www.dystonia-foundation.org/pages/dbs_for_dystonia_2/316.php

Sydenham's Chorea

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Glossary

β-hemolytic *Streptococcus* – Strains of *Streptococcus* that have the ability to induce autoimmune reaction that cross-reacts with antigens of the brain, heart, joints, and skin.

Chorea – Abnormal involuntary movements that are brief, random, usually distal, and without purpose.
Epitopes – Antigens.
Jones criteria – Set of clinical and laboratory criteria used to diagnose rheumatic fever.

Definition and History

Sydenham's chorea (SC) is one of the major features of rheumatic fever (RF). 'Chorea' (derived from the Latin choreus meaning 'dance') refers to abnormal involuntary movements that are brief, random, usually distal, and without purpose. First described in the Middle Ages, the most common illness was perhaps a psychogenic movement disorder, but some cases were probably the postinfectious chorea known now as SC. Despite previous authors', including Paracelsus, having described rheumatic chorea earlier, Thomas Sydenham was the first to provide an accurate description of the condition.

Pathogenesis

SC is thought to result from an autoimmune response triggered by group A β-hemolytic *Streptococcus*, which induces the formation of antibodies cross-reactive with epitopes of the basal ganglia. According to this hypothesis, the antibasal ganglia antibodies cause dysfunction of the loops linking the striatum and frontal cortex. The current evidence supports the existence of these antibodies in virtually all patients with acute SC but their biological role is less certain. A few studies suggest that these antibodies are capable of inducing changes in the intraneuronal concentration of calcium. These findings support thus the notion that the pathogenesis of SC is related to molecular mimicry. There are also data demonstrating that the cell-based immunity is abnormal in patients with SC. The autoimmune nature of the condition is further supported by the observation of improvement of chorea with the use of steroids, as described later in this article. It remains unknown, however, what the predisposing factors to the development of RF and SC are. Not more than 2.5% of patients infected with group A β-hemolytic *Streptococcus* develop acute rheumatic fever (ARF), of whom just 25% have SC. Obvious candidates are genetic factors, but the studies so far have failed to identify which genes are relevant to the pathogenesis of SC.

Epidemiology

Up to the middle of the twentieth century, RF and SC were an important public health problem throughout the world, especially North America and Western Europe. With the development of antibiotics, the incidence of these conditions sharply declined. There are, however, large areas of the world, such as Latin America, Africa, and parts of Asia, where they remain common despite a trend toward reduction of their frequency. Nevertheless, recent studies show that SC is still the most common cause of chorea in children in North America. The usual age of onset is 9 years, being less common in children of less age and very rare, although it may occur, in adults. In most series, it is more common in girls, with a female/male predominance of 3/1.

Clinical Features and Diagnostic Criteria

From a clinical point of view, it is characterized by a combination of motor and nonmotor findings. The chorea in SC is usually generalized but hemichorea is found in 20% of patients. Muscle tone is invariably decreased; in up to 8% of patients in our series, this can be so severe that the subjects become unable to walk or even stand up (chorea paralytica). More recently, there is a controversy surrounding the presence of tics in patients with SC. Because of the similarity of chorea and motor tics, this question has been tackled by the investigation of vocal tics in SC. Studying a large cohort of our SC patients, an investigation at the Federal University of Minas Gerais was able to identify vocalizations in $<10\%$ of them. As there was an association with chorea of the face and lack of features typically seen in tics (e.g., premonitory sensations and ability to suppress them), it was concluded that tics are a rare occurrence in SC. There has also been a great interest in the association between behavioral abnormalities and SC. Several studies have shown that obsessive–compulsive disorder as well as attention deficit and hyperactive disorder is more commonly seen in SC than in controls. In fact, in a study at the Federal University of Minas Gerais, these conditions were diagnosed in, respectively, 23.2% and 30.4%, whereas these numbers for controls were 4% and 8%. Other behavioral abnormalities described in association with SC are irritability, trichotilomania, and psychosis. More recently, there has been an interest in investigating cognitive functioning in these patients. In the majority of patients, there is no abnormality with the exception of decreased phonetic verbal fluency, a finding already suspected by Gowers, who mentioned the 'disinclination to speak' presented by some of his patients back in the nineteenth century. Another recent investigation of our group has confirmed not only this finding, but also showed that 15% of patients have a more global dysexecutive syndrome, suggestive of a frontal–striatal dysfunction. In addition to neurological findings, cardiac valve dysfunction, especially mitral valve insufficiency, is found in up to 80% of patients, being the most important source of disability in SC. In all series of SC, arthritis is consistently less common, being diagnosed in not more than 25% of patients.

The current diagnostic criteria of SC are a modification of the Jones criteria: chorea with acute or subacute onset and lack of clinical and laboratory evidence of alternative

cause. The diagnosis is further supported by the presence of additional major or minor manifestations of RF. Recently, the first validated scale to rate SC has been published. The Universidade Federal de Minas Gerais (UFMG) Sydenham Chorea Rating Scale (USCRS) was designed to provide a detailed quantitative description of the performance of activities of daily living, behavioral abnormalities, and motor function of patients with SC. It comprises 27 items, and each one is scored from 0 (no symptom or sign) to 4 (severe disability or finding). It is important to emphasize that the USCRS is not intended to be used as a diagnostic tool but rather to assess patients already with an established diagnosis of SC.

Differential Diagnosis

SC accounts for virtually all cases of acute chorea in children. There are, however, rare causes, which should be ruled out. The most important ones are cerebral vascular disease and systemic lupus erythematosus (SLE). Stroke, not only of the subthalamus area, can cause chorea. Here are also reports of Moyamoya disease causing this movement disorder in children. Although SLE is a rare condition, which causes chorea in $<2\%$ of patients, it is the most important alternative cause to be ruled out in children with acute chorea. Other causes of chorea in children that should be remembered are encephalitis, acute disseminated encephalomyelitis, and Wilson's disease.

In adults, by far the most common cause of acute chorea is stroke. Diabetes mellitus type II, particularly among Asian patients, is an important cause of chorea. The mechanism is not clear but it seems to be related to microhemorrhages of the pallidum, which are visible on MRI scans. Other causes are infections, particularly AIDS and syphilis, hyperthyroidism, illicit drugs (amphetamines and cocaine), dopaminergic agents, and dopamine receptor blockers.

Diagnostic Workup

Children and young adults with chorea should undergo complete neurologic examination and diagnostic testing to assess the various causes of chorea, as there is no specific biological marker of SC. These are the tests helpful in the diagnostic workup of patients suspected to have rheumatic chorea: Tests of acute phase reactants such as erythrocyte sedimentation rate, C-reactive protein, leukocytosis; other blood tests like rheumatoid factor, mucoproteins, protein electrophoresis; and supporting evidence of preceding streptococcal infection (increased antistreptolysin-*O*, anti-DNAse-B, or other antistreptococcal antibodies; positive throat culture for group A *Streptococcus*; recent scarlet fever). These tests, however, are much less helpful in SC than in other forms of RF due to the usual long latency between the infection and onset of the movement disorder. Anti-DNase-B titers, however, may remain elevated up to 1 year after strep pharyngitis. Heart evaluation (i.e., doppler echocardiography) is mandatory, because the association of SC with carditis is found in up to 80% of patients. Serologic studies for SLE and primary antiphospholipid antibody syndrome must be ordered to rule out these conditions. Spinal fluid analysis is usually normal, but it may show a slight increased lymphocyte count. In general, neuroimaging will help to rule out vascular and other structural causes such as Moyamoya disease. CT scan of the brain invariably fails to display abnormalities. Similarly, head MRI is often normal, although there are case reports of reversible hyperintensity in the basal ganglia area. PET and SPECT imaging may prove to be useful tools in the evaluation, revealing transient increases in striatal metabolism during the acute phase of the illness seen in at least 60% of patients. This contrasts with other choreic disorders (such as Huntington's disease) that are associated with hypometabolism. Increasing interest is now directed to autoimmune markers that may be useful for diagnosis. The test of antineuronal antibodies, however, is not commercially available, being just performed for research purposes. Preliminary evidence, moreover, suggests that these antibodies are not specific to SC. Similarly, the low sensitivity and specificity of the alloantigen D8/17 render it unsuitable for the diagnosis of this condition.

Management

Management of SC is based on the use of medications to treat chorea as well as to prevent new *Streptococcus* infections. In some patients, chorea is mild and does not cause meaningful disability. Furthermore, after 1 year there is remission of the movement disorder in up to 75% of patients. There are instances, thus, where the use of antichoreic agents is not warranted. In patients where there is a need to control the chorea, valproate, at dosages usually employed to treat seizures, is the first choice agent. Although traditionally, dopamine receptor blockers have been the mainstay of control of chorea, currently they are regarded as second-line drugs. The reason for this is the observation that patients with SC are particularly susceptible to developing complications of neuroleptics such as drug-induced parkinsonism and acute dystonia. The current recommendation is to use steroids just in few selected patients who have failed to respond to or tolerate the aforementioned antichoreic agents. In these cases, the recommendation is intravenous methyl-prednisolone followed by oral prednisone. Secondary prophylaxis of *Streptococcus* infection is done with penicillin, or in patients with allergy, sulpha drugs. This has been shown to effectively decrease the risk of neurologic or cardiac problems

with additional streptococcal infections. The recommendation of the World Health Organization is to maintain the secondary prophylaxis up to age 21 years. In instances where the diagnosis of SC is made after this age, the policy is less clear.

Prognosis

There is a long-standing concept of SC as a benign condition, which invariably comes into spontaneous remission. However, contemporary work with careful prospective follow up of patients has shown a different picture. According to these studies, despite best treatment 25–50% of patients remain with active chorea after 2 years. More recently, we have also demonstrated that some of these patients also display cognitive abnormalities, particularly, dysexecutive syndrome. It is also clearly established that SC or even RF without chorea may cause basal ganglia dysfunction, which is silent but may lead to overtly clinical problems. Classical examples of this situation are chorea gravidarum and chorea induced by oral contraceptives. Additionally, one should bear in mind that the cardiac valve lesions are irreversible in most patients. In areas where RF and SC are still endemic, for cardiac surgery, such heart problems are a reason more important than coronary disease.

See also: Chorea Gravidarum; Dopaminergic Agonists in Parkinson's Disease; Subthalamic Nucleus; Wilson, Samuel Alexander Kinnier.

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Synucleinopathies

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Glossary

Alzheimer disease – A neurodegenerative disease characterized by progressive cognitive deterioration together with declining activities of daily living and neuropsychiatric symptoms or behavioral changes.
Dementia with Lewy bodies – Second most common cause of dementia in the elderly, involving visual hallucinations and parkinsonism. Neuropathology is featured by widespread occurrence of Lewy bodies in brainstem and cerebral cortex associated with variable Alzheimer-type pathology.
Lewy body – Intracytoplasmic neuronal inclusion predominantly composed of misfolded α-synuclein, occurring in many areas of the nervous system.
Multiple system degeneration – A degenerative disorder of the central nervous system with parkinsonism, dysautonomic, and cerebellar symptoms. Neuropathological markers are α-synuclein-positive glial cytoplasmic inclusions in oligodendroglia.
Neurodegenerative disease – A disorder caused by the deterioration of certain neurons inducing their dysfunction and eventually bringing about their death.
Pantothenate kinase-associated neurodegeneration (Hallervorden–Spatz syndrome) – Rare autosomal-recessive disorder with dystonia, akinetic rigidity, and dementia, caused by mutation of the PANK2 gene on chromosome 20.
Parkinson disease – A degenerative disorder of the central nervous system that often impairs the sufferer's motor skills and speech.
Parkinson disease with dementia – A neurodegenerative disorder with extrapyramidal

motor dysfunctions and progressing cognitive impairment, caused by cortical Lewy body pathology and/or associated Alzheimer lesions.
Pure autonomic failure – Rare neurodegenerative disorder clinically featured by orthostatic hypotension and other autonomic failures, related to Lewy body pathology, predominantly in the peripheral autonomic system.
Synucleinopathies – A diverse group of neurodegenerative disorders sharing pathological aggregates of misfolded α-synuclein in neurons and glia with a wide spectrum of clinical syndromes.

Definition and History

The synucleinopathies are a diverse group of neurodegenerative disorders sharing common pathologic lesions composed of insoluble, misfolded αSyn protein that forms amyloid-like filamentous inclusions in selectively vulnerable populations of neurons and glia. The synucleinopathy diseases of the human nervous system are summarized in **Table 1**. αSyn, a member of the synuclein family of protein, was initially isolated from the electric plate of Torpedo californica and from rat brain and later as non-amyloid compound (NAC) of amyloid-rich plaques from Alzheimer disease (AD) brain. It is a natively unfolded 14.5 kD presynaptic phosphoprotein with potential for self-oligomerization and fibrillary aggregation under pathologic conditions. Its normal function remains elusive, but it may play important roles in synaptic plasticity and function. Recent improvement in the knowledge of αSyn was stimulated by the discovery of mutations in the SNCA (αSyn) gene (PARK1) on chromosome 4 and other PARK loci in familial forms of Parkinson's disease dementia (PD). Abnormally processed and hyperphosphorylated fibrillary αSyn – together with many other proteins – was demonstrated as a major component of Lewy Bodies (LBs), dystrophic neuritis, and astroglia in PD and glial cytoplasmic inclusions (GCIs) in oligodendroglia in multiple system atrophy (MSA). The histologic presence of insoluble aggregates of αSyn in these and related disorders has played an essential role in the diagnosis of neurodegenerative diseases during the last two decades.

Table 1 Synucleinopathies

1. Invariable forms (consistent occurrence of αSyn)
   - Sporadic Parkinson disease
   - Familial PD (αSyn, PARKIN mutations)
   - Incidental Lewy body disease (preclinical PD)
   - Rapid eye movement (REM) sleep behavior disorder (RSD)
   - Parkinson disease and dementia (PDD)
   - Dementia with Lewy bodies 'pure' form (no or little AD-pathology) LB variant of AD (LBV/AD)
   - Pure autonomic failure
   - Lewy body dysphagia
   - Multiple system atrophy
   - Pantothenate kinase-associated neurodegeneration (Hallervorden–Spatz syndrome)
2. Variable forms (inconsistent occurrence of αSyn)
   - Alzheimer disease (sporadic, familial)
   - Aging brain (with/without dementia)
   - Down syndrome
   - Frontotemporal lobe degeneration
   - Pick disease
   - Amyotrophic lateral sclerosis
   - Amyotrophic lateral sclerosis (ALS)-dementia complex on Guam
   - Progressive supranuclear palsy
   - Other tauopathies
   - Subacute sclerosing panencephalities
   - Ataxia telangiectasia
   - Meige syndrome
   - Gerstmann–Sträussler–Scheinker disease
   - Gaucher disease
   - Traumatic brain lesions

Pathogenesis/Pathophysiology

The etiology of synucleinopathies is thought to involve both genetic and environmental factors, but in most cases, nongenetic factors play a role, probably in interaction with susceptibility genes. Molecular interactions between environmental risk factors and genetic factors, for example, mutations in the αSyn gene, are implicated in the etiology of PD, dementia with Lewy bodies (DLB), MSA, and related disorders. Their pathogenesis has been related to a cascade of multiple noxious factors and events, including misfolded polymerized αSyn, phosphorylated at serine 129 that has a central role in dysregulating the dopamine synthesis and release, formation of free radicals, lipid peroxidation, oxidative and proteolytic stress, mitochondrial dysfunction and nuclear RNA deficits, protein–iron interaction, excitotoxicity from increased glutamatergic input, transcriptional dysregulation, disorders of calcium homeostasis, neuroinflammation, dysfunction of the ubiquitin–proteasome protein degradation system, impaired bioenergetics, and inhibition or loss of neuroprotective mechanisms and complex interaction between these and other factors that need to be carefully analyzed. Protofibrillary rather than fibrillary forms of αSyn have been shown to be cytotoxic, but αSyn containing LBs may be the structural manifestation of a cytoprotective mechanism to confine or eliminate toxic proteins. However, significant intracellular and neuritic protein aggregation may finally contribute to dysfunction and death of involved neurons. The question whether LBs and other αSyn aggregates are harmful or cytoprotective still remains unresolved. Although their formation may reflect

one of several response patterns by the central nervous system (CNS) to upstream dysregulation of αSyn metabolism, the αSyn pathway appears to be an essential factor for the selective multisystemic loss of neurons and glia in many synucleinopaties, for example, PD, Parkinson's disease dementia (PDD), DLB, and related disorders, showing widespread occurrence of LBs and dystrophic neurites with neuronal loss in many regions of the central, peripheral, and autonomic nervous system. They are associated with dysfunction of the dopaminergic nigrostriatal and many other neurotransmitter systems. It also appears to be a key pathway for selective loss of neurons, glia, and myelin in MSA, where αSyn-positive GCIs mainly in oligodendroglia are suitable morphologic markers. Although both clinically and pathologically related to PD, the working model of MSA as a primary glial disorder (oligodendrogliopathy) was strengthened by the finding of dysregulation in the metabolism of myelin basic protein and p25α (tubulin polymerization promoting protein), a CNS-specific phosphoprotein. This is suggested to cause degeneration of the oligodendroglia–myelin–axon–neuron complex associated with synucleinopathy, myelin dysfunction, and axonal damage leading to secondary neurodegeneration.

The pathophysiology of synucleinopathies is determined by the evolution pattern, distribution, and severity of αSyn pathology (LB and GCI density and distribution) and related parenchymal loss. The reliability of assessment of αSyn pathology, its dysfunction in various synucleinopathies, and their animal models have been reviewed recently. αSyn/LB predominance in brainstem is considered a marker for PD and their prominent occurrence in the cortex for PDD and DLB. In PD, DLB, and MSA-P (predominant parkinsonism, previously striato-nigral degeneration (SND)) and pantothenate kinase-associated neurodegeneration (PKAN) motor symptoms-like akinesia and rigidity are negatively correlated to neuron loss in substantia nigra and consecutive loss of tyrosin-hydroxylase and dopamine in striatum. In incidental Lewy body disease (ILBD), a precursor or preclinical form of PD, the lack of clinical symptoms is due to subthreshold αSyn pathology in various parts of CNS and sympathetic nerves. Cognitive decline is related either to abundant cortical αSyn/LB lesions, particularly in the limbic and mid-temporal regions or mixed αSyn and AD pathologies. Autonomic dysfunctions, such as in pure autonomic failure (PAF), PD, and MSA, are related to intensive αSyn/LB pathology in various parts of the central and peripheral autonomic system. However, in general, there is an imperfect correlation between αSyn/LB pathology and the clinical phenotype. Although the presence of LBs in brainstem and limbic cortex is suggestive of PD, PDD, and DLB, their mere presence – even in high numbers – does not reliably match extrapyramidal and cognitive impairment during lifetime. It remains a mystery as to which factors drive the expression of a more peripheral (PAF) or a more central (PD, DLB) versus a combined phenotype, as seen in some cases of sporadic (sPD) and familial Parkinson disease (fPD) with SCNA mutation. PKAN is a rare autosomal-recessive disorders with progressive dystonia, akinetic rigidity, optic atrophy, seizures, and dementia, caused by mutations of the pantothenate kinase 2 (PANK2) gene on chromosome 20. Neuropathology shows rust-brown discoloration of the globus pallidus and reticulata nigrae, neuronal loss, and numerous axonal spheroids in CNS and peripheral nervous system, associated with widespread αSyn-positive inclusions. Synuclein deposits in other diseases, like AD, tauopathies, etc., and in the central and autonomic nervous system of unremarkable aged individuals or those with dementia are not uncommon, but their pathophysiologic impact may be minimal or even nil compared to other pathologies.

Epidemiology/Risk Factors

The most common synucleinopathy is sPD with an annual prevalence of 48–69/1000 and standardized incidence rates of 8–18/100 000 person-years, its prevalence increasing from around 15% in persons aged 65 to 20–52% (age 75–85 years). PDD with incidence rates of 95–112/1000 pat-years and a cumulative prevalence between 48 and 83% after 15–20 years follow-up has a 4–6 times increased lifetime incidence rate compared to age-matched controls. DLB, with a reported prevalence of 0.3% over age 65 years is suggested to account for up to 10–22% of all dementia cases, thus being the second most common cause of dementia after AD. MSA is less common than PD with a prevalence of 1.9–4.9/100 000 and an incidence of 3/100 000 year^{-1}. Most of the other synucleinopathies are rare.

Risk factors

In addition to genetic factors, for example, mutations of SCNA/Parkin genes, aging, and occupational factors (exposure to pesticides, organic solvents, and heavy metals) have been implicated in the development of PD, while relations of increased PD risk with hypertension, hypercholesterolemia, and diabetes are discussed controversially. Smoking and caffein consumption, antioxidants, and increased dietary plasma urate may decrease the risk of PD. The genetic susceptibility and risk factors of most of the other synucleinopathies are hitherto unknown.

Clinical Features and Diagnostic Criteria

Several synucleinopathies, like PD, PDD, DLB, and SND, share common cardinal clinical features – rigidity, akinesia, rest tremor, and postural instability, and other motor (freezing, speach and neuroophthalmic dysfunctions) and

nonmotor disorders, in particular autonomic/dysautonomic, cognitive, and behavioral disorders that, in MSA-C are associated with cerebellar symptoms. Currently, PD is diagnosed upon the appearance of clinical symptoms when over 50–60% of nigral cells and striatal dopamine are lost. In DLB, parkinsonism is associated with visual hallucinations, fluctuating levels of consciousness, and cognitive impairment. Accepted clinical criteria for the diagnosis of probable PD, DLB, and MSA have a high sensitivity but only a moderate specificity, and for a definite diagnosis histopathologic confirmation is required. This also holds for the majority of other synucleinopathies, although modern neuroimaging may promote diagnostic possibilities, for example, in PD, MSA, and PKAN. PAF is featured by orthostatic hypotension and other dysautonomias, mainly related to αSyn/LB pathology in the peripheral autonomic system.

Differential Diagnosis

Parkinsonian disorders can be classified into four types: primary (idiopathic), secondary (acquired, symptomatic), heredodegenerative parkinsonism, and multiple system degeneration including parkinson-plus syndromes, but up to now, there are no definite clinical diagnostic criteria available for differentiating sPD from the various forms of parkinsonism. Although most clinical features have inadequate sensitivity, several of them, such as tremor, early gait abnormality, postural instability, pyramidal tract signs, response to levodopa, early olfactory dysfunctions (hyposmia), supported by (123)I-metaiodobenzylguanidine (MIBG)-cardiac scintigraphy studies and neuroimage techniques (transcranial sonography, functional magnetic resonance image (MRI), positron emission tomography (PET) and FP-CIT single photon emission computed tomography (SPECT), and increased iron content in midbrain in high field strength MRI) can be used to differentiate sPD from other parkinsonian disorders. Different putamen/nigra and putamen/caudate ratios of fluorodopa radioactivity, low cerebrospinal fluid (CSF) DOPA and DOPAC concentrations, and olfactory testing separate sPD from MSA.

Diagnostic Workup/Tests

The diagnosis of the various forms of synucleinopathies still relies on an exact medical and family history, an accurate examination of the patient and on the skills of the examiner. The use of ancillary tests (structural and functional neuroimaging, cardiovascular autonomic tests, neurophysiological investigations, and tests for biological markers) may be of help in the diagnostic workup of patients with synucleinopathies, but the results from many investigations are rarely specific and cost-effectiveness remains to be established. A possible exception is a positive genetic testing which allows the confirmation of rare forms, for example, monogenic autosomal dominant or recessive PD, rare forms of DLB, and PKAN. A number of biological or surrogate markers have been discussed: reduced cardiac MIBG uptake reflects cardiac sympathetic dysfunction in LB disease and MSA. Decreased αSyn and increased levels of DJ-1 in CSF, but increased αSyn expression in fibroblasts have been reported in sPD. Serum urate has been linked to clinical and radiographic progression in PD. Recent studies showed increased CSF 8-hydroxy-2-deoxyguanosine (8-OHdG) and glutathione levels, markers of oxidative damage, but reduced uric acid in sPD. CSF Aβ-42 and total tau levels are different between PD/PDD and DLB that shows significantly lower tau levels than AD, while DLB selectively shows increased Aβ-40. MIBG cardiac scintigraphy was superior to that of CSF markers in distinguishing DLB from AD. Increased CSF levels of neurofilament light chain and tau differentiate MSA-P from sPD, but cannot separate MSA-P and-C, while they are reduced in idiopathic late-onset olivo-ponto-cerebellar atrophy (OPCA).

Management

Current treatment of PD and related disorders, based on dopamine-replacement and dopaminergic agents, is well established but is burdened with adverse effects, and for this and other synucleinopathies, therapies that modify the inexorable progression of the disease are needed. To date, there are few symptomatic therapies available for the autonomic failure of MSA and PAF and practically none for their motor impairment. In patients with dementia, cholinesterase inhibitors may show some efficacy. Neuroprotective, neurorescue therapies and trials with neurotrophic factors have largely failed, while tissue implantation and gene therapeutic approaches are still in the investigative stages. Deep brain stimulation is most effective in patients that respond to levodopa. The future of neuro-gene therapy will depend on the development of gene therapy vectors capable of long-term expression, but will at best only partially address the underlying disease. A new therapeutic target would be αSyn influenced by protofibril activators, and the addition of protofibril-directed neurotherapeutics to the existing armamentarium may both extend the symptom-free stages of synucleinopathies and alleviate pathogenesis.

Prognosis

The natural history of synucleinopathies is variable. Several studies have shown that treating PD has changed its natural history, although the long-term effects of pharmacological and effective deep brain stimulation did not stop continuing progression of the disease. PD patients

have an increased risk of developing dementia with a mortality higher than that in individuals without PD, and the excess mortality increases with disease duration. DLB shows a more rapid progression and a prognosis worse than for PD and AD. Prognosis in MSA is even worse; most patients deteriorate rather rapidly and survival beyond 10 years after the disease onset is rarely seen. Most of the other synucleinopathies also have a poor prognosis because of a lack of efficient treatment options.

See also: Alpha-synuclein; *Caenorhabditis Elegans*; Dementia with Lewy Bodies; DYT13, Cranio-Cervical-Brachial; Hallervorden–Spatz Syndrome (PKAN); Hemifacial Spasm; Lick-force Rhythm Test; Multiple System Atrophy; Myorhythmia; Neuroleptics and Movement Disorders; Paired Pulse TMS; PARK1, Alpha Synuclein; *PARK6, PINK1*; Parkinson's Disease: Definition, Diagnosis, and Management; Parkinsonism: Vascular; Paroxysmal Movement Disorders; Pelizaeus-Merzbacher Disease; Tardive Syndromes.

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T

Tail-pinch Stimulus

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Glossary

6-Hydroxydopamine – 6-Hydroxydopamine, or 6-OHDA, is a neurotoxin used by neurobiologists to selectively kill dopaminergic and noradrenergic neurons in the brain. To this end, 6-OHDA must be injected in specific brain structures, where it enters neurons via the plasma membrane transporters for dopamine and noradrenaline (also called norepinephrine). The main use for 6-OHDA in neuroscience research is to produce models of Parkinson's disease in rats and mice.

Dopamine – Dopamine is a neurotransmitter occurring in a wide variety of animals, including both vertebrates and invertebrates. In the brain, it can activate five types of dopamine receptors – D1, D2, D3, D4, and D5, and their variants. Dopamine is produced in several areas of the brain, but the largest aggregates of dopamine-producing neurons are found in two midbrain nuclei named 'substantia nigra' and 'ventral tegmental area'. Dopamine is also a neurohormone released by the hypothalamus. Its main function as a hormone is to inhibit the release of prolactin from the anterior lobe of the pituitary. Severe dopamine deficiency in the striatum is the prime cause of parkinsonian motor symptoms (in particular, slowness of movement, poverty of movement, difficulty in movement initiation, resting tremor, rigidity).

Locus coeruleus – A nucleus in the brain stem involved in physiological responses to stress and behavioral arousal, and in the control of REM sleep. This nucleus is the principal site for synthesis of noradrenaline (also called norepinephrine) in the brain. Its name is derived from the Latin words 'coeruleus' (or 'caeruleus') and 'locus' meaning, literally, 'the blue spot' because of its somewhat azure appearance in unstained brain tissue (which is due to melanin granules). The axonal projections from this nucleus are widespread and highly ramified, reaching virtually all parts of the brain and spinal cord. The locus coeruleus is studied in relation to clinical depression, panic disorder, anxiety, and neurodegenerative diseases.

Nigrostriatal projection – Axon fibers that originate from neurons in the substantia nigra pars compacta and reach the striatum. This projection uses dopamine as its primary transmitter.

Raphe nuclei – The raphe nuclei (from the Greek word 'raffe', seam) are clusters of serotonin-containing neurons located along the midline in the brain stem (i.e., medulla oblongata, pons, and midbrain). Specific names of these nuclei are (in order from caudal to rostral), nucleus raphe obscurus, raphe magnus, raphe pontis, raphe pallidus, nucleus centralis superior, nucleus raphe dorsalis, nuclei linearis intermedius and linearis rostralis. These neurons have widespread and highly ramified projections that provide a serotonergic input to the entire brain (some nonserotonergic projections also arise from these nuclei, however). Serotonin is involved in a vast variety of cognitive and behavioral processes, and in the regulation of mood, sleep and wakefulness. Selective serotonin reuptake inhibitors (SSRI), which provide a treatment for depression, target the raphe nuclein and their projections.

Behavioral Studies

The first report on the behavioral effects of tail pinch was provided by Antelman and collaborators, who described a reproducible induction of eating, gnawing, and licking behavior by mild tail pinch in rats. This response was dependent on the integrity of the nigrostriatal dopamine

system and was maintained for the duration of the pinch, that is 20 s. Tail pinch was applied using a handheld hemostat and was described as nonnoxious because it did not evoke vocalization or other signs of distress. Since this first report, many rodent studies have utilized tail pinch as a way to induce transient behavioral arousal under standardized conditions. To apply the pinch for minutes (as opposed to seconds), a plastic or metal clip is fastened to the mid-distal portion of the rat tail.

Tail pinch has been extensively used in rats with unilateral 6-hydrodopamine (6-OHDA) lesions of the nigrostriatal pathway in order to transiently induce turning behavior in the direction ipsilateral to the lesion. This response is due to asymmetric activity in dopamine-dependent systems that control posture and locomotion. A particular application of the tail pinch stimulus is the Elevated Body Swing Test (EBST), which was developed for the behavioral assessment of unilaterally 6-OHDA-lesioned rats, but is now used also in other models of unilateral brain lesion. In the test, a rat is held ~3 cm above a table by a point 3 cm from the base of its tail. In 30 s, the number of left-biased swings and right-biased swings are counted. A normal rat does not exhibit side bias in the swinging behavior (50% swings towards each side), while a rat with a nearly complete unilateral nigrostriatal dopamine lesion shows a swinging bias in the direction contralateral to the lesion.

In Vivo Electrophysiology and Neurochemistry

In addition to its application in behavioral studies, the tail pinch stimulus has been extensively used in the neuroscience literature in order to assess whether specific categories of neurons respond to behavioral arousal. Tail pinch increases the firing rate of locus coeruleus neurons and of some neurons in the serotonergic raphe nuclei. The tail pinch stimulus readily enhances transmitter release and turnover in the terminal fields of ascending noradrenergic, serotonergic, and dopaminergic projections. The extent of this response may exhibit regional differences. In particular, the increase in dopamine and noradrenaline efflux induced by tail pinch is much more pronounced in the prefrontal cortex and nucleus accumbens than in the caudate-putamen.

See also: 6-OH Dopamine Rat Model; Basal Ganglia; Dopamine Receptors; Locus Coeruleus and Norepinephrine; Serotonin and Tryptophan; Substantia Nigra.

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Tardive Dystonia

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Glossary

Drug-induced movement disorders – Includes parkinsonism, dystonia, tardive dyskinesias, and akathisia. Most though not all are due to dopamine-blocking medication. Some appear early (acute) while others are delayed (tardive). Treatment and prognosis are variable depending on the condition. More than one drug-induced movement disorder may be present at a time.

Dystonia – Involuntary twisting and turning movements caused by coactivation of agonist and antagonist muscles. The position may be fixed, affected by movements, and associated with jerky irregular tremor. Dystonia is due to dysfunction

of the basal ganglia. There are many different causes of dystonia.

Neuroleptic – Literally, 'that which grips the nerve.' These medications block the dopamine receptors and are effective in treating psychosis (and are often called 'antipsychotics'). Neuroleptic medications blocking the D2 dopamine receptors may cause drug-induced movement disorders, including acute dystonic reactions.

Tardive dystonia – Persistent dystonia that occurs typically after months to years of chronic dopaminergic blocking medication use. This condition is often uncomfortable and disabling. Retrocollis and trunk hyperextension are classic features. In contrast to idiopathic dystonia, tardive dystonia tends to improve with activity and is less responsive to sensory tricks. The overall prognosis is guarded; treatment includes stopping or switching medications. Symptomatic treatment with dopamine depleting agents or anticholinergics may be effective.

Definition and History

Chronic dystonic reactions were noted in the late 1950s. However, the term 'dystonia tarda' was first described by Keegan and Rajput in a single case in 1973 followed by Burke et al. who described a case series of 42 persons with tardive dystonia (TDyst) in 1982. An association between dopamine blocking agents and TDyst was noted, though causality was difficult to prove. Dopamine blocking agents were felt to play a causative role as the rate of dystonia was much greater than expected for sporadic or inherited dystonia.

The term tardive means 'delayed.' While TDyst typically occurs months to years after medication exposure, sometimes only a few days or weeks of exposure are enough to produce TDyst; rare cases have occurred after a single exposure to medication. Unlike acute dystonia, TDyst does not quickly resolve upon withdrawal of the causative agent.

Pathogenesis and Pathophysiology

Chronic dopamine receptor blockade is believed to underlie TDyst. While there is individual susceptibility, no consistent findings regarding dopamine receptor polymorphisms have been found. The biochemical basis appears different for tardive dyskinesias (TD); while anticholinergics tend to improve TDyst, they worsen TD.

Rarely, medications without dopamine-blocking properties have been linked to TDyst. Given the usual long latency before development of TDyst, it can be extremely difficult to establish a link between a nondopamine blocking medication and dystonic symptoms.

Epidemiology and Risk Factors

The risk of TDyst increases with longer duration of treatment. While more common after months to years of treatment (one study by Kiriakakis et al. report median 5 years and mean 6.2 years), there is no 'safe period' as TDyst may begin after a few days of medication or even after a single dose.

In a 1996 baseline study of drug-induced extrapyramidal syndromes among all psychiatric inpatients of the Netherlands Antilles, 194 patients were evaluated who were on or had used neuroleptics for the prior 3 months. The 13% prevalence of TDyst in this mostly chronic population was higher than that was previously reported. However, mild dystonia was included. If only moderate to severe dystonia cases were counted, the prevalence would be 2.9%, similar to what other studies have reported.

TDyst occurs at an earlier age than TD, which more often affects elderly females. Unlike acute dystonia, there is no marked decline in incidence after the age of 40 for TDyst as it may affect all age groups. Males with TDyst are about a decade (or more) younger than females. While some studies report no gender predilection, others report male to female ratios between 1.6 and 2.7. In a series of 100 cases (26 males, 74 females) with tardive syndromes from five movement disorders units in Spain, Orti-Pareja and colleagues reported 16% had TDyst. By comparison, 72% had orobuccolingual dyskinesias (TD). Unlike other tardive syndromes (dyskinesias, akathisia, and tremor), which had clear female predominance in this study, males and females had similar risk for TDyst.

One study reported an association with a history of acute dystonia with TDyst although the numbers are too small to definitively state that an acute dystonic reaction predisposes to TDyst.

A study by Yassa et al. focusing on severe TDyst and severe TD found prevalence rates of 1.4% and 2.0% in a combined inpatient and outpatient psychiatric population respectively. Only eight cases of severe TDyst were found, with a 3:1 male: female ratio. TDyst is often painful and distressing, while many patients with TD are unaware or only slightly bothered by it. Even in severe cases, only 60% of the TD cases were aware of their symptoms in contrast to all the TDyst cases. In this study, TDyst developed in a shorter time period with less total neuroleptic dose than TD.

Clinical Features and Diagnostic Criteria

TDyst may be indistinguishable from idiopathic torsion dystonia. In adults, the dystonia is more often focal or segmental, while in younger persons, it is more often generalized. The craniocervical region and upper limbs are the most commonly affected body parts. Retrocollis and trunk hyperextension are classic features of TDyst. Internal rotation of the arms, elbow extension, and wrist

flexion are seen in the upper limbs and are almost never seen in idiopathic dystonia. Lower limb dystonia is more commonly seen in young persons. Findings in the cranial musculature may be similar to the acute dystonic reactions, and occasionally intermittent oculogyric crisis has been reported.

Unlike idiopathic dystonia, TDyst tends to improve with action (including walking) and is generally less responsive to sensory tricks (*geste antagoniste*).

Onset of TDyst is insidious, with progression over weeks to months followed by stabilization. It is an often painful and disabling condition.

Patients may have concomitant TD (orobuccal lingual movements), tardive akathisia, or drug-induced parkinsonism.

Criteria to diagnose TDyst include:

1. duration for more than 1 month,
2. occurring during or within 3 months of stopping a neuroleptic,
3. secondary causes of dystonia have been ruled out,
4. negative family history of dystonia or documented exclusion of known mutations.

It is not necessary for dystonia to be the predominant movement disorder to diagnose TDyst.

Differential Diagnosis

The differential diagnosis for TDyst is more extensive than for acute dystonia. As noted above, idiopathic dystonia may be indistinguishable from TDyst. Genetic causes of dystonia, including DYT1 mutations should be considered in young persons. Unmasking of cases with genetic dystonia without clinical findings may also occur with neuroleptics. Secondary causes of dystonia should be considered. Wilson's disease, a reversible illness due to abnormal copper metabolism, should be excluded by 24 h urine copper, serum ceruloplasmin, and ophthalmological exam for Kayser–Fleischer rings. Brain MRI can exclude underlying structural causes. Young onset Parkinson's disease may present with dystonia. Dopa-responsive dystonia often has diurnal variation with improvement after rest.

Stiff person syndrome can cause painful trunk hyperextension with lumbar muscle hypertrophy and should be considered in the appropriate setting.

Psychogenic dystonia may also be considered in the differential diagnosis only if the clinical picture appears inconsistent with TDyst and appropriate investigations are negative.

Management

The mainstay of treatment is to remove the offending agent. Improvement is often delayed and incomplete. Judicious use of antipsychotic medications would also reduce the overall prevalence of TDyst.

Symptomatic treatment is often necessary. Anticholinergics and dopamine depleting agents are the two most common types of medications.

Anticholinergics including benztropine, trihexyphenidyl, and biperiden have been used with overall moderate success. The doses required may be extremely high and are less well tolerated by older adults. Adverse effects are common including dry eyes, dry mouth, constipation, urinary retention, confusion, blurred vision, and bradycardia. Anticholinergics may also improve drug-induced parkinsonism but worsen TD.

Dopamine depleting agents including tetrabenazine and reserpine are also used with good effect. Adverse effects from both medications include depression and hypotension. While tetrabenazine may rarely cause drug-induced parkinsonism, it does not cause TD.

Increasing the dose of the neuroleptic may temporarily improve the TDyst; however, it is not in the best long-term interest of the patient.

As a number of patients on neuroleptics have an underlying psychiatric illness requiring treatment, it may be impossible to stop neuroleptics entirely. In patients who require antipsychotic medications, switching to an atypical agent such as olanzapine or quetiapine is suggested. Both these drugs may cause improvement of the dystonia for several weeks; however, olanzapine itself may cause TDyst, and long term results of quetiapine are not available.

Clozapine is an atypical antipsychotic which may provide sustained benefit in TDyst. It is uncertain whether the benefit from clozapine is due to its anticholinergic properties, its 'loose' binding of dopamine receptors, or the fact that the offending agent has been removed. A rare but potentially fatal adverse effect is agranulocytosis, and blood work must be checked regularly.

Clozapine has also been reported to cause tardive oculogyric crisis; rapid withdrawal of clozapine may also cause severe dystonias and dyskinesias.

Medications that work on the GABAergic system such as benzodiazepines and baclofen have been used with variable success and are worth trying if there is no improvement or there are problems tolerating other medications. Occasionally dopamine agonists, amantadine, and clonidine have been helpful.

For focal dystonia, botulinum toxin injections into the affected muscles can be quite helpful. For severe refractory dystonia, bilateral deep brain stimulation (DBS) of the globus pallidus interna (GPi) significantly improved both motor and disability scores by at least 80% in six cases followed by Sako et al. for a mean of 21 months. Moreover, the psychiatric status remained stable in each case.

Prognosis

Unlike TD, this syndrome is less responsive to treatment and is often painful. Significant disability in severe cases of TDyst is not uncommon. In a study by Kiriakakis and

colleagues of 107 TDyst patients, there was only 14% remission over a mean follow-up of 8.5 years. Discontinuing neuroleptics increased the remission rate four-fold, while those on neuroleptics for 10 years or less were five times more likely to remit. Patients with TDyst on neuroleptics for more than 10 years have essentially no chance of remission.

In a follow-up study conducted in 2008 by van Harten and colleagues, in the 26 patients (mean age 53.3 years) with TDyst at baseline, 64% recovered, 20% persisted, and 16% had an intermittent course over a 9 year follow-up. The cumulative incidence of TDyst (in those without baseline TDyst) over 9 years of follow-up was 16.1% (27/168). Mean age was similar at 57.6 years, and this group did a bit better – 80% recovered, 8% had persistent dystonia, and 12% had an intermittent course (defined as anything other than TDyst at all assessments or TDyst absent at last assessment). The most common sites of involvement were the upper limbs, eyes, neck, and mouth. While they mentioned whether the patients were on a first generation antipsychotic or one of olanzapine, clozapine, or risperidone at each visit, the dosages were not given nor was any information regarding symptomatic treatments. The prognosis in this carefully followed population is better than what has previously been reported in TDyst.

See also: Anticholinergics and Movement Disorders; Dopamine Depletors and Movement Disorders; Dystonia; Dystonia, Drug-induced (Acute); Neuroleptic-induced Nonhuman Primate Models of EPS and TD; Neuroleptics and Movement Disorders; Tardive Syndromes.

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Tardive Syndromes

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Glossary

Dopamine – A neurotransmitter that functions in several areas in the brain, including the basal ganglia. It affects multiple brain functions including motor planning, reward, and attention. Once released, it interacts with the dopamine receptor to trigger its effects.

Neuroleptic – An antipsychotic medication that acts to change cognition or behavior.

Tardive akathisia – A disturbing sense of inner restlessness, with the outward manifestation of

semi-voluntary fidgety movements, that occurs as a chronic side effect of dopamine-blocking medications.
Tardive dyskinesia – Repetitive, stereotyped movements, most commonly of the mouth and tongue, that occur as a chronic side effect of dopamine-blocking medications.
Tardive dystonia – Sustained twisting movements, most commonly of the neck and trunk, that occur as a chronic side effect of dopamine-blocking medications.

Definition and History

In 1952, chlorpromazine (Thorazine) became the first dopamine-blocking agent used clinically in the treatment of psychosis. Four years after its release, the first case report of abnormal mouth movements as a side effect was published. The term 'tardive dyskinesia' was coined in 1964, as it became clear that the movements were the late effects of treatment.

Tardive syndromes are now understood to be a group of movement disorders that emerge after chronic treatment with centrally acting medications that block the dopamine receptor. There are three major classes of movements that can be seen in this setting: tardive dyskinesia, tardive dystonia, and tardive akathisia. Each has its own clinical features, natural history, prognosis, and treatment. Tardive dyskinesia refers to repetitive, stereotyped movements that most typically involve the mouth and tongue. Tardive dystonia refers to sustained twisting movements, most commonly of the neck and the trunk. Tardive akathisia refers to a disturbing sense of inner restlessness, with the outward manifestation of semivoluntary fidgety movements. Other types of movements attributed to dopamine blockade, such as tardive myoclonus, tardive tics, tardive chorea, and tardive tremor, have also been described. More than one of these conditions can exist in the same patient. Because these conditions can persist for years and can even be permanent and because they are caused by medications prescribed by physicians, they are a particularly problematic complication of therapy with dopamine-blocking agents.

Tardive syndromes must be distinguished from acute movement disorders that occur due to dopamine blockade, which are significantly more treatable and reversible. Acute dystonic reactions, including oculogyric crises, are responsive to antihistamines (such as diphenhydramine), anticholinergics (such as benztropine), and benzodiazepines (such as diazepam). Even if they are not treated, they always resolve over time after the cessation of the dopamine-blocking agent. Acute akathisia can be responsive to beta-blockers or anticholinergics and also resolves with the removal of the offending agent. Drug-induced parkinsonism is a common and well-described phenomenon, which can look identical to idiopathic Parkinson's disease (PD), but may be more symmetric in onset. Although it may take several months after neuroleptics are stopped for parkinsonism to resolve, it almost always does. If parkinsonism does not resolve, a diagnosis of idiopathic PD must be considered, as these agents may unmask the symptoms of PD. The existence of the diagnosis of tardive parkinsonism remains in question.

Dopamine-blocking medications include 'typical' antipsychotics such as chlorpromazine (Thorazine), thioridazine (Mellaril), trifluoperazine (Stelazine), and haloperidol (Haldol). The newer antipsychotic medications such as olanzapine (Zyprexa) and risperidone (Risperdal) have been referred to as 'atypical.' A lower risk of tardive syndromes has been linked to these drugs compared with the typical medications, although the risk is not zero. Ziprasidone (Geodon) and aripiprazole (Abilify) are newer, but have also been shown to cause tardive movements. The only truly atypical antipsychotics are quetiapine (Seroquel) and clozapine (Clozaril), although there are case reports of even these medications causing tardive syndromes. Antipsychotics are not the only type of medication that can cause dopamine blockade. Medications for nausea, including metoclopromide (Reglan) and prochlorperazine (Compazine), can also cause tardive syndromes. Interestingly, medications that act on the presynaptic dopamine system such as reserpine and tetrabenazine (TBZ) have not yet been shown to cause tardive syndromes.

Pathogenesis/Pathophysiology

The pathophysiology most accepted for tardive disorders is that with chronic use of dopamine-blocking agents, the dopamine receptors become oversensitized, leading to abnormal movements. The details of how that process occurs are not well understood. There are five known dopamine receptor subtypes, D1 through D5, which are present in various locations throughout the brain. Blockade of the D2 receptor is responsible for the tardive phenomenon. Agents that preferentially block other dopamine receptor subtypes are safer in this regard. One theory suggests that movements result from an imbalance between D1 and D2 signaling – with the blockade of the D2 receptor, D1 signaling is unchecked.

One classic feature of tardive syndromes is that they are more likely to start or become worse if the dopamine-blocking medications are stopped or reduced quickly, leading the oversensitized receptors to be released from their blockade. This also explains why increasing the dopamine-blocking medication can be used as a method to quickly suppress the tardive movements when they

start, although the suppressed symptoms may later reemerge and be more severe.

Other neurotransmitters, besides dopamine, such as acetylcholine, GABA, and glutamate have been implicated in the development of tardive movements. Theories include the disruption of the balance of dopamine and acetylcholine in the basal ganglia, direct damage to striatal cholinergic and/or GABAergic interneurons, insufficient GABAergic inhibition of dopamine release, or excessive glutamatergic stimulation. In addition, oxidative damage has been hypothesized to play a role. Treatments that counteract these abnormalities have been suggested and tested (see the Management section).

Epidemiology/Risk Factors

Incidence and prevalence of tardive dyskinesia vary widely between studies, due to the differences in assessment, the types of medications used, and the type of population under study, among other variables. Prevalence has been shown to range from 12.3% for psychiatric outpatients to 37.4% among psychiatric inpatients. In one study, the prevalence of tardive movements among patients in an outpatient psychiatric center was found to be as high as 44%.

In 1988, Kane et al. determined the incidence of tardive dyskinesia in the setting of first generation antipsychotics to be 5% per year, increasing to 19% by 4 years. The prevalence rate of tardive dyskinesia tends to stabilize around that time, as the remission rates equalize with rates of new cases. The rates in the population of over 55 years of age, however, were higher than 19%. In 1998, Woerner et al. studied a group of elderly neuroleptic naïve patients and found that the rates of tardive dyskinesia were 25%, 34%, and 53% after 1, 2, and 3 years of treatment respectively, leading to the conclusion that the elderly population is 3–5 times more susceptible to this condition.

The introduction of a new generation of antipsychotics brought with it the hope and possibility of lower rates of tardive syndromes. In 2008, Correll and Schenk conducted a meta-analysis comparing the rates of tardive due to first and second generation antipsychotics. Across all ages, first generation antipsychotics had an annual risk of tardive dyskinesia of 5.5%, while second generation antipsychotics had an annual risk of 3.9%. However, some individual studies showed annual rates of less than 1% for second generation antipsychotics. This variation between studies may reflect the inherent difficulty of screening patients properly for all the past exposures to first generation neuroleptics. The Correll and Schenk meta-analysis determined that the prevalence of tardive syndromes in adults was 13% for second generation antipsychotics and 32% for first generation medications. Rates of tardive dyskinesia in children are low. One study showed an annual rate of 0.35% for second generation medications.

It has been reported that schizophrenics never exposed to dopamine-blocking agents have a higher rate of spontaneous facial dyskinesia than the general population, and that this can confuse epidemiological studies. This assertion relies on accurate prior medication reporting, which is difficult to assess in the schizophrenic population.

Epidemiologic studies have revealed many interesting features of the tardive population. Age is a major risk factor for tardive syndromes. Incidence increases and remission rates decrease with age. Other risk factors include increased duration of exposure to medications, increased total dose administered over time, presence of alcoholism or preexisting brain damage, higher severity of psychiatric illness at baseline, and poor response to antipsychotic medication. In addition, trials of multiple different agents increase the risk over maintaining a single agent, although this risk factor is difficult to separate from the severity of psychiatric illness. Stopping and restarting the medications increases the risk as well. The development of acute or early symptoms from these medications may predispose an individual to the later development of tardive syndromes. Elderly patients on antipsychotics in the context of dementia develop tardive syndromes less frequently than those on antipsychotics for schizophrenia or affective disorders. Finally, gender is a risk factor, and elderly women have higher rates of tardive dyskinesia than elderly men.

The risk factor profile for tardive dystonia is somewhat different than tardive dyskinesia. Kang et al. showed in 1986 that in contrast to tardive dyskinesia, younger patients tend to have more severe tardive dystonia than older patients. In 1998, Kiriakakis et al. showed that tardive dystonia develops after a shorter exposure in men than in women.

Not all treated individuals with the same risk factor profile will behave similarly in their development of tardive syndromes. Genetic risk factors that may help to explain the diversity of response to these medications have begun to be identified. Polymorphisms in the dopamine D3 receptor, the serotonin 5-HT2C receptor, and the superoxide dismutase-2 enzyme have all been associated with increased risk of tardive dyskinesia.

Clinical Features and Diagnostic Criteria

The diagnostic criteria for tardive dyskinesias have been developed by the American Psychiatric Association Task Force on Tardive Dyskinesias. The movements should improve with an increase of the neuroleptic dose and worsen with a reduction or discontinuation of the medications. The movements should develop either while the patient is on neuroleptics or within a few weeks of discontinuing the medication. They should be present for at

least 4 weeks, after at least 3 months of total cumulative neuroleptic exposure. Although these are the guidelines, tardive symptoms have been reported to start months to years after the medication is stopped and after only a single dose of dopamine-blocking medications. In general, tardive dystonia is more likely to start after a briefer exposure to medication than tardive dyskinesia.

Tardive Dyskinesia

The most common and well described of the tardive syndromes is tardive dyskinesia. Classically, this movement disorder involves oro-buccal-lingual movements, including lip puckering, tongue popping, and lateral jaw movements. Breathing can also be affected, with repetitive gasping and respiratory dysrhythmia. Rhythmic abdominal and pelvic movements can also be seen. The repetitive flexion and extension of the fingers, known as 'piano-playing' fingers, is another manifestation. The flexion and extension of the toes can also occur. The movements are stereotyped, and this differentiates them from choreic movements, which are by definition, erratic and affect various parts of the body in a random, flowing manner. Tardive movements are typically suppressible to some degree.

Tardive Dystonia

Tardive dystonia presents most commonly as retrocollis, back arching, and internal rotation of the shoulders with flexion at the elbows. The dystonia often has a jerky quality, with sustained bursts of stereotyped movements. Blepharospasm and jaw dystonia are other common manifestations. Other forms of cervical dystonia are also possible such as anterocollis, laterocollis, or torticollis, but retrocollis is most often associated with tardive dystonia. Tardive dyskinesia may accompany dystonia. Unlike tardive dyskinesia, which is often not noticed by the patient, tardive dystonia is typically very distressing. The dystonia may be indistinguishable from idiopathic dystonia and accompanied by many of the same features, including sensory tricks. Dystonia tends to begin focally, and then to spread. Younger people are more likely to have generalized disease than older people. The head and the neck are most commonly affected first and are the most severely affected body parts.

Tardive Akathisia

Since akathisia is a well-described acute reaction to dopamine-blocking medications, it was not immediately recognized by the medical community that this phenomenon could also develop as a chronic side effect. In 1989, Burke et al. presented their experience with this disorder. They described the movements that the clinician sees, which are often volitional and are a reflection of the agitation, such as trunk rocking, knee abduction/adduction, marching in place, and leg crossing/uncrossing. The lower body is most often involved, although trunk rocking and complex hand movements can also be seen. Most patients with tardive akathisia also have tardive dyskinesia and/or tardive dystonia. Akathisia is probably the most distressing of the three major syndromes to the patient.

Other Tardive Disorders

In a study by Tominaga et al., 24% of patients taking neuroleptics for more than 3 months demonstrated postural myoclonus, documented by electromyogram (EMG). Clonazepam reduced these movements.

The withdrawal emergent syndrome causes chorea in the setting of an abrupt withdrawal of a neuroleptic. Although tardive dyskinesia is stereotyped and rhythmic, the chorea of this syndrome migrates from place to place without pattern. Withdrawal emergent syndrome occurs mostly in children and usually resolves completely with reinstatement of the dopamine-blocking agent and the institution of a slow taper. Motor and vocal tics have been reported as tardive phenomena. Tardive tremor is a rare phenomenon and refers to a rest and postural tremor that develops in a patient previously exposed to dopamine-blocking agents.

Differential Diagnosis and Diagnostic Work-up

The patterns of both tardive dyskinesia and tardive dystonia tend to be very characteristic, and an experienced clinician may strongly suspect the diagnosis even before obtaining a history of neuroleptic use. The suspicion may be so high that even if the patient is not aware of past neuroleptic use, a thorough investigation may reveal it. On the other hand, if other neurological features exist on examination, then an alternative explanation for the movements should be sought. There are no laboratory or imaging tests that can confirm tardive syndromes.

Tardive Dyskinesia

Differential diagnosis for tardive dyskinesia includes Huntington's disease, although unlike tardive dyskinesia, the choreic movements of Huntington's move from one part of the face to another, without a distinguishing pattern. Huntington's disease also involves the upper face, which is not present in tardive dyskinesia, unless it is complicated by tardive blepharospasm. Other causes of choreic mouth movements include hyperthyroidism and systemic lupus erythematosis. Idiopathic oromandibular dystonia can look like tardive dyskinesia as well, although these movements tend to have more of an effect on talking

and eating. In the right setting, edentulous dyskinesias must be considered. Parkinsonian tremor of the jaw can be confused with tardive and may be attributable to the use of dopamine-blocking agents or to PD itself. Other diagnoses to consider include facial tics, hemifacial spasm, myokymia, brainstem infarctions, neuroacanthocytosis, and epilepsy partialis continua.

Tardive Dystonia

It may be difficult to distinguish tardive dystonia from idiopathic dystonia. Inherited dystonias, dopamine-responsive dystonias, and Wilson's disease should be considered in the younger population.

Tardive Akathisia

Tardive akathisia can be difficult to distinguish from an agitated depression, which may be the reason the dopamine-blocking agent was given in the first place. Distinguishing these two conditions is important as they have opposite treatments; akathisia requires the removal of the dopamine agonist, whereas agitated depression may require an increased dose. Restless leg syndrome may resemble tardive akathisia, although it is typically present only at night and only involves the legs.

Management

Tardive Dyskinesia

As tardive syndromes can be difficult to treat, the clinician's focus should always be on prevention, by avoiding or minimizing exposure to dopamine-blocking agents. Dopamine-blocking agents should be reserved for patients with appropriate problems, and generalists and neurologists might benefit from a psychiatric consultation on alternative options to these agents. The lowest dose of the drug should be used. The treatment plan should be periodically reassessed to see if the dopamine-blocking agent is still needed. The patient should be periodically examined to determine if tardive symptoms are present. It is generally advised that frequent initiation and withdrawal of the medications should be avoided.

If the patient is on a dopamine-blocking agent when the tardive movements begin, the first plan of action should be to slowly titrate the patient off of the medication if possible. Stopping the medication too quickly can exacerbate the disorder. If the patient is dependent on neuroleptics because of a psychiatric condition, the patient can be switched to clozapine. Although there are case reports that suggest that clozapine causes tardive syndromes, in virtually all these reports, the patient had prior exposure to other neuroleptics. Regardless, if there is a risk of tardive syndromes with clozapine, it is very low. Clozapine, however, is associated with a 1% risk of agranulocytosis and requires weekly blood draws for monitoring. It is therefore not an ideal medication for many patients.

The literature remains unclear as to whether clozapine treats tardive dyskinesia or is just the neuroleptic of choice to avoid the syndrome. In most studies, clozapine had a beneficial effect on movements, but these tended to return when clozapine was stopped. A minority of patients had sustained improvement. Clozapine likely suppresses tardive movements successfully until the natural history of the condition plays out and improvement or remission is achieved.

If the movements persist despite stopping the dopamine-blocking agent, a number of other strategies can be tried. Tetrabenazine (TBZ) and reserpine are dopamine-depleting agents, which work as vesicular monoamine transporter (VMAT) inhibitors. VMAT normally transports norepinephrine, serotonin, and dopamine into presynaptic vesicles. If the transporter is inhibited, the neurotransmitters are not protected and are degraded by monoamine oxidase (MAO) and cathechol-*O*-methyl transferase (COMT), thereby leading to dopamine depletion. This class of medicine has been used for other hyperkinetic disorders such as chorea, hemiballismus, and tics. TBZ has some dopamine receptor blocking action, but this mechanism appears to be clinically inconsequential, since tardive dyskinesia has not been reported with the use of this drug. α-Methyl-*para*-tyrosine (AMT) is a tyrosine hydroxylase inhibitor and can also be useful in tardive syndromes by decreasing the dopamine availability. It is a milder agent than TBZ or reserpine and normally is effective only if it is added either to one of these agents or to a neuroleptic. Combinations of TBZ and AMT are more effective at controlling these movements than each alone. Combining reserpine and AMT, however, may cause excessive hypotension.

Recently, the Food and Drug Administration (FDA) approved TBZ for the treatment of chorea in Huntington's disease, and it is now available in the USA. Prior to this, only certain movement disorder centers had access to this medication, and patients were required to pay out of pocket for it. Depression and parkinsonism are serious side effects of TBZ and reserpine, which limit their use in predisposed individuals. All patients exposed to TBZ must be followed with vigilance for subtle emergence of depressive signs. Whereas tardive dyskinesia has not been described with TBZ, the overall population exposed to this drug chronically remains relatively small, and since it is used to treat patients with hyperkinetic disorders, the emergence of tardive dyskinsesia may be difficult to distinguish from the underlying disorder being treated (Huntington's disease, tics). For this reason, consultation with movement disorder specialists may be particularly useful when patients are treated with TBZ.

A vast number of other medications have been tried with varying degrees of success. Most of the studies that

report benefit were conducted on very small populations. In addition, very few were randomized, double-blinded, case-controlled and placebo-controlled studies, and are therefore hard to interpret. Cholinergic medications were not successful, although anticholinergic medications seem to make tardive dyskinesia worse. Modifiers of the GABA system such as baclofen, valproic acid, and benzodiazepines all showed mixed results in various trials. Although trial results of lithium have been mixed, recent evidence suggests that lithium may confer protection from tardive phenomena, reducing the risk of onset of tardive dyskinesia as well as improving the outcome of tardive dyskinesia when it occurs. Although the data from these various trials may be unclear, a small percentage of patients appear to derive benefit from these medications. In clinical practice, it is therefore prudent to try benzodiazepines, valproic acid, baclofen, and lithium when faced with a patient who has failed the dopamine-depleting agents.

Other medications that have been tried in mostly non-randomized studies include amantadine, calcium channel blockers, branched-chain amino acids, gabapentin, and a combination of acetazolamide and thiamine. The results of these studies are difficult to interpret because of trial design. The antioxidant Vitamin E has been subjected to multiple trials with some promising results. More recently, double-blind, placebo-controlled studies of melatonin, the combination of naltrexone and clonazepam, Vitamin B6, piracetam, and levetiracetam were conducted, all showing efficacy. However, these studies were typically done in small groups of patients for short periods of time. Botulinum toxin has been tried with some promising results.

The fact that so many different medications with varying mechanisms of action have been tried for this condition indicates that the field has yet to find a truly effective treatment. Larger trials are needed to further examine the effects of drugs found promising in smaller trials.

The clinician should always remember that if the movements are not bothersome to the patient, they do not need to be treated, besides the removal of the offending agent. If, on the other hand, the tardive movements are very severe and cannot be tolerated, restarting a neuroleptic should work to control the movements in the short term, although there is a real danger that, in the long run, this will worsen the movements.

Tardive Dystonia

Unfortunately, tardive dystonia is harder to treat than tardive dyskinesia and spontaneous remissions occur less often. Many of the same principles outlined for the treatment of tardive dyskinesia hold true. If possible, the neuroleptic should be tapered off very slowly and clozapine should be the neuroleptic of choice. In 1982, Burke et al. showed a 68% improvement with TBZ. Clonazepam may also offer relief.

There are some treatment options that are unique to tardive dystonia. Burke et al. showed in 1982 that anticholinergics that are effective in idiopathic dystonia improved tardive dystonia in 39% of patients, although they may worsen tardive dyskinesia. Botox injections can be helpful if the dystonia is isolated to a few injectable muscles.

Pallidotomy and thalamotomy were demonstrated to be effective for the treatment of tardive dystonia in some small case series. The first case report of deep brain stimulation for the treatment of tardive dystonia was published in 2001. Electrodes were placed into both the globus pallidus pars interna (GPi) and the ventral intermediate (VIM) thalamus. Only the stimulation of the GPi was effective in reducing the patient's dystonia. Since then, this finding has been repeated in a number of case reports and case series.

Tardive Akathisia

This syndrome may be the hardest of the three main syndromes to treat. A study by Burke et al., 1989, showed TBZ and reserpine to be the most effective medications in this condition, producing improvement in 87% and 58% of patients treated. Benzodiazepines may be useful as well.

Prognosis

Tardive Dyskinesia

There is an exceedingly wide variation in reported remission rates in the published literature, from 0% to 92%. Remission rates are difficult to calculate, as many patients with this condition continue to take neuroleptics, which as discussed earlier, can suppress the movements in the short term. Remission rates also vary by age, as it is well recognized that younger people have higher remission rates than the elderly. Finally, the length of follow up of the study is crucial, as tardive syndromes can wax and wane in their presentation. Wegner and Kane reevaluated patients previously determined to have undergone remission of their tardive dyskinesia. All of the five patients studied had persistence of abnormal movements.

In 2001, Fernandez et al., examined the natural history of tardive dyskinesia in an inpatient psychiatric facility over the course of 14 years. Of the 53 patients that were followed, 19% worsened, 15% stayed the same, 4% improved, and 62% had resolution of symptoms. These results were in the setting of ongoing neurolepticuse. However, patients with the most improvement in their tardive symptoms tended to have worse parkinsonism. Other studies have shown that complete recovery is unusual, but that the majority of patients have substantial improvement with time.

Tardive Dystonia and Akathisia

Kiriakakis et al. showed in their 1998 study that remission rates for tardive dystonia were 14%, over a follow-up period of 8.5 years. Interestingly, patients with less than 10 years of exposure to neuroleptics had a 5 times greater chance of remission than those with greater than 10 years of exposure. In 1989, Burke et al. showed remission rates of 33% in tardive akathisia.

The tardive movement disorders are a collection of difficult-to-treat syndromes that result from exposure to dopamine-blocking agents. Although prevention of exposure to these medications is the best way to avoid these syndromes, this is not always possible. The syndromes may remit, but often do not. TBZ is the most effective drug to date and has recently been approved in the USA. The side effect of depression, however, makes it a poor choice for many psychiatric patients. Multiple other medications have been tried for these conditions, but none has convincingly shown a benefit. A number of small trials of various compounds have recently been conducted which have shown some promise. Larger trials of these medications are necessary to investigate their potential as treatments for this difficult array of diseases.

See also: Akathisia; Dopamine; Dopamine Depletors and Movement Disorders; Drug-induced Movement Disorders; Dystonia, Drug-induced (Acute); Neuroleptic-induced Nonhuman Primate Models of EPS and TD; Neuroleptics and Movement Disorders; Oral Dyskinesia; Tardive Dystonia.

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Relevant Websites

www.movementdisorders.org – Movement Disorder Society.

Tauopathies

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Glossary

Alternative splicing – Modification of a mRNA transcript due to exclusion and/or rearrangement of exons.
Apraxia – Loss of the ability to carry out learned purposeful movements, despite having the physical ability to perform them.

Atypical parkinsonian disorders – Parkinsonian disorders that differ from Parkinson's disease as patients exhibit features such as rapid progression, poor or transient response to dopaminergic therapy, early falls, oculomotor abnormalities, early autonomic failure, pyramidal and cerebellar signs, hallucinations, early cognitive impairment, apraxia, and alien hand syndrome.

Dystonia – Abnormal movement characterized by sustained muscle contraction, leading to twisting, abnormal postures, or repetitive movements.
Freezing – Manifestation of akinesia characterized by sudden incapacity to continue moving or to start a movement.
Neurodegeneration – Pathogenic process, usually of unknown or genetic etiology, that leads to progressive cell loss in specific neuronal populations, with consequent loss of previous normal functions.
Oculogyric crisis – Dystonic movement in which the eyes deviate tonically, usually upwards.
Parkinsonism – Clinical syndrome characterized by bradykinesia and at least one of the following features: rest tremor, rigidity, or postural instability.
Pseudobulbar palsy – Dysfunction of lower cranial nerves responsible for swallowing and speech, caused by lesions in the pathways that connect higher cortical centers and the nuclei localized in the medulla (bulbar). It mimics a bulbar palsy, but lower cranial nerve nuclei are preserved.
Supranuclear gaze palsy – Oculomotor abnormalities originating in cortical or subcortical oculomotor centers or linking pathways with oculomotor nuclei in the brainstem. Because the oculomotor nuclei are preserved, the oculocephalic reflex is intact.

Definition

Neurodegenerative disorders are primary disorders of the central nervous system (CNS) in which there is progressive neuronal loss. They are grouped depending on neuropathological characteristics, particularly the proteins present in the specific inclusions. In neurodegenerative causes of parkinsonism, the major component of the intracellular inclusions can be α-synuclein, tau protein, or TDP-43, leading to their classification as α-synucleinopathies, tauopathies, and TDP-43opathies. Although there are clinical features that may suggest the diagnosis, differentiation of tauopathies from α-synucleinopathies and TDP-43opathies is not always possible on clinical grounds and definite diagnosis relies on neuropathology.

The three major tauopathies that present as movement disorders are progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17). Other tauopathies are listed in **Table 1**. Most occur sporadically, but some can be inherited, such as FTDP-17. Some disorders do not have a 'pure' tau pathology, such as Alzheimer's disease (AD) (**Table 2**).

The Normal Tau Protein

Tau is a cytoskeletal phosphoprotein codified by the MAPT gene in the chromosome 17q21. It promotes microtubule polymerization and stability, playing a fundamental role in axoplasmatic transport, axonal growth, neuronal polarity, and neuronal integrity. It may also regulate intracellular signal transduction, development, and viability of the neurons.

In the normal adult brain, there are six isoforms of tau protein that result from alternative splicing of the MAPT gene. A microtubule-binding domain is present in exons 9, 10, 11, and 12. The alternative splicing of exon 10 gives rise to the 3R and the 4R isoforms, respectively, with three and four microtubule-binding domains. Additionally, the alternative splicing of exons 2 and 3 leads to three N isoforms. The normal brain has a ratio of 3R/4R isoforms of ~1:1. **Figure 1**

Table 1 Tauopathies – clinical entities

- Progressive Supranuclear Palsy
- Corticobasal ganglionic degeneration
- Lytico-Bodig disease (or amyotrophic lateral sclerosis and parkinsonism-dementia complex of Guam)
- Guadeloupean Parkinsonism
- Postencephalitic Parkinsonism
- Pallido-nigro-luysial degeneration
- Pick's disease
- FTDP-17
- Argyrophilic grain disease
- Neurofibrillary tangle dementia/tangle only dementia
- Progressive subcortical gliosis
- Diffuse neurofibrillary tangles with calcification
- Sporadic multisystem tauopathy with dementia

Table 2 Diseases with tau-positive neurofibrillary inclusions, but in which these are not the main pathological feature

Disease	*Predominant neuropathologic feature*
Alzheimer's disease	Amyloid deposition
Down's syndrome	
Dementia pugilistica	
Familial British dementia	
Familial Danish dementia	
Creutzfeldt–Jacob disease	Prionic protein deposition
Gerstmann–Sträussler–Scheinker disease	
Prion protein cerebral amyloid angiopathy	
Niemann–Pick type C	Glycolipids inclusions
Pantothenate kinase-2 deficiency	Iron containing pigments

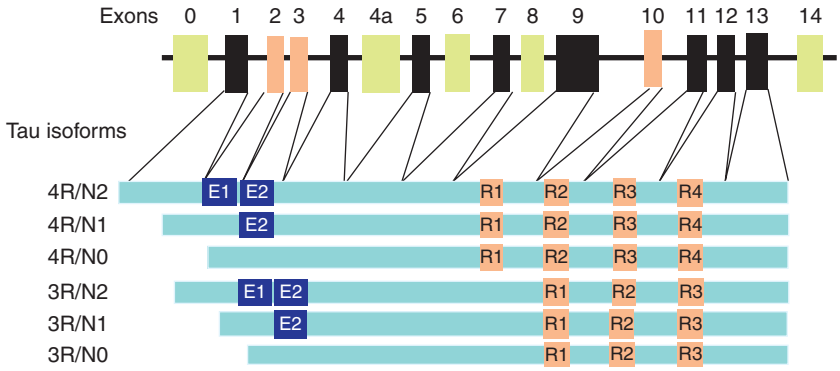

Figure 1 The MAPT gene and the six tau isoforms. The MAPT gene contains 16 exons (E). Alternative splicing of E2, E3, and E10 produces the six isoforms. Exons 9–12 encode microtubule-binding repeats (R1 to R4). Alternative splicing of E10 produces the 3R and 4R tau isoforms and alternative splicing of E2 and E3 produces the N0, N1, and N2 isoforms. Exon 3 is always co-expressed with exon 2, explaining why only three isoforms result from alternative splicing of these two exons. E6, E8, and E4a are not transcribed in human CNS. Reproduced from Forman MS, Lee VMY, and Trojanowski JQ (2000) New insights into genetic and molecular mechanisms of brain degeneration in tauopathies. *Journal of Chemical Neuroanatomy* 20: 225–244, with permission from Elsevier.

shows the six different tau isoforms and their relationship with the alternative splicing of exons 2, 3, and 10.

Tau protein undergoes posttranslational modifications, including phosphorylation, glycosylation, glycation, ubiquitination, truncation, and nitration, that determine its functional state.

Tau Pathology in Tauopathies

The tau-positive intracellular inclusions are composed of insoluble fibrillary aggregates of hyperphosphorylated tau. The abnormal hyperphosphorylated tau protein may form two kinds of filaments: the paired helical filaments (PHF), with a periodic helical twist, and the straight filaments (SF), that lack the helical periodicity. The various tauopathies accumulate different kinds or proportion of filaments, which constitutes an important ultrastructural differential marker (**Table 3**). In addition, the ratio of tau isoforms in the insoluble aggregates is specific for different tauopathies, allowing the biochemical classification as 3R, 4R, and 3R–4R tauopathies (**Table 4**).

The neuropathological heterogeneity of tauopathies is also reflected in the intracellular location and type of the inclusions (**Table 5**), the vulnerable cell types that are affected (**Table 5**), and the anatomical distribution of the lesions in the CNS (**Table 6**). This diversity is not understood at the present time and may be related to the predominant tau isoform or interaction with still unknown specific cofactors.

Mechanisms of Neurodegeneration in Tauopathies

The mechanisms that lead to neurodegeneration in tauopathies are still largely unknown. The tau protein is thought to play an important role along with genetic, epigenetic, and environmental factors that may influence the clinical and pathological manifestations.

Table 3 Ultrastructure of tau inclusions in tauopathies and AD

	PHF	*SF*
AD	+++ (width 8–20 nm, twist: 80 nm)	±
PSP	±	+++ (15–18 nm)
CBD	++	++
Pick disease	++ (width 15–28 nm; twist:130–180 nm)	++ (10–15 nm)
Argyrophilic grain disease	–	+++ (9–18 nm)
Lytico-Bodig disease	+++	±
Postencephalitic parkinsonism	+++	±

Table 4 Biochemical classification of Tauopathies

4R tauopathies	*3R and 4R tauopathies*	*3R tauopathies*
• PSP • CBD • Argyrophilic grain disease • GP • Sporadic multisystem tauopathy with dementia • Pallido-nigral-luysial atrophy • Neurofibrillary degeneration of CA2	• AD • Postencephalitic parkinsonism • Lytico-Bodig disease • Amyotrophic lateral sclerosis and parkinsonism-dementia complex of Kii peninsula of Japan • Neurofibrillary tangle dementia • Diffuse neurofibrillary tangles with calcification	• Pick disease

Table 5 Typical tau-positive inclusions in tauopathies and AD

	Neurons		*Glial cells*	
	Cell body	*Neuronal processes*	*Astrocytes*	*Oligodendrocytes*
AD	Flame-shaped neurofibrillary tangles	Neuropil threads, neuritic plaques	No glial pathology	
PSP	Globose neurofibrillary tangles, balloned cells (uncommon)	Neuropil threads (sparse)	Tufted astrocytes, thorn-shaped astrocytes	Coiled bodies threads
CBD	Achromatic ballooned cells, neurofibrillary tangles	Neuropil threads (numerous)	Astrocytic plaques	Coiled bodies threads
Pick's disease	Pick's bodies, Pick's cells (ballooned neurons)	Neuropil threads (variable)	Glial pathology is less prominent than neuronal Thorn-shaped astrocytes	 Coiled bodies
Argyrophilic grain disease	Pretangle neurons, balloned neurons	Argyrophilic grains	Bush-like astrocytes, thin astrocytic plaques	Coiled bodies
Lytico-Bodig disease	Neurofibrillary tangles, Hirano bodies	Neuropil threads (sparse)	Granular hazy inclusions	Coiled bodies (sparse)
Postencephalytic parkinsonism	Neurofibrillary tangles		Cytoplasmatic inclusions, astrocytic tufts	

Table 6 Anatomical distribuition of tau pathology in different tauopathies

Disease	*Cortex*	*Subcortical structures*
PSP	Frontal lobe: precentral and premotor areas	Pallidum, subthalamic nucleus, substantia nigra, striatum, oculomotor complex, periaqueductal grey matter, superior colliculi, basis pontis, dentate nucleus
CBD	Asymmetric involvement of frontal and temporal lobes (mainly pre- and postcentral regions)	Substantia nigra, basal ganglia, brainstem nuclei
Pick's disease	Frontal and anterior temporal lobes, Dentate gyrus (granule cells), subiculum, entorhinal cortex (pyramidal cells)	Amygdala, external pallidum, substantia nigra, locus ceruleus, pontine nuclei
Argyrophilic grain disease	CA1, Entorhinal and transentorhinal cortex	Amygdala, hypothalamic lateral tuberal nuclei
Lytico-Bodig disease	Hippocampus, frontal and temporal lobes	Substantia nigra, locus ceruleus, hypothalamus (thalamus, basal ganglia)
Postencephalitic parkinsonism	Hippocampus, Insular cortex, frontal and temporal lobes	Substantia nigra, locus ceruleus, brainstem
Multisystem tauopathy with dementia	Frontal, temporal, and parietal neocortex	Basal ganglia, brainstem nuclei

Genetic Factors

The discovery of MAPT mutations in the most common familial tauopathy – FTDP-17, and their biochemical and pathogenic consequences, widened the knowledge about pathogenic mechanisms. There are around 40 mutations described since 1998. Mutations are clustered around the microtubule-binding domains and two types can be identified: mutations that decrease the ability of the tau protein to bind to microtubules and mutations that change the ratio of 3R/4R isoforms. Most mutations appear to affect the alternative splicing of exon 10 (**Figure 2**) with consequent alteration of the ratio of 3R to 4R tau isoforms.

The neuropathology of FTDP-17 is highly heterogeneous and can mimic the specific neuropathology of different sporadic tauopathies. The isoform that accumulates, the cellular type in which tau accumulation occurs and its subcellular topography are highly dependent on the nature and position of tau mutation.

FTDP-17 also can present clinically as any of the sporadic tauopathies. **Table 7** gives some examples of tau mutations and illustrates the heterogeneity in biochemical, neuropathological, and clinical phenotypes.

The H1/H1 haplotype has been identified as a genetic risk factor for the development of some of the 4R tauopathies such as PSP, CBD, and possibly also Guadeloupean parkinsonism (GP) and pallido-nigro-luysial degeneration (PNLD). This haplotype includes several polymorphisms that are in linkage desequilibrium in a genetic region that includes the MAPT gene. Two independent single nucleotide polymorphisms of MAPT

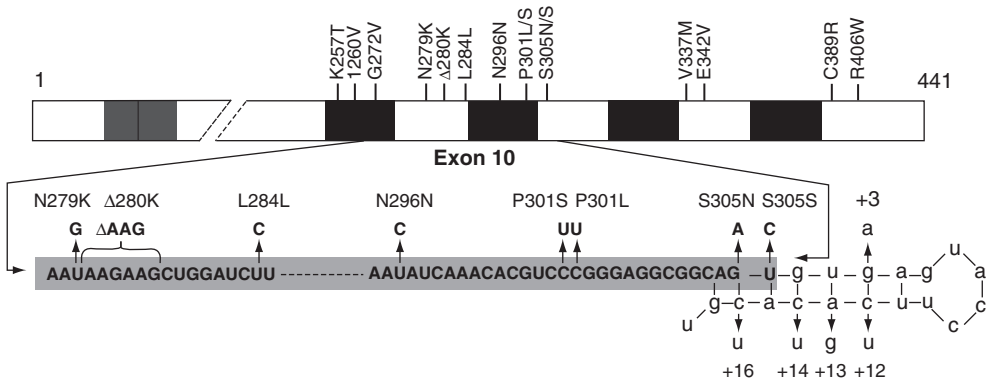

Figure 2 Schematic representation of MAPT mutations described in FTDP-17. The majority of MAPT mutations have been found in exons 9–13. The longest tau isoform is shown. Black boxes represent microtubule-binding domains. The second microtubule-binding domain is codified by exon 10, which is subject to posttranslational alternative splicing. Part of the pre-mRNA transcript that corresponds to exon 10 and downstream intron is detailed and mutations in this region are shown. A significant percentage if mutations occur in a stem-loop structure in the pre-mRNA transcribed at the downstrem end of exon 10 that regulates splicing of the exon 10 transcript. The lower case nucleotides correspond to intronic nucleotids. Reproduced from Lee VM, Goedert M, and Trojanowski JQ (2001) Neurodegenerative tauopathies. *Annu Rev Neurosci* 24: 1121–1159.

Table 7 Tau mutations and the heterogeneity of biochemical, neuropathological, and clinical phenotypes, mimicking sporadic tauopathies

Exon	*Mutation*	*Biochemical/neuropathological phenotype*	*Clinical phenotype*
1	R5L	4R > 3R, subcortical	PSP
1	R5H	4R > 3R, widespread	Late-onset dementia
9	I260V	4R only	FTD
9	G272V	4R = 3R, Pick bodies	Pick's
9	K257T	3R > 4R, Pick bodies	Pick's
9	L266V	Cortical/subcortical 3R = 4R, Pick-like pathology	Early-onset FTDP
10	N279K	Widespread, 4R > 3R*	FTDP, PSP-like
10	_280K	3R > 4R	FTD
10	L284L	4R > 3R	Presenile FTDP
10	P301L	4R > 3R, mini-Pick-like bodies (4R) and glial inclusions (3R)	FTDP
10	P301S	Widespread, 4R > 3R	Early-onset FTDP; CBD-like; supranuclear gaze palsy
10	N296N (ESS site)	CBD-like 4R ? 3R	CBD-like or FTDP
10	N296H	Cortical and subcortical: 4R?3R	FTDP
10–1	S305S	4R > 3R	FTDP or PSP-like
10–2	S305N	4R > 3R	FTDP
+ 11	T–C	4R > 3R, brainstem	FTDP with MR
+ 12	C–T	Pure 4R aggregates and 4R > 3R soluble	FTDP
+ 13	A–G	4R > 3R	FTD
+ 14	C–U	4R > 3R	DDPAC
+ 16	C–T	CBD-like 4R > 3R	FTDP or PSP-like
+ 19	C–G	3R soluble > 4R: no stable aggregates	FTDP
+ 29	G–A	3R soluble > 4R or 3R = 4R: no stable aggregates	FTDP
11	S320F	4R > 3R, Pick path. No N03R	Early Pick's
11	L315R	4R = 3R, Pick-like inclusions. No N03R	FTD, incomplete penetrance
12	V337M	4R = 3R, all six isoforms	FTD, paranoid and antisocial
12	E342V	Picks path, 4R > 3R; 4R0N ↑, 4RN1 and 4RN2 ↓	Pick-like
12	K369I	Pick's, severe temporal atrophy	Pick's
12	Q336R	3R and 4R: ratio not determined	Pick's
12	S352L,homozygous	Not determined; 4R present	Recessive, respiratory failure
13	G389R (GGG > AGG)	3R = 4R, Pick's	Pick-like
13	G389R (GGG > AGG0)	Not determined	Pick body-like inclusions and widespread tau filaments
13	R406W	4R = 3R, Pick's	Pick's

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N, amino acid, N-terminal insert; ESS, exon splice silencer; MR, mental retardation.

gene have been shown to influence the risk for developing Guam neurodegeneration. It is thought that these polymorphisms might influence exon 10 splicing.

It is suggested that the Val380Leu polymorphism of PARK2 gene may be protective for the development of sporadic or familial PSP.

Epigenetic Factors

Whether hyperphosphorylation is the cause or a consequence of tau protein instability is not yet known, but it seems to play a role in tau accumulation. There is also a putative role of unbound tau in the destabilization of the microtubule network, with consequent disruption of axonal transport.

Environmental and Toxic Factors

Studies on patients with GP support the role of mitochondrial dysfunction in neurodegeneration, two epidemiologic studies show significant exposure to tropical plants, such as *Annona muricata* (corossol, soursop), that contain high levels of mitochondrial enzyme complex I inhibitors. Annonacin, one of the toxic compounds has been shown to induce nigral and striatal neuronal degeneration in rats. Mitochondrial involvement with decreased complex I activity has also been demonstrated in cell lines expressing mitochondrial genes from PSP patients. There are markers of oxidative injury in specific brain regions in PSP patients, and oxidative stress has been proposed to result in kinase activation and consequent hyperphosphorylation.

These studies favor the role of mitochondrial dysfunction, environmental toxins, and oxidative stress in the pathogenesis of tauopathies.

Clinical Manifestations

Parkinsonism and dementia are the main clinical syndromes that characterize the tauopathies. Some have more prominent parkinsonism while others have more cognitive and behavioral impairment, but in later stages both usually coexist. The parkinsonism is characterized by an akinetic-rigid syndrome, usually without rest tremor, and mostly unresponsive to levodopa; dementia is usually of frontotemporal type (FTD). Typical features may help us identify a specific disorder.

The clinical picture of FTDP-17 includes frontal dementia, parkinsonism, dystonia, as shown in the sporadic tauopathies. Apart from a positive familial history and a younger age at onset, these tauopathies are not clinically nor pathologically distinguishable from the sporadic diseases. Molecular genetic analyses are required for the diagnosis.

Tauopathies with a Predominant Parkinsonian Syndrome

Progressive supranuclear palsy

PSP is a 4R tauopathy also known as Steele–Richardson–Olszewsky syndrome, honoring those who first described this disease in 1964. It is the most common sporadic tauopathy, accounting for 5% of parkinsonian patients seen in a movement disorder clinic. Its age of onset is usually in the sixties, and typically presents insidiously with early postural instability with falls within the first year of symptom onset, a predominantly axial, symmetrical and levodopa unresponsive akinetic-rigid syndrome, supranuclear gaze palsy mainly affecting vertical gaze, pseudobulbar palsy, and frontal cognitive and behavioral features. This typical phenotype is known as the Richardson's syndrome (RS). Frontal cognitive impairment, with marked executive dysfunction and apathy, is frequent. Validated clinical diagnostic criteria are highly specific for PSP tau pathology. Although these criteria have high sensitivity to the classical syndrome, they are much less sensitive to diagnose the atypical variants of the disease such as PSP – parkinsonism (when parkinsonism is preponderant and other classical features are missing), pure akinesia with freezing of gait, isolated FTD and corticobasal syndrome. The neuropathological differences in these variants are mostly quantitative and topographic, but some differences in isoform composition of tau fibrillary lesions have been described.

Corticobasal degeneration

CBD is also a 4R tauopathy originally described by Rebeiz and coworkers in 1967. It accounts for 1% of parkinsonian patients seen in a Movement Disorders Clinic. Age at onset is, on average, in the sixties, and there are two main clinical presentations: the classical lateralized corticobasal syndrome and a dementia syndrome. In the classical phenotype, both cortical and motor symptoms are unilateral or markedly asymmetric. The most common initial symptom is an asymmetrical progressive clumsiness and difficulty using one limb, usually the arm, related to apraxia, dystonia, rigidity, and less commonly alien limb. The dementia phenotype is characterized by early development of severe frontotemporal dementia usually accompanied by incontinence, pyramidal signs, bilateral parkinsonism, and followed then by a full-blown dementia with added cortical features (memory, attention, language, and frontal behavior disturbances). This cognitive phenotype tends to develop in the absence of motor symptoms.

Lytico-bodig disease

The Lytico-bodig disease was previously known as Guamanian amyotrophic lateral sclerosis/parkinsonism-dementia complex. It is an endemic 3R–4R tauopathy found in the indigenous Chamorro population at the island of Guam on the Western Pacific. Several environmental factors, such as plant neurotoxins, including the

one that exists in the cycad seeds (*Cycas micronesica*), have been proposed to explain the high prevalence and geographical clustering. Phenotype correlates with age at onset: youngest patients present with amyotrophic lateral sclerosis; oldest patients predominantly develop dementia; and parkinsonism is the prominent feature in middle age individuals. In all forms of disease, more than half (56%) of patients have a retinal pigment epitheliopathy that is also present in 16% of Chamorros.

Guadeloupean parkinsonism

GP occurs on the French West Indian island of Guadeloup and accounts for two-thirds of parkinsonian patients in that geographical location. The clustering of this disease has been associated with exposure to alkaloid toxins contained in fruits of the *Annonaceae* family. Two main syndromes characterized by both atypical parkinsonism with early postural instability and dementia have been described: one with supranuclear gaze palsy that resembles the RS and another one, without oculomotor abnormalities, that was named GP-dementia complex. Classical PSP can be distinguished from the Guadeloupean PSP-like phenotype by the presence of autonomic dysfunction, hallucinations, rapid eye movement (REM) sleep behavior disorder, and tremor (usually postural) in more than half of patients. Both phenotypes share identical neuropsychological and neuroimaging profiles. Brain MRI shows enlargement of the third and lateral ventricles and hypointense signals of basal ganglia, particularly substantia nigra but also putamen, globus pallidum and red nucleus, and midbrain atrophy, particularly in PSP-like syndromes.

Postencephalitic parkinsonism

Postencephalitic parkinsonism is a late complication of encephalitis lethargica, also known as 'sleep sickness,' first described by von Economo after the World War I. Influenza A virus has long been suspected as a cause. The most prominent clinical characteristics are: young onset, levodopa-responsive parkinsonism, slow progression over more than 10 years, oculogyric crisis and previous history of encephalitis. Nowadays, with the disappearance of encephalitis lethargica, the diagnosis of postencephalitic parkinsonism is unlikely.

Pallido-nigro-luysial degeneration

PNLD is a rare 4R tauopathy that involves the globus pallidus (pallido), the sustantia nigra (nigro), and the subthalamic nucleus of luys (luysial). Clinically, it is characterized by a slowly progressive akinetic-rigid syndrome, postural instability and vertical supranuclear gaze palsy, mimicking PSP. However, the timing of the features is different in PSP and PNLD: age at onset is on average 10 years younger and the initial signs are usually gait and handwriting disturbances. Dementia is absent even in advanced stages. Some investigators suggest that PNLD may be a clinical and pathological variant of PSP.

Tauopathies with Predominant Dementia Syndrome

Pick's disease

Pick's disease is a 3R tauopathy that was first described in 1892 by Arnold Pick. The term Pick's disease is usually applied to the cases of dementia with Pick's bodies. It accounts for 0.4–6.0% of all dementias. Onset is usually before age 65 years, and patients initially present with prominent FTD features. Parkinsonism is usually a late feature. Neuroimaging shows marked circumscribed frontal and/or anterior temporal atrophy. Fluorodeoxyglucose PET scan shows frontal and temporal hypometabolism.

Argyrophilic grain disease

Argyrophilic grain disease is a 4R tauopathy that accounts for 5% of all cases of dementia. Clinically, it is different from the above described FTD, as predicted by the more restrictive distribuition of tau pathology in mesial temporal and limbic regions. It is a late-onset dementia with mean age of onset of 75–80 years. The most common presenting symptoms are memory disturbances and personality changes, followed by delusions (mostly of persecution), dysphoria, and apathy. There are no other cognitive or sensory-motor functions remarkably affected. Clinicopathological studies have shown that it is overrepresented in the amnestic type mild cognitive impairment.

Other tauopathies presenting with dementia

Neurofibrillary tangle dementia or tangle only dementia is a sporadic subset of a very late-onset dementia, mainly in females over age 80 years. It is suggested to be a variant of AD occurring in the oldest-old.

Diffuse neurofibrillary tangles with calcification or Kosaka–Shibayama disease, has rarely been described in the literature, almost always in Japanese patients. Clinical phenotype is defined as an overlapping syndrome comprising memory changes, disorientation, dressing apraxia, and perseveration, like in AD, plus FTD. Parkinsonism is the most prominent accompanying motor feature. CT/MRI scan shows a localized temporal or temporofrontal atrophy with pronounced basal ganglia calcification.

Progressive subcortical dementia is a rare form of dementia with age of onset in the fifties, clinically characterized by abnormal behavior, cognitive impairment, and parkinsonism.

Sporadic multisystem tauopathy with dementia is a rare 4R tauopathy characterized by FTD with severe temporal atrophy and mild frontal and parietal atrophy. The clinical syndrome is not clearly defined.

Treatment

There are no current effective treatments for the tauopathies. Physical, occupational, and speech therapies to improve the quality of life and help prevent complications are the mainstays of treatment. Trials with inhibitors of

GSK3β such as lithium and valproic acid to slow disease progression are underway. In a near future, therapeutic approaches will probably focus on the modulation of hypothesized pathogenic mechanisms, such as regulation of alternative splicing, inhibition of tau aggregation and/or hyperphosphorylation, enhancement of mitochondrial metabolism, or induction of neurotrophic factors. Dopaminergic agents may be considered for the parkinsonian features, although these disorders are less likely responsive to levodopa than Parkinson's disease; monitoring for adverse effects on cognition and behavior is necessary.

Conclusion

Tauopathies are neurodegenerative disorders pathologically defined by the presence of intracellular tau-positive inclusions and clinically characterized by dementia and/or parkinsonism. Different tauopathies have specific clinical and neuropathological features, but significant overlap exists. Tau mutations leading to hyperphosphorylation have a significant a role in neurodegeneration. Clinical and pathological heterogeneity in familial tauopathies show that additional epigenetic and environmental factors probably play a role. Pathogenesis is far from being completely understood in the sporadic diseases. Tauopathies are a heterogeneous group of neurodegenerative disorders characterized by tau-positive inclusions. Definitive diagnosis is based in specific neuropathological features. Clinically, they present with atypical parkinsonism or dementia, both usually present in later stages. There is a significant clinical overlap between the different tauopathies. This heterogeneity and the clinical and neuropathological overlap are not understood at present time. MAPT mutations, posttranslation hyperphosphorylation of tau, oxidative stress, and mitochondrial dysfunction are thought to play a role, but other genetic, epigenetic and environmental factors are yet to be discovered. This huge complexity suggests that the pathogenesis is far from being completely understood, and hampers the development of specific neuroprotective strategies.

See also: Akinetic-Rigid Syndrome; Alien Limb; Amyotrophic Lateral Sclerosis/Parkinsonism-Dementia Complex of Three Pacific Isolates; Corticobasal Degeneration; Encephalitis Lethargica and Postencephalitic Parkinsonism; Eye Movement Abnormalities in Movement Disorders; Pallido-Nigro-Luysian Degeneration; PARK1, Alpha Synuclein; Progressive Supranuclear Palsy; Synucleinopathies.

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www.psp.org – Working for a world free of PSP.

Thalamotomy

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Glossary

Collimator – A device that filters a beam of rays so that only those traveling parallel to a specified direction are allowed to go through.

Gamma knife – A method of radiation therapy in which gamma radiation from multiple sources in a spherical distribution converge in a small target region. This method has been used for thalamotomy as an alternative method to the classic stereotactic surgical technique.

Microelectrode recording – A method of recording brain cells through a very fine electrode so that individual neurons can be recorded.

Radiofrequency coagulation – Targeted coagulation or lesioning of tissue by heat production resulting from high- (radio-) frequency electrical activity through a special electrode.
Thalamotomy – Stereotactic ablation of specific thalamic nuclei, primarily the ventral intermediate nucleus (Vim), for the treatment of movement disorders, particularly tremor.

Definition and History

Thalamotomy is ablation of pallidal receiving (ventral oral, Vo) and cerebellar receiving nuclei of the thalamus (nucleus ventral intermediate, Vim) for the treatment of movement disorders. It was first introduced by Hassler, who reasoned that the improvement in Parkinson's disease (PD) following lesions of the pallidum might also be gained following lesions of Vo, which receives input from the pallidum. Using microelectrode recordings, the area posterior to Vop, which was identified as the cerebellar receiving zone (Vim), was later found to have rhythmic bursting activity close to the frequency of tremor. Vim then became the thalamotomy target of choice for tremor of all types. The use of this operation has decreased significantly with the advent of deep brain stimulation (DBS) for the treatment of tremor.

Stereotactic Surgical Technique

Radiologic and physiologic landmarks are used to accurately localize the target for ablative procedures. Many surgeons employ radiologic localization of the anterior commissure (AC), posterior commissure (PC), and of the border between the capsule and thalamus, using CT or MRI scans. The radiologic estimate of location is refined, before radiofrequency lesioning, by microelectrode recording, semimicroelectrode recording, or by macrostimulation. The relative efficacy and safety of these different techniques have not been examined systematically.

Microelectrode recording in the ventral caudal nucleus (Vc), posterior to Vim, reveals sensory cells responding to sensory stimulation in small, well-defined, receptive fields. There is a well-described mediolateral somatotopy within Vc, proceeding from representation of oral structures medially to leg laterally. In Vim, neuronal firing is related to passive joint movement (deep sensory cells) or to active movement (voluntary cells), or to both (combined cells). Stimulation in Vc will evoke somatic sensations. Stimulation in Vim may produce brief movements or alter ongoing tremor or dystonia. An analysis of the locations of tremor cells suggests that the optimal target for thalamotomy is located 2 mm anterior to Vc and 3 mm above the ACPC line.

Targets in thalamotomy have been placed among deep sensory cells anterior to the cutaneous sensory cells and sites at which hand somatic sensory cells can be recorded. Lesions have also been made in the region where electrical stimulation produces effects on tremor and anterior to the region where cutaneous sensations are evoked.

Lesions are made by the technique of radiofrequency coagulation using an electrode with a 1.1 mm outer diameter and a 3 mm exposed tip and a thermister at the tip of the electrode (TM electrode, Radionics Inc., Burlington, MA). Temperature is held constant at 60 °C over a 1-min interval and then increased in 5–10 °C steps during subsequent 1-min intervals to a level of approximately 80 °C. Neurologic examination is carried out throughout coagulation and stresses function of adjacent structures such as cutaneous sensory, pyramidal, and cerebellar function, plus speech.

Randomized Controlled Trial of Vim Thalamotomy Versus Vim-DBS

A recent trial compared Vim thalamotomy with DBS in patients with Parkinson's tremor (PT) ($n = 45$), or essential tremor (ET) ($n = 13$), or intention tremor ($n = 10$). Across all types of tremor, functional status was improved in significantly more patients following Vim-DBS (54%, 18/33) than thalamotomy (24%, 8/34). Overall, tremor was abolished or a minimal residual was left in 30/33 (90%) of patients treated with Vim-DBS and 27/34 (79%) of patients treated with thalamotomy. Overall, significantly more patients (16/34) had complications postthalamotomy than following Vim-DBS stimulation (6/33).

Prospective, Uncontrolled Studies of Thalamotomy

The American Academy of Neurology recommendation regarding safety and efficacy of thalamotomy for PT was based upon a systematic evaluation of the literature. Overall, inexperienced centers had less success and more complications. Contraindications were cognitive, medical, or psychiatric conditions and abnormal imaging studies including focal lesions or atrophy greater than expected for age. Patients with advanced age derived less benefit.

For thalamotomy, 18 articles were found in this study, but only four studies met the study criteria. Thalamotomy was recommended as effective and safe for asymmetric, severe, medically intractable PT, particularly for the tremor variant of PD. This was a positive recommendation based on the results of prospective studies with historical controls.

It was judged possibly effective for the treatment of dyskinesias and rigidity, but not for micrographia, bradykinesia, or difficulties of gait or speech. Thalamotomy on the other hand was felt to be effective for the treatment of tremor but to be associated with a high incidence of speech and swallowing difficulty. Therefore a class D negative recommendation was made for bilateral thalamotomy; Vim-DBS was recommended on the second side.

Clinical series of thalamotomy for ET report that the majority of patients have a significant reduction in tremor. Complete cessation or slight residual tremor was reported in 68–83% of cases, while moderate reductions in tremor were reported in the remainder. Most patients were able to discontinue their pharmacological therapy, and many were able to return to work.

Studies of patients with intention tremor of different etiologies show complete abolition or significant reduction in 44–82% of patients.

Complications of Thalamotomy

Complications from stereotactic surgery can arise from infection or intracranial hemorrhage. Infection of pin sites and meningitis have been reported in about 1% of stereotactic surgeries. Hemorrhages occur in 1–6% of procedures. Hemorrhages may occur at the lesion site or at cortical sites resulting in intracerebral or subdural hematomas. The risk of radiologically defined hemorrhage during functional stereotactic procedures employing coagulation is 9/57 (17%) overall, and 5/23 (22%) for Vim thalamotomy.

Functional deficits account for most of the postoperative complications in thalamotomy. In a series of 60 patients with ET, PT, or cerebellar tremor, functional deficits in the immediate postoperative period were reported in 58% of patients. These transient deficits included weakness (34%), dysarthria (29%), ataxia (8%), dystonia (5%), and sensory deficits (3%). Transient deficits may have occurred from edema surrounding the acute lesion site. Functional deficits persisted in 23% but were generally mild and did not increase disability.

Radiosurgical Thalamotomy

The use of MR imaging to provide radiologic localization has led to the development of stereotactic radiosurgical ablation. The majority of stereotactic gamma knife procedures are carried out with a 50% iso-dose plan using 4-mm collimators. Lesions with a volume of approximately 250 mm^3 are created. The lesion placement is estimated from the usual location of Vim in relation to the AC and PC and the internal capsule.

In the largest of these series, MRI-guided gamma knife procedures (4 mm collimator, 110–165 Gy, 50% isodose line at the medial edge of the internal capsule) were carried out in 34 patients with PT at high risk for standard stereotactic procedures. Good to excellent results were found in 78–56%, depending upon the dose, and no complications were reported at minimum follow-up of 5 months (median 28 months).

In contrast to this series is a report of nine complications encountered at Emory University among an estimated 118 patients with gamma knife ablations for movement disorders carried out at a nearby medical center. Complications included weakness or paresis ($n = 3$), visual loss, speech/bulbar symptoms ($n = 3$), and dysphagia-aspiration pneumonia-death ($n = 1$). The conservative interpretation of these results is that gamma knife is indicated for thalamotomy in patients whose high surgical risk precludes a microelectrode-guided, radio-frequency procedure.

See also: Deep Brain stimulation; Pallidotomy for Parkinson's Disease; Surgery for Movement Disorders, Overview, Including History; Tremor; Tremor, Essential (Syndromes).

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Theta Burst TMS

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Glossary

Active motor threshold (AMT) – The minimum stimulation intensity over the motor hot-spot that could elicit an MEP of not less than 200 μV in 5 out of 10 trials during a voluntary contraction of the contralateral target muscle.
Resting motor threshold (RMT) – The minimum stimulation intensity over the motor hot-spot that could elicit an MEP of not less than 50 μV in 5 out of 10 trials.

Definition and History

Transcranial magnetic stimulation (TMS) is a noninvasive and painless method of stimulating the brain. It uses a magnetic field to carry a conventional electrical stimulation pulse across the barrier of the skull and scalp where it activates axons of neurones in the cerebral cortex and the underlying white matter. In animal experiments, there is a wealth of evidence that repeated stimulation of neural pathways in the cortex can change effectiveness of the synaptic connections within those pathways. This leads to long term potentiation or depression of transmission (LTP or LTD) that can last from hours to days or weeks, and is thought to be a fundamental process for learning and memory as well as in the reorganization that occurs after neural damage.

TMS machines are now available that allow us to stimulate human cortex repeatedly (rTMS) and produce effects that are thought to be analogous to those observed in animal preparations. Thus, rTMS of motor cortex can increase or decrease cortical excitability for up to an hour or more after the end of stimulation. Since the effects are influenced by drugs that interfere with transmission at NMDA receptors (which are an essential component of many forms of LTP/LTD), they are likely to involve changes in synaptic transmission in cortical circuits. Given the potential role of such synaptic 'plasticity' in reorganization of the CNS after damage, there has been an upsurge of interest in the possibility of using such interventions to treat brain diseases such as depression, stroke, tinnitus, and others.

Initial experiments with rTMS used regular stimulation at a range of frequencies from 0.2 to 20 Hz with up to 2000 pulses in total. The effects are readily observed on motor, visual, parietal, and other areas of the cortex using physiological measures of cortical excitability or behavioral testing. However, they are often variable and last for a relatively short period of time. In addition, one of the most popular protocols, 1 Hz stimulation with 1000+ pulses, takes 10–20 min to apply and employs relatively high intensities of stimulation (>100% threshold for eliciting hand movement from the motor cortex: resting motor threshold, RMT) which can be uncomfortable, particularly if given over frontal or temporal areas of the scalp due to the contraction that each pulse produces in underlying scalp muscles.

Theta Burst Stimulation

Theta burst stimulation (TBS) is a modification of the regular rTMS protocols and was developed in order to

replicate some of the more powerful LTP/LTD conditioning protocols used in animal experiments, which were themselves based on the physiological pattern of neuronal firing found in the hippocampus.

The basic element of TBS is a short burst of high frequency stimulation that is repeated 5 times per second (5 Hz: the theta frequency in EEG terminology). In humans, this initially consisted of a three-pulse burst at 50 Hz given in every 200 ms (**Figure 1**). Because of safety concerns, the initial stimulus intensity was low, at 80% active motor threshold (AMT for stimulation of the hand area of motor cortex). TBS in humans was first introduced by Huang et al. in an article describing its effects on the hand area of the motor cortex that was published in 2005. However, more recently, other authors have experimented with modifying the number of pulses, the rate at which they are applied, and the intensity of stimulation.

Given the possibility that TBS interacts with natural processes of synaptic plasticity, there has been an increasing interest in applying TBS as a therapy in a number of disease states. Although few studies have been published, TBS has been found to be safe in stroke, tinnitus, and depression, but there are no formal large scale trials as to efficacy.

The Effect of TBS

The effect of TBS relies on the pattern that is given. A regular series of bursts at 5 Hz (continuous TBS, cTBS) tends to depress the cortical excitability, whereas if there are gaps in the stimulation (e.g., 2 s stimulation, 8 s pause followed by 2 s stimulation, etc.: intermittent TBS, iTBS), then excitability may be potentiated. The duration of the effect depends on the total number of stimuli applied: 300 pulses may last for 20 min, whereas 600 pulses may last for 40 min (**Figure 2**). Both these protocols are effective in many different areas of the brain, including the primary and secondary motor cortices, visual cortex, and even the cerebellum. The advantage of TBS is the speed of application since 600 pulses of cTBS takes only 40 s to apply. In addition, the low stimulus intensity makes the protocol less likely to cause scalp muscle contraction. Recent work has shown that the effects of TBS can be further prolonged if several sessions of TBS are given at intervals of 20 min or so.

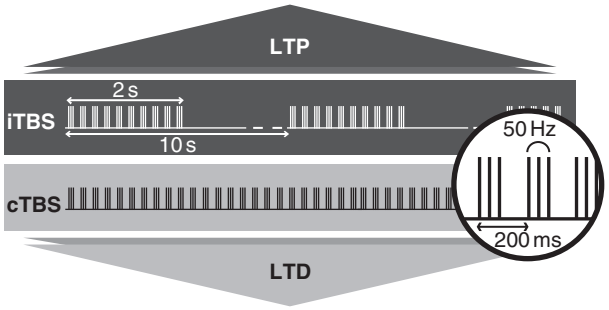

Figure 1 When short trains of TBS are given intermittently (e.g., iTBS), the LTP-like effect is induced. On the contrary, when bursts are given every 200 ms continuously (e.g., cTBS), the LTD-like effect is induced.

The Mechanism of TBS

Although the precise mechanism of TBS remains unclear, it seems clear that the effects are caused by changes in excitability of the cortical circuits rather than at any other level in the CNS. The evidence for this comes from experiments on the motor cortex. Stimulation with a suprathreshold TMS pulse evokes a series of high frequency volleys of activity in the axons of the corticospinal tract that are caused by the synaptic bombardment of pyramidal neurones in the grey matter. These volleys can be recorded directly in human patients who have had electrodes implanted in the spinal epidural space for relief of pain. The fact that the number and amplitude of the volleys change after TBS protocols indicates that TBS has affected the excitability of intracortical circuits. The most likely mechanism is thought to be through processes involving synaptic plasticity. This is because the effects of TBS are dependent on the NMDA receptor, which is a critical receptor for plasticity induction. Memantine, a NMDA antagonist, blocked both the facilitatory effect of iTBS and the suppressive effect of cTBS, while the partial NMDA agonist D-Cycloserine reversed the facilitatory effect of iTBS into inhibition.

Effect of Brain Activity on TBS

The response to TBS depends on the amount of activity in the stimulated area before, during, or even after TBS has been applied. This has been demonstrated most clearly in

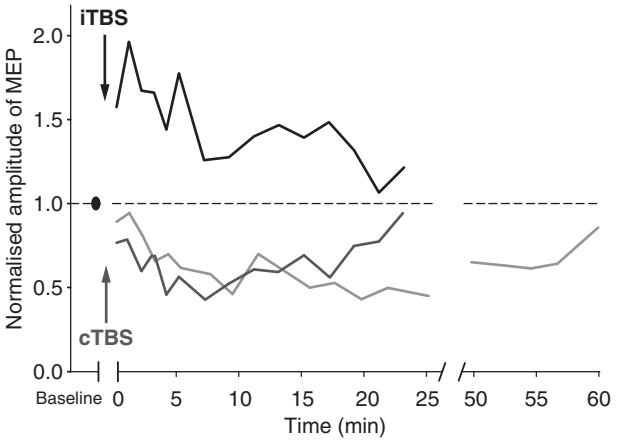

Figure 2 cTBS for 20 or 40 s suppress the size of motor evoked potentials (MEPs) for 20 or 60 min, respectively (gray lines), whereas iTBS for 190 s facilitates MEPs for ~20 min (black line).

the motor cortex. Huang and colleagues showed that mild tonic contraction (10–20% of maximum contraction) of the target muscle during iTBS or cTBS conditioning abolishes almost all the aftereffects of cTBS and iTBS. Similarly contraction immediately after conditioning for 1 min enhances the effect of iTBS, and converts the suppressive effect of cTBS into a facilitation effect. Contraction at 10 min after cTBS had no long lasting effect. Gentner and colleagues found that cTBS of 20 s produced mild enhancement, instead of depression of the corticospinal excitability, unless it was conditioned by voluntary contraction of sufficient duration (5 min). The stimulus intensity of TBS is usually referenced to the AMT. This implies that before TBS is applied, subjects are required to contract the target muscle for ~3–5 min to complete the assessment of AMT. They suggested that this preactivation might be crucial to produce the excitability depressing effect of a 20 s period of cTBS. A similar requirement for isometric contraction was not noted for cTBS of 40 s. Moreover, Iezzi and colleagues demonstrated that a brief sequence of phasic finger movements before TBS converted the facilitatory effect of iTBS to suppressive and the suppressive effect of cTBS to facilitatory. These data imply that the state of the cortex plays a crucial role in determining the response to TBS and is a factor that must be considered when applying to patient groups, particularly if used as a therapy.

Conclusion

In conclusion, theta burst rTMS is capable of modulating cortical excitability for up to an hour, possibly through changing the excitability of synaptic mechanisms. This technique has advantages over classic regular pulse rTMS including speed of delivery and low intensity of stimulation. This makes TBS an attractive form of stimulation to use in the experimental and particularly the clinical setting, where ease and speed of administration is of great importance.

See also: Paired Pulse TMS; rTMS; Single Pulse TMS.

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Tics

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Glossary

CBIT (Comprehensive Behavioral Intervention for Tics) – A behavioral therapy for tics based on habit reversal therapy.

Coprolalia – The repetitive utterance of socially inappropriate words or short phrases as a complex vocal tic.

Echolalia – Repeating the words of another person.

Echopraxia – Mimicking the gestures of another person.
Exposure and response prevention (E/RP) – A behavior therapy method used in the treatment of obsessive–compulsive disorder in which sustained volitional suppression of the manifest behavior (compulsions) produces diminution in the frequency both of compulsions and of the uncomfortable premonitory event (obsessions).

Definition and History

Tics are brief, nonrhythmic, stereotyped abnormal movements that most often affect the head, neck, and shoulders. Traditionally tics have been divided in a 2×2 fashion into simple and complex tics and motor and vocal (or, phonic) tics. These points are perhaps defined more clearly with examples (**Table 1**).

Tics that do not fit easily into this rubric include dystonic tics and sensory tics (discussed in the Clinical Features section). One comment that needs to be highlighted early is that coprolalia – perhaps the most well-known type of tic – is in fact relatively uncommon.

As vocal tics are just motor tics of the muscles of respiration and phonation, many experts feel that the motor/vocal division is arbitrary. Supporting this view are the observations that subjects with vocal tics usually have motor tics at other times in life and have elevated rates of motor tics in family members. Nevertheless, the division is of historical importance and figures in the currently accepted nosology of primary tic disorders. Interestingly, contemporaneous commentary on a well-documented historical figure who clearly had tics presaged several current topics in debate and research on tics. Samuel Johnson, the author of the first widely accepted dictionary of the English language, described his tics once as 'involuntary' and another time as 'a bad habit.' Some of his peers ascribed his movements and noises to a psychological disturbance; others thought that it was a sequela of rheumatic fever. The volitional or involuntary character of tics, their relationship to habit formation and to cognitive and affective symptoms, and the question of shared features with rheumatic chorea are all areas of intense current interest or debate.

Table 1 Examples of tics

	Simple	*Complex*
Motor	Forceful blinks, eyebrow raising, head shaking, shrugging, finger tapping, tensing of abdominal muscles, kicking	Touching the face or objects or other people, echopraxia, orchestrated sequences of simple tics
Vocal	Sniffing, humming, throat clearing, coughing, squealing, forceful nasal exhalations	Saying word fragments or words or short phrases, echolalia, palilalia (repeating one's one words)

Pathogenesis/Pathophysiology

Published research on the pathophysiology of tics has grown at an ever-faster rate in the past 30 years. Only a few notable results will fit within the text of this article. Surprisingly, little is known about the causes or pathophysiology of transient tics, although these are much more common. Most of the information that follows comes from research on people with chronic tic disorders.

Tic disorders are highly heritable, with monozygotic twin concordance much higher than concordance in dizygotic twin pairs. Although recent large, collaborative genetic studies have found probable linkage, no specific gene has yet been associated with a primary tic disorder.

Tics appear most commonly in the prepubertal period, peak in severity around ages 9–12, and on average wane thereafter. Although most youth with chronic tics still have tics when examined as adults, some do not even notice their tics, and only about a third of them have tics that bother them enough to seek continuing medical care. Thus, abnormalities in neurodevelopment are thought to be crucial in the development and maintenance of tics. Consistent with this hypothesis, a fascinating recent study showed that correlation of activity among various brain regions at rest showed a pattern in cognitively normal adolescent tic subjects that was seen in tic-free control subjects who were 4–5 years younger.

Tics are about 5 times more likely to occur in boys than in girls. This clue may relate to known differences in the rate of cortical maturation in boys and girls, or to androgen-sensitive brain regions during prenatal development. Male and female patients with chronic tic disorders differ in the volume of specific cortical regions as assessed by in vivo MRI volumetry.

Several brain regions differ in volume in patients with chronic tics compared with age-matched controls. One of the most compelling such findings is that caudate volume measured in childhood inversely predicts the severity of both tics and compulsions in adolescence. Thus, possible injury to brain cells by chronic or severe tics cannot explain the entire association of caudate volume with tics. More likely, some pathophysiological process produces reduction in caudate volume and leads to tics, obsessions, and compulsions in tic patients.

One possible relevant pathology has been recently discovered in histological studies of the small number of

Tourette syndrome (TS) patients with brain material available from autopsy who were carefully characterized clinically during life. Striatal interneurons that stain positive for parvalbumin are significantly fewer in the striatum and external pallidum from TS brains, but significantly increased in the internal pallidum. A defect in the migration of these cells during brain development has been proposed as one possible mechanism for these findings.

Mink has drawn attention to the common role of the basal ganglia in selecting some behaviors at the expense of suppressing others. He proposed that tics could reflect focal thalamocortical disinhibition. This disinhibition would be produced by a diminished firing of selected clusters of inhibitory basal ganglia output cells in the internal pallidum or the analogous substantia nigra pars reticulata (GPi/SNr), nuclei that normally provide a 'brake' on thalamocortical output. The model proposes that these clusters of GPi/SNr are abnormally inhibited by clusters of striatal neurons (specifically, matrisomes) that are firing excessively and out of context. Variability over time in which matrisomes are more active would be reflected by changes in which tics are manifest over time. The Mink model also provides a link to the dopamine system by proposing that dopamine would reinforce the abnormal activity in these circuits over time.

Numerous studies of the dopaminergic system have been prompted by the response of tics to dopamine antagonist medications. Postsynaptic D2 receptor binding is normal, but studies increasingly suggest a reduction in presynaptic dopaminergic markers in ventral striatum. These studies include positron emission tomography (PET) and single-photon emission computed tomography (SPECT) studies of levodopa uptake and dopamine production, of the VMAT2 site in mesostriatal dopaminergic neurons, and of the dopamine reuptake site, plus PET studies consistent with greater striatal dopamine release in response to intravenous amphetamine. A cognitive-pharmacological interaction functional MRI (fMRI) study examined nonmotor areas of brain and found several regions with a dopamine-sensitive abnormality in brain activity in response to a working memory task, despite normal task performance.

At rest, subjects with tic disorders show higher activity, measured as regional blood flow or metabolism, in primary sensorimotor cortex (possibly a nonspecific marker of increased movement) and a reduction in activity in striatum, perhaps especially ventral striatum. The spontaneous correlation of brain activity at rest between different anatomically defined brain regions also differs in TS from that seen in control subjects. The urge to tic has been associated with an increased brain activity in the right caudate nucleus and in anterior cingulate cortex, supplementary motor area, and insula.

Cognitive tasks intended to probe striatal circuits have been examined using neuropsychological methods and fMRI. Although declarative memory and sensorimotor task learning are normal in patients with chronic tics, habit learning assessed by a 'weather prediction' task was significantly impaired, and the impairment correlated with the severity of tics. Thus, habit learning may be specifically abnormal and may contribute to the persistence of tics.

Deficient habit learning relates to a model of tic maintenance that posits that tics can reduce preceding discomfort (see section on Clinical features), and this reinforces tics (i.e., maintains the likelihood that they will persist). This model has explanatory power in relation to certain behavioral observations and the efficacy of habit reversal therapy (see section on Treatment). However, critics of this theory observe that many children with tics report neither premonitory sensations nor a sense of relief on ticcing. This observation could mean either that the premonitory sensations are an epiphenomenon and not central to tic genesis or (as this author prefers) that children can tic long before they are able to notice or verbalize the relationship of tics to premonitory sensations.

In this connection, it is interesting to note that when a person suppresses tics by effort in the natural world, such suppression is often for relatively brief periods of time (e.g., while a physician looks directly at the person, or during a job interview). In such settings, a rebound effect often occurs when tic suppression is no longer needed, that is, tic frequency increases above the presuppression rate. By contrast, no rebound is observed after tic suppression is sustained for a much longer duration ($\geq$90 min) during a professionally conducted session of exposure and response prevention (E/RP). In fact, E/RP clearly diminishes ticcing and the urge to tic even after overt patient observation ends and the patient is instructed that it is now okay to tic. However, these observations occur in such very different settings as not to indicate discordance. Presumably, the key difference is that the E/RP session is long enough that the patient habituates to the discomfort engendered by not ticcing, so that by the end of the session a tic no longer reinforces the urge to tic. The tic at this point would tend to extinguish or become less frequent.

Another theory of tic genesis derives from Peterson and Leckman's observation of the timing of tics, with tics tending to cluster in what are called bouts of tics. On a longer time scale, patients also tend to have clusters of days or months with greater tic frequency and severity. A recent review by Leckman and colleagues discusses this observation on a smaller time scale, in relation to the periodic discharge of neurons in frontal-striatal circuits.

Epidemiology/Risk Factors

Until relatively recently, tics were thought to be uncommon. However, now several independent, competent

epidemiological studies have examined tic prevalence in children, and they agree remarkably well that chronic tics (lasting at least a year) are present in about 3% of all children ages ~5–15 years. Transient tics are even more common. Lifetime prevalence of transient tics is hard to determine with certainty; the very definition means that the odds of observing them in an individual who will ever have them is lower than for chronic tics. However, extrapolating from several cross-sectional studies, probably as many as 30% of the population will have tics for a month or two but will be tic-free before a year passes.

Tics occur around the world in people of diverse ethnic and racial backgrounds. However, the relative prevalence of tics across cultures is not clear. Two American studies have found a significantly higher rate of tics in African-American children compared with white children. However, it is difficult to reconcile this result with the observation that few black children are diagnosed with tics or attend lay groups for tic disorders. Conceivably, the disparity is entirely the result of inequitable access to health care. Alternatively, differences could exist in whether mild tics are taken to indicate disease, or in the actual rate of tics in different groups. Both studies alluded to above diagnosed tics using parental report or a lay interviewer, and there may be cultural differences in the description or identification of tics. One large, unpublished study in South Africa found extremely low prevalence of tics in the Xhosa population.

There are a few known risk factors for tics other than age and male sex. Tics are very heritable. Discordant monozygotic twin pairs have been reported, but one study used a national referral campaign to find such pairs for a brain imaging study, and found only 5 pairs. Even then, all 10 twins had tics, but in each pair one twin had more severe tics than the other. Tics are much more common in children with learning disabilities.

Some environmental factors are known to be related to tic production. If one monozygotic twin was smaller at birth or had greater birth complications (e.g., forceps delivery) than his or her co-twin, tics tend to be more severe in the twin with more complications. More recently, maternal smoking during pregnancy was associated with a greater likelihood of tics.

Clinical Features and Diagnostic Criteria

Tics were described briefly in the first section of this article as discrete, intermittent, brief, nonrhythmic, stereotyped abnormal movements. Blinking, throat clearing, touching objects, and saying words are typical tics that exemplify the traditional orthogonal categories of motor versus phonic (vocal) tics and simple versus complex tics. Complex tics occasionally predominate the clinical picture in chronic tic patients, but in such cases the possibility of obsessive–compulsive disorder (OCD) without tics must be maintained in mind. Generally, patients with chronic tics have a mixture of simple and complex tics or simple tics alone. Outside the simple/complex and motor/vocal paradigm, phenomena that have been described as tics include sensory tics and dystonic tics.

Most adults with tics (about three fourths) report uncomfortable premonitory sensations, sometimes called sensory tics, just prior to motor or vocal tics. Often this is a focal discomfort such as a scratchy throat before a loud harrumph, or itchy eyes before a pair of forceful, brief blinks. Other preceding phenomena are less localized or less purely sensory. Examples include akathisia-like discomfort or detection of sharp corners in the peripheral visual field. These phenomena and their relationship to tics are reminiscent of the link between obsessions and compulsions. Some historical writers on tics even called compulsions 'mental tics.' However, typically premonitory phenomena before tics are sensory in nature, whereas obsessions are generally cognitive, imaginal, or affective.

The description 'dystonic tics' is most appropriate in less common cases such as a man who presented for treatment of blepharospasm. His eye movements resembled those of primary eyelid dystonia, with forceful eye closures sustained for several seconds at a time and a sensory trick. However, the patient reported that the blepharospasm had been present for 2 years, disappeared for 5 years, and reappeared 3 years before. He also had lifelong simple tics that had come and gone over the years, and he could suppress the blepharospasm temporarily upon request. Dystonic tics are also sometimes diagnosed for the more common situation of a patient some of whose tics are longer than brief movements, like pressing a heel against the floor for 1–2 s or twisting the head to one side for a similar duration. These might perhaps be more accurately called 'tonic tics.'

Typically, tics change over time in anatomic location, frequency, type, complexity, and severity. This is in fact a defining feature of the Tourette Syndrome Study Group (TSSG) criteria for tic disorders.

Tics most commonly involve the head and upper body, for reasons that are unknown. One possibility is that a disproportionate fraction of the mammalian brain is devoted to control of muscles that are used in social communication, including gesture, eye contact, contextual facial expression, affect, and prosody in addition to language. A rodent model that has been proposed as relevant to tics is the so-called syntactical chain grooming, describing stereotyped sequences of rostral body behaviors.

Like nearly all movement disorders, tic severity worsens with emotional stress and anxiety. In school-aged children, September and the return to school often mark a period of worsened symptoms. However, the fluctuation of tic severity in response to other environmental variables is remarkable and also helps distinguish tics from other abnormal movements. For instance, many patients

report that tics improve when they are engaged in purposeful activity, either concentration-requiring activity such as vocal performance or surgery, or physical activity such as running. Several patients describe an impression that they have a certain amount of mental energy that 'has to' express itself either as purposeful activity or as tics. Although unlikely as a pathophysiological explanation, this description has heuristic value in understanding many patients' fluctuating severity in different activities.

Tics are not volitional in the usual sense of being a desired, intended action. However, tics can be suppressed with an effort of will. The perception of volition varies but when people are paying attention to their tics, they are most often experienced as an inevitable capitulation to an almost irresistible urge. Probably fewer than 10% of adults with tics describe them as truly involuntary (e.g., 'look at that, my arm just moved'), and most children with tics use words such as 'I do this' or 'I have to blink.' This sense of volition is an important feature, when present, in distinguishing tics from other movement disorders. On the other hand, many patients report that tics are so common that they are often ticcing without thinking about the tic or even noticing it.

The ability to suppress tics can be substantially affected by providing rewards carefully timed to follow short periods of successful tic suppression (differential reinforcement of zero-rate ticcing). Like the ringing bell of Pavlov's experiments, these rewards can be paired with neutral stimuli (like a purple light) until a conditioned response develops so that even without any direct instruction to suppress tics, tics are less frequent when the purple light is illuminated. These experimental results suggest one mechanism by which tics may become more frequent in one environment (like home) compared with another (like a school bus).

There is no universally accepted definition of tics. Two sets of diagnostic criteria for idiopathic tic disorders are widely accepted: the DSM-IV-TR criteria and the TSSG criteria. Although minor differences exist, in fact both criteria sets identify essentially the same patients. For TS, for instance, both definitions require motor and vocal tics that begin in childhood or adolescence, occur many times a day for most of a year, and for which a specific neurological or systemic cause cannot be identified.

Interestingly, although the diagnostic criteria now focus exclusively on tics, most tic patients who come to the doctor's office have other neurological or psychiatric symptoms.

Differential Diagnosis

Tics are distinguished from other abnormal movements by several clinical features. Most importantly, tics are stereotyped. In other words, across relatively long intervals of time, a few tics are preferentially repeated and become somewhat predictable in character to the observer. Someone with chorea may be 'that man who is continually moving,' whereas someone with tics may be 'that man who blinks and shakes his head.' However, tics are nonrhythmic, which separates them not only from tremor but also from other stereotypies such as typical tardive dyskinesia, akathisia, or the agitation of anxiety or major depression. Tics are generally brief, discrete movements, in contrast to the more sustained postures of dystonia. The patient characteristically can suppress tics for a period of time, whereas myoclonus is not suppressible (and involves much briefer movements). Finally, in contrast to most other involuntary movements, tics more often than not are sensed as volitional (discussed in the section on Clinical features).

Tics are classified as primary if no specific illness is identified as causing them. Primary tic disorders include transient tic disorder, chronic tic disorder (motor or vocal), and TS (motor and vocal tics). Schlaggar and Mink discuss several causes of secondary tic disorders, including developmental or degenerative illnesses and focal brain lesions. However, these are uncommon.

Diagnostic Workup/Tests

If the patient is developing normally and has normal cognition, the physical examination is normal except for the tics, and the patient meets the diagnostic criteria for a primary tic disorder (including age of onset), there is no compelling reason to perform further laboratory or radiologic testing. This is especially true when the tics have persisted for many years without other evidence of impairment. Wilson's disease and carbon monoxide poisoning may be the most treatable and serious secondary causes.

Management

More than 20 different classes of treatments have produced positive results in at least one double-blind, randomized controlled trial. However, the first important question in management is whether treatment is necessary at all. Factors to consider in that judgment include impairment in school or work, social life, self-esteem, or relationships with parents, spouse, or close others. Often reassurance and education suffice. Education as to the side effects and the likely maximum benefit is also useful; no known tic treatment suppresses more than about 50–75% of symptoms on average. Expectations need to be managed.

A second treatment principle is to identify which symptoms are most problematic at present. Many patients present for management of (say) TS, yet obsessions or hyperactivity or anger outbursts are the more compelling clinical concern. Since the management of all of these is ameliorative rather than curative, one can start by treating the most severe or most impairing symptom.

The nonspecific management of chronic tics can be valuable. This can include referral to the Tourette Syndrome Association, neuropsychological evaluation and treatment if school or work function is impaired, and consultation regarding legal protections at school or in the workplace.

Only two drugs are approved by the US FDA for the management of a tic disorder (haloperidol and pimozide), and neither is currently recommended as first-line treatment for most patients. The most efficacious treatments for tics according to replicated studies include newer antipsychotics such as risperidone, ziprasidone, olanzapine, and aripiprazole, and habit reversal therapy, now dubbed Comprehensive Behavioral Intervention for Tics (CBIT) for Comprehensive Behavioral Management for Tics. Clonidine may be one of the most widely prescribed medications for tics. Several recent articles review medications with proven antitic efficacy.

A number of newer treatments are in early testing but show some evidence of efficacy. These include midline repetitive transcranial magnetic stimulation, and deep brain stimulation in the thalamus (centromedian-parafascicular nuclei) or in the GPi. In monitoring and judging the efficacy of any treatment, it is important to remember that tics usually improve and worsen spontaneously over time. Additionally, patients are most likely to begin a new treatment when symptoms are at their worst. These factors combine to make judging the benefit difficult in most patients. Thus, randomized controlled trials are essential for testing any new treatment.

Prognosis

On average, patients improve after about age 12 in terms of tic frequency and severity. Most patients even with fairly severe symptoms in childhood will have substantially reduced tic frequency and severity as adults. Symptom severity in childhood does not accurately predict severity as an adult. However, individual patients can have variable courses.

See also: Tics, Complex; Tics, Simple; Tourette Syndrome; Tourette Syndrome: Animal Models; Yale Global Tic Severity Scale (YGTSS).

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Tics, Complex

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Glossary

Autistic spectrum disorders – Neurodevelopmental disorders characterized by impaired socialization and communication skills with stereotyped or restricted patterns of interest or behavior.
Coprolalia – Involuntary utterance of profanities.
Deep brain stimulation – Treatment of movement disorders which applies electric current to basal ganglia or thalamic targets via surgically implanted leads.
Encephalopathy – A disturbance of consciousness caused by medical illness, infection, or drug toxicity.
Rett syndrome – A neurodegenerative disorder with typical onset in childhood, commonly accompanied by loss of motor and social skills, seizures, and stereotypies.
Tourette syndrome – A developmental neuropsychiatric disorder characterized by the onset of both motor and vocal tics in childhood, lasting longer than 1 year.

Definition and History

The Tourette Syndrome Classification Study Group defines tics as brief movements (motor tics) or sounds produced by the movement of air through the mouth, nose, or throat (vocal tics). As a movement disorders phenomenological category, tics are characterized by not being constantly present (unless very severe), occurring out of a background of a normal motor activity, often mimicking normal movements, lacking in rhythmicity, varying in intensity, often changing in quality, and having some element of temporary voluntary suppressibility. Patients with tics often recognize an urge to execute the tics and a feeling of relief after their tics.

Clinical Features and Diagnostic Criteria

Both motor and vocal tics can be divided into simple and complex types. Complex motor tics are distinct, coordinated patterns of sequential movements. They may appear purposeful, as if performing a voluntary action, such as tapping, touching, punching, kicking, hopping, or smelling. Other examples include copropraxia (obscene gestures) and echopraxia (mimicking the movements of others). A repetitive coordinated sequence of simple tics (e.g., facial grimace with head jerk, shoulder shrug, and arm jerk) may not appear purposeful and would be considered to represent a form of complex tics.

A complex vocal tic has linguistic meaning, consisting of a partial word (syllables), word, or phrase. Examples include coprolalia (obscene or insulting words often truncated such as 'fu-'), echolalia (repeating the words of others), and palilalia (repeating one's own words such as 'How are you today, today, today?'). Like simple tics, complex tics are often associated with premonitory sensations and irresistible urges.

Complex tics must be distinguished from stereotypies, which are seen in patients with autistic spectrum disorders, mental retardation, Rett syndrome, psychosis, encephalopathies, and congenital blindness and deafness. Contrary to complex tics, stereotypies tend to be more repetitive and continual (e.g., body rocking, hand flapping), or vocalization (e.g., moaning, yelling) occurring over and over for prolonged periods of time. Stereotypies are not known to be associated with premonitory sensations and may be more difficult to suppress than tics.

Since tics and obsessive-compulsive disorder commonly occur together, it may be difficult to distinguish complex motor tics and compulsions. Contrary to tics, compulsions are performed in response to an obsession (e.g., hand washing to prevent contamination), to ward off future problems (e.g., counting to prevent harm to a loved one), to reduce anxiety, or according to certain rules. This latter rule-based (ritualistic) quality is characteristic of compulsions. Examples of rules include a certain number of times, in a certain order, equally on both sides of the body ('evening up'), or a certain time of day (e.g., morning or bedtime rituals). In our experience, some specific actions have the qualities of both tics and compulsions, and it is impossible to distinguish the two phenomena. We use the term 'compulsive tic' or 'compultic' for these overlap behaviors. We have also found that some complex motor tics have impulsive, socially inappropriate qualities and use the term 'impulsive tic' or 'impultic' for these actions. Examples of impulsive tics include hitting others, self-injury, touching a hot stove, and stepping into oncoming traffic. Some actions have mixed tic, compulsive, and impulsive qualities (e.g., pushing or hitting someone after they coughed to avoid contamination) and could be considered 'compulsive/impulsive tics.'

As discussed elsewhere in this encyclopedia, Tourette's syndrome (TS) is the primary tic disorder, and is characterized by childhood onset of chronic motor and vocal tics. In individual patients, tics can be simple, complex, or

of both types. It is very unusual to see complex tics in the absence of simple tics, often helping to clarify the phenomenology of a complex action. Although coprolalia is the feature of TS most responsible for the notoriety of the condition, we find this feature only rarely (~1–2%) in our TS patients. Some patients have only internal, nonverbalized, obscene words, thoughts, or images, termed 'mental coprolalia.' In our experience, the secondary causes of tic disorders are usually associated with simple rather than complex tics.

Pathogenesis

Information on the course, pathogenesis, and the treatment of tics is provided in the Chapter 'Simple Tics.'

Management

Complex motor and vocal tics tend to produce greater disability in patients than do simple tics, and therefore, their presence often signifies the need for tic-suppressing therapy. For debilitating and dangerous complex tics, such as loud coprolalia or self-mutilating tics, we tend to initiate medication therapy with an antipsychotic drug in order to achieve more rapid and predictable control. Intramuscular or intralaryngeal injections of botulinum toxin may reduce some disabling complex motor or vocal tics respectively. Some TS patients with self-harming behaviors have not tolerated deep brain stimulation surgery due to self-induced damage to the equipment or infection related to constant picking at the operative sites. Surgical anterior cingulotomy can be considered for patients with medication refractory self-harming behavior. For patients with complex phenomenology (e.g., compulsive tics, impulsive tics, compulsive/impulsive tics), a combination of tic-suppressing medications, obsessive-compulsive disorder therapies (e.g., cognitive behavioral therapy, selective serotonin reuptake inhibitors), and impulse control therapies (e.g., behavior therapy, stimulants, mood stabilizers) may be needed for optimum control.

Acknowledgments

Video from 'Tourette Syndrome: A Guide to Diagnosis' was provided with permission by the Tourette Syndrome Association, Bayside, NY, Copyright 1990.

See also: Deep Brain stimulation; Obsessive-Compulsive Disorder; PANDAS; Rett Syndrome; Tics; Tics, Simple; Tourette Syndrome; Yale Global Tic Severity Scale (YGTSS).

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http://wemove.org – We Move™ Worldwide Education and Awareness for Movement Disorders.

Tics, Simple

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Glossary

Deep brain stimulation – Treatment of movement disorders which applies electric current to basal ganglia or thalamic targets via surgically implanted leads.

Huntington disease – A neurodegenerative genetic disorder characterized by movement disorders, cognitive deficits, and psychiatric disturbances.

Neuroacanthocytosis – A neurodegenerative genetic disorder characterized by thorny appearing red blood cells ('acanthocytes') and often accompanied by involuntary movements including chorea or tics.

Definition and History

The Tourette Syndrome Classification Study Group defines tics as brief movements (motor tics) or sounds produced by the movement of air through the mouth, nose, or throat (vocal tics). As a movement disorders phenomenological category, tics are characterized by not being constantly present (unless very severe), occurring out of a background of normal motor activity, often mimicking normal movements, lacking in rhythmicity, varying in intensity, often changing in quality, and having some element of temporary voluntary suppressibility. Patients with tics typically express an urge to have their tics and relief after making the movement or sound.

Pathogenesis

The neurobiological basis for tics remains largely unknown. There is substantial evidence for the importance of hereditary factors in Tourette syndrome (TS), but no specific gene locus has been identified. The observed response to dopamine receptor antagonist medications in concert with the finding of reduced levels of the dopamine metabolite homovanillic acid in the cerebrospinal fluid (CSF) of patients with TS suggested an underlying state of postsynaptic dopamine receptor supersensitivity. More recently, neuroimaging studies have suggested the presence of reduced tonic synaptic levels of dopamine and increased phasic release of dopamine in the basal ganglia. Other neuroimaging investigations have yielded conflicting information about whether or not there is an increase in presynaptic dopamine transporters or excessive dopaminergic innervation. Overall, there appears to be a dysfunction of inhibitory activities in corticostriatal circuits, perhaps allowing the expression of unwanted motor programs as tics.

Clinical Features and Diagnostic Criteria

Both motor and vocal tics can be divided into simple and complex types. Simple motor tics are abrupt, sudden, and brief movements occurring in single and isolated fashion. Some of the more common examples include an eye blink or wink, a head jerk, a shoulder shrug, or a dart of the eyes. Some simple motor tics have a slower, often twisting or tightening quality and have been termed 'dystonic tics' because of their resemblance to dystonia. Common examples of dystonic tics include facial grimacing, torticollis-like head/neck twisting, blepharospasm-like prolonged forceful eye closure, and abdominal muscle tensing.

Simple vocal tics consist of inarticulate noises or sounds that are produced by the movement of air through the mouth, nose, or throat. Thus, a clicking noise produced by knocking the teeth together, for example, would be considered a motor tic and not a vocal tic. Common simple vocal tics include throat clearing, sniffing, snorting, and grunting. Both simple motor (especially dystonic) tics and vocal tics are commonly associated with a premonitory sensation, sometimes referred to as a 'sensory tic.' Such sensations are typically uncomfortable and localized at the site of a tic (e.g., in the throat for vocal tics). Patients often describe a need to tic in order to relieve the abnormal sensation, but it inevitably returns to induce more tics.

Simple motor tics must be distinguished from myoclonic and choreic jerks, which tend not to be repetitive in the same location like tics. Simple motor tics are often accompanied by complex motortics, allowing them to be identified based on 'the company they keep.' Contrary to torsion dystonia, dystonic tics occur in abrupt bursts of movements, are not continuous, and tend to produce abnormal postures for a shorter time period. Dystonic tics are usually associated with more typical motor tic jerks, revealing the nature of the movement disorder.

TS is defined by the presence of chronic (at least 1 year) motor and vocal tics, with onset in childhood or adolescence. When only one type of tic is present, the diagnoses of Chronic Motor Tic Disorder (CMTD) or Chronic Vocal Tic Disorder (CVTD) are used. TS, CMTD, and CVTD are considered to represent a spectrum of primary tic disorders, thought to occur on a largely genetic or idiopathic basis. It should be pointed out that since the movement of air needed to produce a vocal tic involves the contraction of muscles in the mouth, pharynx, larynx, or diaphragm, the distinction between motor and vocal tics per se probably does not reflect neurobiological differences and largely exists from historical perceptions. With this consideration, most clinicians view TS, CMTD, and CVTD as the same condition.

Epidemiological studies indicate that at least transient tics occur commonly in the course of childhood development, possibly resulting from the process of normal basal ganglia synaptogenesis. The term 'physiological tics' has been applied to this phenomenon. Tics can be seen in the setting of a wide variety of conditions linked to abnormal brain development or cerebral damage, and these cases are referred to as 'secondary tic disorders.' Included are mental retardation, autism, pervasive developmental disorder, neuroacanthocytosis, Huntington's disease, encephalitis, and traumatic brain injury. Tics may be a manifestation of tardive dyskinesia or withdrawal-emergent dyskinesia related to chronic antipsychotic drug use. A variety of medications (e.g., carbamazepine, levodopa, calcium channel antagonists) have been reported to induce tics. Secondary tic disorders are usually evident by the presence of neurological signs in addition to tics.

In TS patients, tics have their onset usually around age 6–7 years. They tend to follow a waxing and waning course of severity, with exacerbations and remissions occurring over periods of weeks or a few months. Tics often occur in

waves, with one set of tics being replaced by another set over time. Some patients have a few persistent tic types throughout the different waves. Tic severity tends to peak around age 10–12 years. In about two thirds of cases, tics either fully resolve or substantially lessen as TS patients grow into adulthood, so the ultimate prognosis is usually good.

Management

When tics are disabling in causing social embarrassment, discomfort or interference with daily activities, tic-suppressing medications are available. Most clinicians start with the alpha-agonist drug guanfacine (0.5–4 mg per day; h.s. or b.i.d.). If there is inadequate response or problems with tolerability, one can either switch to or add an antipsychotic medication. The atypical antipsychotics risperidone (0.25–16 mg per day) or aripiprazole (5–30 mg per day) are the most commonly prescribed. Classical neuroleptic antipsychotics such as haloperidol (0.5–10 mg per day), pimozide (0.5–10 mg per day), or fluphenazine (0.5–20 mg per day) may be of value. Other tic-suppressing agents to consider include clonazepam (0.5–10 mg per day) and tetrabenazine (25–200 mg per day). Local intramuscular injections of botulinum toxin may be helpful when there is a small number of disabling motor tics. Deep brain stimulation surgical therapy has been reported to benefit some patients with severe, medication-refractory tics, but the best anatomical target and proper subject selection criteria remain to be determined as does the overall efficacy and safety of this approach.

Acknowledgments

Video from "Tourette Syndrome: A Guide to Diagnosis" was provided with permission from the Tourette Syndrome Association, Bayside, NY, Copyright 1990.

See also: Obsessive-Compulsive Disorder; PANDAS; Tics; Tics, Complex; Tourette Syndrome; Yale Global Tic Severity Scale (YGTSS).

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http://wemove.org – We Move™: Worldwide Education and Awareness for Movement Disorders.

Tocopherol Transfer Protein and Ataxia with Vitamin E Deficiency

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Glossary

Abetalipoproteinemia – An autosomal recessive disease due to mutations in the microsomal triglyceride transfer protein, characterized clinically by peripheral neuropathy, ataxia, acanthocytosis, retinitis pigmentosa, and steatorrhea, and treated with vitamin E supplementation.

Microsomal triglyceride transfer protein – A protein which catalyzes the transport of triglyceride, cholesteryl ester, and phospholipids from phospholipid surfaces. It is isolated as a soluble protein from the lumen of the microsomal fraction of liver and intestine.

***RRR*-α-tocopherol** – A form of vitamin E, which is extracted from plants; also known as α-tocopherol or vitamin E.

***TTPA* gene** – The gene that encodes the α-tocopherol transfer protein, αTTP.

Definition and History

The term vitamin E refers to a family of plant-derived neutral lipids. The different forms of vitamin E are distinguished from each other by the pattern of methylation on the chromanol ring (α vs. β vs. γ vs. δ), the saturation level of the phytil side-chain (tocopherols vs. tocotrienols), and the stereochemical configuration of three chiral carbon centers (*S* vs. *R* configuration for each center). Vitamin E supplements sold over-the-counter typically contain a synthetic mixture of tocopherols, whereas 'natural source' vitamin E extracted from plants contains primarily *RRR*-α-tocopherol. Regardless of intake composition, only *RRR*-α-tocopherol accumulates in plasma and tissues at significant levels, while other forms of the vitamin are degraded in the liver and excreted in urine. This remarkably efficient discrimination between different forms of vitamin E has led to the common definition of *RRR*-α-tocopherol as the 'biologically active' form of vitamin E. In clinical analyses, the terms 'vitamin E' and 'α-tocopherol' are used synonymously.

The essential role of α-tocopherol in preserving normal neurologic function is demonstrated by the occurrence of acquired and hereditary disorders that cause vitamin E deficiency. Most instructive are the observations that genetic mutations in the *TTPA* gene (encoding the α-tocopherol transfer protein, αTTP) result in low to absent plasma and tissue levels of vitamin E accompanied by neurologic abnormalities, especially ataxia.

The first indications of the critical neuroprotective role of vitamin E in humans were observed in patients with the hereditary disease abetalipoproteinemia. In this autosomal recessive disorder, mutations in the microsomal triglyceride transfer protein (MTTP) impair the assembly of apolipoprotein B-containing particles, i.e., chylomicrons, very low density lipoproteins (VLDLs) and low density lipoproteins (LDLs). These defects result in inability of the patients to absorb dietary fat (including fat-soluble vitamins), and to circulate lipids from the liver to peripheral tissues. By the second decade of life, neurologic abnormalities such as progressive peripheral neuropathy and spinocerebellar ataxia appeared; other clinical features included acanthocytes, retinitis pigmentosa, and a celiac-like malabsorption syndrome. Since specific laboratory determinations of vitamin E levels were not commonly performed at the time, early patients were diagnosed as subjects with Friedreich's ataxia. Closer analyses of plasma and tissue lipid profile revealed extremely low or non-detectable levels of vitamin E. When patients received supplementation with extremely high doses of vitamin E, the neurologic abnormalities could be ameliorated. Furthermore, it was found that supplementation at infancy protected patients from developing the debilitating neurologic symptoms associated with this syndrome.

Interest in vitamin E biology intensified when patients diagnosed with 'Friedreich's ataxia' were found to have exquisitely low plasma levels of α-tocopherol, despite having intact fat absorption and normal lipid profile. The availability of deuterium-labeled forms of vitamin E allowed investigation and consequently the 'mapping' of the physiological routes of vitamin E after ingestion. Thus, it was established that isomer composition of postprandial vitamin E mirrors that of intake, and that discrimination in favor of *RRR*-α-tocopherol occurs only later, during hepatic incorporation of vitamin E into VLDL and LDL. Patients diagnosed with the so-called 'variant Friedreich ataxia' were investigated by several groups. The recognition that a large number of affected individuals were from defined geographical locations such as the Mediterranean basin – specifically Tunisia, stimulated intense search for hereditary abnormalities. The high incidents of consanguinity coupled with a high birth rate made many patients in these areas available for studies of heritability patterns and for the identification of the molecular 'culprit' behind the syndrome.

Laboratory studies previously have identified a protein isolated from rat liver extracts that bound α-tocopherol with high affinity and catalyzed the transfer of the vitamin between membranes – the α-tocopherol transfer protein (αTTP). Once the rat liver protein was purified to homogeneity and sequenced, its mRNA was genetically cloned; the human transcript encoding αTTP was cloned shortly thereafter, and the *TTPA* gene mapped to the q13 region of human chromosome 8. Further studies in cultured cells established that αTTP facilitates the secretion of α-tocopherol from hepatocytes to lipoprotein acceptors outside the cell. Specifically, TTP is thought to catalyze the intracellular transport of the vitamin from lysosomes to the site of secretion in the plasma membrane. The syndrome characterized by ataxia coupled to vitamin E deficiency due to mutations in the *TTPA* gene was originally termed familial isolated vitamin E deficiency (FIVE). The term ataxia with vitamin E deficiency (AVED) was later coined, and is more commonly used at present. AVED

and FIVE describe the same disorder, and are therefore synonymous.

The importance of αTTP in regulating vitamin E status is also underscored by mice models in which expression of αTTP is disrupted (αTTP knock-out or $\alpha TTP^{-/-}$ mice). These animals are particularly useful in analyzing changes in the brain under states of vitamin E deficiency, especially in the cerebellum. As expected, $\alpha TTP^{-/-}$ mice exhibit high lipid peroxidation products in the brain, especially in degenerating neurons. As $\alpha TTP^{-/-}$ mice age, they display the classical neurological symptoms associated with AVED. Interestingly, postmortem analyses revealed increased expression levels of αTTP in cerebellar Purkinje cells in brains of patients suffering from oxidative-stress-related diseases such as Down syndrome and AVED.

Pathogenesis/Pathophysiology

Multiple mutations in the *TTPA* gene have been described in AVED patients. These genetic changes result in a αTTP protein that is either compromised with regard to its biochemical activities, or is missing altogether. As a result, vitamin E is not incorporated into liver-assembled lipoproteins, and is not distributed to peripheral tissues. While all nonhepatic tissues in AVED patients become depleted of vitamin E, the central nervous system appears to be especially sensitive, and degeneration of neuronal tissue ensues early in life, followed by progressive ataxia. The presence of multiple genetic alterations in the *TTPA* gene accounts for the wide variety of clinical syndromes presented by affected individuals, ranging from severe ataxia apparent at early childhood, to mild symptoms that manifest only after the second decade of life. The pathogenic scenarios may involve altered activity of αTTP that is expressed in the central nervous system, especially in the cerebellum. The function of brain-αTTP is presently not known.

Epidemiology

Heritable mutations in the *TTPA* gene are very rare, with fewer than 100 cases reported to date. The disease is inherited in an autosomal recessive pattern. In the reported cases, over 22 different mutations in the *TTPA* gene have been described. Some mutations arise from nucleotide deletions or insertions that cause incorrect initiation or termination of transcription or shifts in the translation reading frame. Such drastic changes in αTTP's primary structure often cause severe, early-onset form of the pathological disorder. Other mutations result from single amino acid substitutions that produce a full-length protein with compromised activity. Such missense mutations can affect TTP activity in different ways, leading to various clinical phenotypes ranging from mild, late-onset ataxia, to the most debilitating, early-onset variant of the disease. In most cases, the effect of a specific mutation on TTP's biochemical activity in vitro correlates to the clinical severity presented by the patient carrying the mutation(s). It should be noted, however, that some mutations do not alter TTP's activity in tocopherol binding and transfer, yet they impart clinical vitamin E deficiency on human carriers. The molecular-level bases of these observations are still not known.

Clinical Features

It is important to note that comprehensive neurological examination by itself is not sufficient for distinguishing between clinical consequences of vitamin E deficiency and other forms of cerebellar ataxias (e.g., Friedreich's ataxia). Neurological symptoms usually appear between early childhood and late teens. Patients initially present with progressive ataxia and clumsiness of the hands, loss of deep tendon reflexes, dysarthria, and gait disturbances. In some cases, these symptoms may be accompanied by head titubation, loss of visual acuity, positive Babinski sign, and cardiomyopathy.

Differential Diagnosis

The neurological symptoms characteristics of vitamin E deficiency are similar to those presented in other unrelated disorders. Friedreich's ataxia patients present with similar symptoms, but do not exhibit diminished plasma vitamin E levels. Fat malabsorption disorders such as abetalipoproteinemia, cystic fibrosis and short bowel syndrome are accompanied by vitamin E deficiency, but abetalipoproteinemia is uniquely characterized by an abnormal lipid–lipoprotein profile.

Diagnostic Workup

Clinical neurologic examination, including electrophysiologic evaluation may aid in diagnosis, but resultant findings cannot specifically implicate vitamin E deficiency. Neurologic evaluation must be accompanied by analytical determination of plasma vitamin E and lipid profile (levels of HDL, LDL, VLDL, cholesterol, and triglycerides in plasma after 12 h fast). Molecular sequencing of the *TTPA* gene is the ultimate diagnostic tool, but may not be readily available.

Management

Patients carrying mutations in the αTTP should be supplemented with high doses of vitamin E throughout their life. Plasma vitamin E levels should be monitored routinely, and maintained at the high-normal range.

Prognosis

Routine, high-dose supplementation with vitamin E ameliorates, overcomes, and protects against the pathological consequences of mutations in TTP. If diagnosed early, supplementation with vitamin E can reverse some of the neurologic features of the disease.

Summary

Available information supports special awareness in Movement Disorder clinics to possible AVED diagnosis in any patient presenting with spinocerebellar ataxia. Plasma vitamin E levels should be determined in such patients. This is especially critical in light of the profound efficacy of supplemental vitamin E therapy for this disorder.

See also: Ataxia with Isolated Vitamin E Deficiency; Glucocerebrosidase Gene Mutations and Parkinsonism; SCA1; SCA2; SCA3, Machado–Joseph Disease; SCA4; SCA5; SCA6; SCA7, Spinocerebellar Ataxia with Macular Dystrophy; SCA8; SCA10; SCA11; SCA12; SCA13, 14, 15, and 16; SCA17; SCA27; Scale for the Assessment and Rating of Ataxia (SARA); Spinocerebellar Ataxia Type 19, 20, 21, 22, 23, 26; Spinocerebellar Ataxias Genetics.

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Torsin A

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Glossary

Caenorhabditis elegans – A nematode used in laboratory genetic studies.
Chaperone proteins – Cellular housekeeping proteins with functions such as protein quality control, protein folding, degradation, protein complex assembly, cytoskeletal regulation, and vesicular transport.
Dystonia – A hyperkinetic movement disorder characterized by abnormal sustained postures and repetitive movements.
Inclusion bodies – Aggregations of proteins within cells, usually indicative of a pathological process.

Definition

TorsinA is a 332 amino acid protein encoded by the *DYT1* or *TORA* gene, located on chromosome 9q34. Homologues of human torsinA are found in rat, mouse, zebrafish, *Drosophila*, and *Caenorhabditis elegans*, suggesting an evolutionarily important function. TorsinA is found throughout the brain and in various organs including liver, kidney, and muscle.

TorsinB is encoded by the gene *TOR1B*, located adjacent to the *DYT1* gene, which has 70% homology to torsinA. In the nervous system, it has similar, although not identical, localization to torsinA, but does not appear to functionally compensate for mutation of torsinA.

Mutations of the *DYT1* gene are responsible for one of the commonest forms of autosomal dominantly-inherited child-onset dystonia, DYT1 dystonia. To date only one

dystonia-causing mutation has been identified, namely a GAG deletion in exon 5, which results in loss of a glutamic acid at either position 302 or 303, near the carboxy terminus of the protein (ΔE-torsinA). Other mutations initially postulated to cause dystonia, such as the 18-base pair deletion, have not been unequivocally shown to cause the disease.

About 30% of the carriers of a single mutant copy of the *DYT* gene will develop dystonia. The typical phenotype is the onset of dystonia in a limb during mid-late childhood, with generalization during adolescence. Adult-onset focal dystonia is rarely associated with mutations of torsinA, especially when the disorder develops after the age of 26 years, but occasionally may be seen below this age. The penetrance of the mutation appears to be influenced by a single nucleotide polymorphism at position 216. When histidine is present rather than aspartic acid on the nonmutant allele, penetrance is significantly reduced. The presence of aspartic acid on the mutant allele appears to be associated with increased likelihood of developing the disease. As these effects were not absolute, it is very likely that other genetic or possibly environmental factors influence the disease manifestation.

The lack of prominent neuropathological abnormalities in the *postmortem* tissue of humans with DYT1 dystonia, in concert with clinical observations, strongly suggests a functional role for torsinA, for example, related to neurotransmitter release.

Localization

TorsinA appears to be present in all neurons in normal brain in all mammalian species examined (mouse, rat, macaque, and human), but not, under normal circumstances, in glia. Reports of torsinA being present in higher amounts in dopaminergic neurons of the substantia nigra pars compacta (SNc) are likely due to the large size of these neurons, as immunohistochemical labeling using antibodies to torsinA demonstrates prominent labeling in all areas of high neuronal density and/or size such as cerebellar Purkinje cells, neurons of the pontine nuclei, and the pyramidal cell layer of the hippocampus. Double-labeling immunohistochemical studies showed that torsinA was present in the vast majority of neuronal types throughout the brain, and in particular in projection neurons and interneurons of the striatum.

TorsinA is present in neuronal cell bodies, where it is localized in the lumen of the endoplasmic reticulum (ER), and in the space between the inner and outer membranes of the nuclear envelope. The 19 amino acid hydrophobic domain near the N-terminus may serve to anchor torsinA to the membrane. This position may put torsinA in a unique position to fulfill functions related both to the nuclear envelope and to cytoskeletal components. In the nuclear envelope, torsinA appears to interact with lamina-associated polypeptide 1 (LAP1), and in the ER, it interacts with the homologous, luminal domain-like LAP1 (Lull1), both of which may be its substrates. In addition, torsinA is present in synaptic terminals of axons and dendrites, suggesting a role in neurotransmitter function.

In cell cultures overexpressing ΔE-torsinA, the protein relocalizes from the ER to the nuclear envelope where it forms whorled aggregations containing several nuclear envelope proteins. This has been a consistent finding from a number of different laboratories, and it is hypothesized that somehow, maybe due to an abnormal function, the mutant protein gets trapped in the nuclear envelope. This effect appears to be specific to neurons rather than other cell types, consistent with the absence of symptomatology outside the nervous system, despite the widespread presence of torsinA in many organs. It remains unclear whether the protein accumulations found in cell culture studies are related to the inclusion bodies reported in the brainstem of some torsinA transgenic mouse models or in a small number of human *postmortem* brains with DYT1 dystonia, and whether they are related to the disease pathogenesis, as is true of other disorders involving mutation of nuclear envelope proteins.

Mutant, but not wild-type, torsinA is degraded by the proteasome system, which handles abnormal and misfolded proteins, and has a shorter half-life as compared to the wild-type.

Potential Functions

Chaperone Function

The function of torsinA is suggested by its homology to the AAA + superfamily of proteins (ATP-ases associated with a variety of cellular activities). Having a single ATP-binding site, it is classified as a member of the Class 2-type HSP100/Clp subfamily. Many of these proteins are chaperone proteins with cellular housekeeping functions such as protein quality control, protein folding, degradation, protein complex assembly, cytoskeletal regulation, and vesicular transport. Energy to drive these reactions comes from binding and hydrolysis of ATP. TorsinA has been shown to bind ATP, but the functional significance of this is not yet known, and this is not affected by the mutation. The mutation does not affect the Walker A and B sequences which are highly evolutionarily conserved and are likely to play a significant role in function. The Walker A domain binds ATP, while the Walker B domain is responsible for ATP hydrolysis. The carboxy terminus, where the ΔE mutation is located, forms a helical subdomain that in general appears to be important for the functions of the AAA + protein superfamily.

The GAG deletion does not cause any major changes in biochemical properties or protein conformation.

TorsinA forms hexamers, and it is hypothesized that the dominant negative effect of the mutation is due to an effect of the mutant form when it is complexed with normal protein in hetero-oligomers. As the carboxy terminus is important for these interactions, it is likely that the mutation in this region will affect interactions with other proteins in the oligomer.

A number of studies support a chaperone-type role for torsinA; however, the relationship of this function to the development of dystonia is not known. TorsinA has been found to be upregulated in a number of studies of cell cultures and animal models in response to a variety of stresses, including hypoxia/ischemia, oxidative stress, and serum deprivation, consistent with a role as a chaperone protein. Oxidative stress, but not other stresses, resulted in the redistribution of torsinA to inclusions on the nuclear envelope, and a small increase in molecular weight.

A role in enhancing protein degradation was suggested by the finding that overexpression of normal torsinA can reduce aggregates in cell culture because of mutant α-synuclein overexpression. Similar results were found in the nematode *C. elegans,* in a model of protein aggregation due to trinucleotide repeat expansions. In these organisms, when torsinA was overexpressed, a reduction in protein aggregation was found. Overexpression of wild-type torsinA in *C. elegans* also protected dopaminergic neurons from neurodegeneration caused by the neurotoxin 6-hydroxydopamine. This protective effect was lost when either ΔE-torsinA or a combination of mutant and wild-type protein was expressed. Cell culture studies in which mutant ε-sarcoglycan, the gene that causes inherited myoclonus-dystonia, was coexpressed with torsinA suggested that torsinA was able to facilitate clearance and breakdown of the abnormal protein.

TorsinA was found to alter the transcription of several members of the heat shock protein family, an effect which was not affected by ΔE-torsinA. This would argue against impaired chaperone functions causing dystonia.

Using immunohistochemical methods, a decrease in torsinA in the entopeduncular nucleus (rat homologue of globus pallidus internal segment) was seen in rats that had undergone unilateral dopamine depletion and then treatment with levodopa to render them dyskinetic. This decrease was seen only in animals that developed dyskinesias, and it remains unknown whether this was a primary or secondary effect. TorsinA immunolabeling was not altered in several rodent models of dystonia.

Cytoskeletal Functions

There is significant evidence for a role of torsinA in the development of the cytoskeleton. This is supported by the finding of an increase in the levels of protein (and also of torsinB) during prenatal and early postnatal periods, particularly during periods of dendrite and synapse formation.

The *C. elegans* homologue of torsinA, OOC-5, is involved in nuclear rotation of the nuclear-centrosome complex during embyrogenesis, and mutations affecting this protein result in polarity defects of embryos.

In cell cultures, torsinA associates with the retain cytoskeletal proteins kinesin light chain and vimentin, and plays a role in neurite outgrowth and cell adhesion. TorsinA appears to be transported down the axons to synapses by anterograde transport in association with kinesin. TorsinA also interacts with tau, a microtubule-associated protein that contributes to the development of polarity and neurite development. ΔE-torsinA interferes with cytoskeletal events, and it may thus interfere with neuronal development and synapse formation. Wild-type torsinA, when overexpressed, appears to inhibit neurite outgrowth, while cells with the mutant form develop abnormally long neurites and growth cones.

Neurotransmitter-Related Functions

TorsinA may regulate the distribution of membrane-associated proteins, such as the dopamine transporter. Studies of protein interactions found that torsinA bound to SNAP-25, which is required for vesicle docking, and interacted with synaptotagmin. Overexpression of both wild-type and ΔE-torsinA interfered with synaptic vesicle recycling but in opposite ways. ΔE-torsinA appeared to enhance membrane recycling, but caused mislocalization of synaptic vesicle proteins. Human fibroblasts from patients with DYT1 dystonia showed a reduction in secretory function, which, intriguingly, could be blocked by small interfering RNA (siRNA).

In *C. elegans*, overexpression of torsinA resulted in downregulation of the dopamine transporter, which is responsible for the uptake of dopamine into neurons. The vesicular monoamine transporter (VMAT2), important in packaging of dopamine into vesicles for synaptic release, has been found in the whorled aggregations associated with the nuclear envelope found in cells in culture that overexpress mutant torsinA.

Electrophysiological studies of slices from one line of transgenic mice overexpressing human ΔE-torsinA found an alteration in responses to dopamine of striatal large cholinergic interneurons, mediated by dopamine D2 receptors. The neurons showed an excitatory response rather than an inhibitory response following D2 receptor activation, because of increased inhibition of the N-type calcium channels that resulted in a reduction of the after-hyperpolarization. This would result in increased acetylcholine release from these interneurons that play a major role in regulation of striatal efferents. This finding implies an overactivity of these striatal interneurons in dystonia,

and may be of clinical relevance and significance as anticholinergic drugs have long been a mainstay of antidystonic therapy.

Transgenic Animal Models

A number of transgenic mouse models have been generated to try and understand the pathogenesis of DYT1 dystonia. TorsinA appears to be critical for the development as mice without the mouse *DYT1* gene or with two mutant copies die soon after birth.

Other studies have examined the effect of overexpression of the mutant form of human torsinA. The methodology for producing mouse models varies, including the use of different insertion sites and promoters. In some cases, lines overexpressing ΔE-torsinA were compared with animals overexpressing normal human torsinA. Findings have been somewhat heterogeneous and in general disappointing in either shedding light upon the pathophysiology of DYT1 dystonia, or as a potential tool for novel therapies. One limitation of some of the mouse studies has been the time frame. As DYT1 dystonia tends to manifest during childhood and evolve during adolescence, it is important to study mice at corresponding ages, which has not always been done. Abnormalities in only a proportion of mice, corresponding, perhaps coincidentally, to the penetrance of disease in human carriers were only apparent in the reports from one laboratory. This transgenic mouse model was the only one with a severely hyperkinetic phenotype, manifested as marked motor hyperactivity, and dystonic neck and limb posturing. In lines from other laboratories, by employing other methodologies, motor deficits were more subtle and showed a mixture of hypo- and hyperkinetic features with motor incoordination, in some cases with impaired learning; however, these lines may be more stable and the findings more reproducible.

Examination of striatal tissue for dopamine neurochemistry demonstrated heterogeneous results, showing variably either increased or decreased turnover. In addition, one line showed abnormally decreased dopamine release following amphetamine administration, in the absence of other abnormalities of dopamine neurotransmission such as tissue levels or transporter binding. Serotonin levels and its metabolite 5-HIAA were reported to be increased in the brainstem in one model.

Neuropathological findings in ΔE-torsinA transgenic mice have been subtle and variable. No signs of gross neuroanatomical changes or frank neurodegeneration have ever been reported, but in some models abnormalities of the nuclear membrane were seen, similar to those found in cell cultures, or intracellular inclusions in the brainstem containing torsinA, nuclear envelope proteins, and ubiquitin-related proteins. These were found both in the mice overexpressing ΔE-torsinA, and to a lesser extent in those overexpressing human wild-type torsinA.

Studies of TorsinA in Humans

Studies of neuropathological tissue from patients with Parkinson's disease demonstrated the presence of torsinA in Lewy bodies in the SNc. Tissue from patients with trinucleotide repeat disorders, including Huntington's disease, Huntington's disease-like 2, and spinocerebellar ataxia 3, also found immunoreactivity to torsinA localized to the intranuclear inclusion bodies typical of these disorders, which characteristically comprise ubiquitin, the causative mutant protein and various other proteins.

Neuropathological studies of a very small number of brains of patients with DYT1 dystonia did not show any gross abnormalities or areas of neuronal loss, although dopaminergic neurons of the SNc appeared to be larger and closer together. The neuropathological findings in brains of patients with varying forms of dystonia, prior to the discovery of the *DYT1* gene, are heterogeneous.

Examination of selected regions (SNc, striatum, neocortex, cerebellum) in a single case of DYT1 dystonia did not disclose any abnormalities. Neuronal inclusions in the pedunculopontine nucleus were reported in a small series of DYT1 dystonia cases. These inclusion bodies were immunoreactive for torsinA, lamin A/C, and ubiquitin. Lamin A/C proteins are also associated with the nuclear envelope, while the presence of ubiquitin suggests that there was degradation of abnormal proteins via the ubiquitin–proteasome system.

Summary

The identification of torsinA as the cause of DYT1 dystonia was a major breakthrough in the field. Ten years later we understood more about the functions of this protein; however, a lot remains to be discovered regarding exactly how and where it malfunctions to cause the brain dysfunction which results in the appearance of dystonia in only a proportion of carriers of the mutation.

See also: Dystonia; DYT1.

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Tottering Mouse - a Definition

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Glossary

Absence seizure – Brief, recurring seizures that are characterized by loss of alertness. The seizure often presents as a vacant stare by which the patient appears to be 'absent.' There is no recollection of the seizure after its occurrence (post-ictally). Absence seizures are occasionally accompanied by involuntary muscle movements.

Ataxia – Ataxia is a neurological sign consisting of lack of coordination of voluntary movements, especially with respect to ambulation. It typically presents as a staggering, or wobbling gait, or instability while walking/standing.

Cerebellum – The 'hindbrain.' This distinct brain region is directly associated with coordination of movement. More recently, it has been implicated in other functions such as cognition as well.

Dystonia – Involuntary muscle movements, which may be repetitive and sustained. They can result in aberrant limb movement or positioning, or disturbed body posture.

$GABA_A$ receptor – The principal inhibitory receptor in the mammalian brain. $GABA_A$ receptors are made up of five subunits, and typically involve combinations of three types of subunits, $\alpha\beta\gamma$ are the most commonly occurring combination. However, several other subunit subtypes can also substitute for γ; often this involves a δ subunit, or other less-abundant units. $GABA_A$ receptors are ligand-gated, and respond to the amino acid transmitter GABA. When activated, the receptor gates an intrinsic ion channel selective for Cl^-. For the most part, the transmembrane $[Cl^-]$ gradient favors Cl^- leaving the cell. Thus, $GABA_A$ receptors typically move the membrane potential away from the action potential firing threshold, that is, hyperpolarize.

P/Q-type Ca channel – Also known now as Cav2.1. P/Q-type Ca channels are a member of the high voltage-activated class of channels, meaning that strong depolarizations from the resting potential are needed to induce activation of the channel. These channels were originally described in cerebellar Purkinje cells where they occur in high abundance (~80%). Hence, they are named P-type channels to signify their Purkinje cell origin. So-called Q-type channels arise as a splice variant of P-type. Both comprise an $\alpha 1$, β, and $\alpha_2\delta$ subunit, where the pore-forming subunit α_{1A} is distinct from other Ca channel phenotype $\alpha 1$ subunits. P/Q-type channels are blocked with high affinity by a peptide toxin isolated from the venom of the funnel web spider (*Agelenopsis aperta* – agatoxin IVA). P/Q-type channels couple to many physiological functions, but are best known for participating in the regulation of release of chemical neurotransmitters.

Purkinje cell – The sole 'outflow' path from the cerebellar cortex to other brain regions. Purkinje cells have an extremely extensive dendritic arborization. They are themselves inhibitory, but receive both inhibitory and excitatory input. The latter includes both an intrinsic and external pathway in the cerebellum. The intrinsic pathway is mediated by the parallel fibers of the cerebellar granule cells. The extrinsic pathway derives from the inferior olive, and is known as the climbing fibers.

Vestibule – A region of ion channel proteins located at the internal and external hydrophilic and external region of the channel. The vestibule is charged with an appropriate charge so that it attracts the type of ion (i.e., cation) that permeates the channel. Having a vestibule improves ion channel function by facilitating ion entry when the channel is activated.

Voltage-gated ion channel – A transmembrane protein responsible for passage of ions into or out of the cell. The channel 'opens,' or is gated by a change in the transmembrane potential. Voltage-gated ion channels are typically relatively selective for the permeant ion, and ion transport occurs in the absence of input of cellular energy.

Introduction

'Tottering' refers to one of a series of naturally occurring mutations in mice in the pore-forming (α_1) subunit of a specific subtype of voltage-gated calcium channel (Cav). The *tottering* (*tg*) (B6.D2-Cacna1atg/J) genotype is an inherited autosomal recessive mutation on chromosome 8 in the gene encoding the α_{1A} subunit gene (e.g., *CACNA1A*) of the P/Q type (Cav2.1) Ca^{2+} channel. This type of Ca^{2+} channel is ubiquitously expressed throughout the central and peripheral nervous system, but effects of *tg* are not uniformly directed at all neurons. Regions with high density of P/Q-type channels have more prominent pathophysiology. P/Q-type channels are extensively expressed in the cerebellum. This is especially true in the Purkinje cells, where these channels were first described, and are the sole output cells from the cerebellar cortex. Cerebellar dysfunction likely contributes substantively to the motor dysfunction. *Tg* encodes a single amino acid substitution (proline to leucine, both of which are nonpolar and hydrophobic) in the S5–S4 extracellular region of repeat domain II of the α_{1A} subunit protein. This site is located near the so-called 'outer vestibule' of the pore of the channel. The mutation affects the functional properties and likely the expression of the Cav2.1 channel and presumably results in the observed pathophysiology; however, other proteins are also affected in the *tg* mice. Whether their alterations occur specifically as a result of the deficiency in the Cav2.1 channels is yet unknown.

Behavioral Phenotype

The *tg* mutation causes a delayed-onset neurological disorder that is characterized by ataxia, episodes of dystonia, and myoclonic motor seizures. The latter resemble absence epilepsy in humans. The ataxia and episodic dystonia have been associated with dysfunction in the cerebellum. However, these two signs appear to be dissociated in that surgical resection of the cerebellar vermis prevents the dystonic attacks without appreciably affecting the ataxia. The absence-like seizures exhibit aberrant EEG responses, and can be attenuated using conventional antiseizure treatment for petit mal seizures.

The onset of the *tg* phenotype is delayed. Absence epilepsy and motor dystonia appear 3–4 weeks postnatally. This may reflect maturation of processes that depend on the P/Q-type Ca^{2+} channel, but for which other Ca^{2+} channel phenotypes can substitute prior to developmental shift. The behavioral responses have been attributed to impairment of excitatory glutamatergic transmission at synapses between cerebellar granule cells and Purkinje cells – the so-called 'parallel fiber' synapses. However, other proteins are also affected in *tg* mice.

Cellular Consequences of *tg* Mutation

P/Q-type Ca^{2+} channels were first described in cerebellar Purkinje cells, where they occur in high abundance. They are found throughout the cerebellum, including the granule as well as Purkinje cells. P/Q-type Ca channels contribute to control of a number of critical neuronal functions. Among these are neurotransmitter release, regulation of transcription, and $[Ca^{2+}]$ regulation within the nucleus. As a result of *tg* mutation, those functions that depend on P/Q-type channels are affected. P/Q-type channels typically coexist with other subtypes of Cav – typically Cav2.2 (N-type), Cav2.3 (R-type), or Cav1.2 (L-type). The purpose of this redundancy is unknown, as is the basis for a particular combination of overlapping channel phenotypes. Several studies have examined physiological responses of *tg* mice to characterize the phenotype. Rather subtle changes occur in function of P/Q-type channels in Purkinje cells of *tg* mice. These include reduction (~40%) in whole cell current density, and alteration of current inactivation (the ability to sustain current amplitude) following prolonged depolarization.

Effects on P/Q-type Ca^{2+} channels are not the only proteins whose expression is altered in the *tg* mice. However, the extent to which other protein alterations contribute to the phenotype is yet unknown. One important alteration is in the expression of receptors for the inhibitory neurotransmitter GABA. *Tg* mice have a reduced expression of certain $GABA_A$ receptor subunits found specifically at cerebellar granule cells, namely the α6 and δ subunits. This effect could have profound effects on granule cell excitability and contribute to the abnormal glutamatergic transmission along the parallel fibers – the axons of cerebellar granule cells – observed in *tg* mice. Another protein whose expression is significantly altered in *tg* phenotype is tyrosine hydroxylase, the rate limiting step in the synthesis of catecholamines.

Compensation for Lack of Cav2.1 Function

When the P/Q-type channel is mutated, the relative contribution of other types of Ca^{2+} channels increases, presumably in a pleiotropic response to try to maintain the critical functions. For example, at hippocampal and cerebellar parallel fiber synapses, release of the neurotransmitter glutamate normally exhibits a high dependance on P/Q-type Ca^{2+} channels. However, in *tg* mice, the N-type (Cav2.2) channels assume control of secretion. Conversely, L-type (Cav1.2) Ca^{2+} channels are upregulated in the cerebellum and basal forebrain of *tg* mice, and stereotypic behavior can be induced by the L-type channel dihydropyridine agonist BayK 8644, whereas no such effect

occurred in wild-type (*wt*) mice. Moreover, L-type Ca channel α_{1C} subunit mRNA was upregulated in Purkinje cells of *tg* mice, suggesting that the L-type phenotype was now either newly present, or unmasked in these animals. L-type channels may not be as involved in transmitter release as compared to other processes including neuronal plasticity or membrane excitability.

In the peripheral somatic nervous system, P/Q-type Ca^{2+} channels are the primary regulators of acetylcholine (ACh) release at mammalian neuromuscular junctions, so their dysfunction might be expected to result in neuromuscular weakness. However, *tg* mice have no significant neuromuscular impairment, despite their obvious gait abnormality. Several subtle effects on neuromuscular transmission do occur mostly related to release at high rates of stimulation. In adult *tg* mice, N- and R-type (Cav2.3) channels become responsible for ACh release. Thus, other types of Cav are upregulated in the *tg* mutants; the other channel types are relatively effective in maintaining normal function. This compensatory response is a property seen at synapses in several of the naturally occurring mutations and transgenic strains of mice with alterations in P/Q-type Ca^{2+} channels.

Other Tottering Loci

Two naturally occurring variants of the *tg* genotype have recently been identified and characterized; both arise as spontaneous mutations in the *Cacnala* gene. One is semidominant, and arises in the tottering-5J allele (*Tg-5J*), while the other is recessive and occurs on the tottering-4J allele (*tg-4J*). In the *Tg-5J* mutation, there is a shift from positively charged and conserved arginine to an uncharged glutamine, while in the *tg-4J* mutant, the switch is from a valine to alanine, both of which are nonpolar and hydrophobic. Both mutations caused functional changes that were unique from those seen in mice with other *tg* alleles. Similarly, the typical triad of behavioral manifestations seen in *tg* mice are recapitulated in *tg-4J*, whereas *Tg-5J* homozygotes are typically lethal. Ataxia is present in the heterozygotes, but appears to be distinct from that of other *tg* loci; it is characterized by a shaky gait with the hind limbs splayed laterally from the body. The characteristic spike-wave discharge pattern associated with *absence* seizures in the other mutants is not observed, so *absence* seizures are not associated with this mutation. Also, dyskinesia is not seen in *Tg-5J* heterozygotes.

Several other naturally occurring mutations in the α_{1A} subunit have been identified. These include '*leaner*' and '*rolling Nagoya*,' both of which occur as a result of a single locus on the gene encoding for the α_{1A} subunit. They either affect the expression or functional properties of the encoded channels. While the overall site of the mutation is similar, and motor dysfunction occurs with each mutation, the phenotypes of these genotypes vary considerably from that of *tg* both in terms of pattern and severity. In conjunction with *tg*, these mutations have been used as models to study naturally occurring spontaneous mutations in the Cav2.1 α_{1A} subunit, such as those responsible for spinocerebellar ataxia (SCA)6, familial hemiplegic migraine (FHM), and episode ataxia (EA) in humans.

See also: Ataxia.

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Tourette Syndrome

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Glossary

Compulsions – Repetitive, purposeful behaviors usually performed in response to an obsession, or according to certain rules, or in a repetitive fashion.
Coprolalia – The uncontrollable and excessive use of foul or obscene language.
Echolalia – Pathologically repeating (echoing) the words of another person.
Neuroleptics – Antipsychotic medications.
Obsessions – Recurrent ideas, thoughts, or impulsions that intrude on conscious thought and are persistent and unwelcome.
Palilalia – Pathologically repeating one's own words.
Stereotypies – Involuntary, repetitive, and rhythmic movements that have a predictable pattern and location, seem purposeful but serve no obvious function, tend to be prolonged and are able to be suppressed.
Tics – Involuntary, sudden, rapid, repetitive, nonrhythmic stereotyped movements, or vocalizations.

Definition and History

Tourette syndrome (TS) is named after the French physician Georges Gilles de la Tourette who, in 1885, reported nine patients with chronic, involuntary motor, and phonic tics. These patients also experienced a variety of neuropsychiatric problems such as obsessive–compulsive and anxiety symptoms. Since that time there have been numerous advances, from genetics to therapeutics, although we are far from fully understanding this complex disorder. Here, we aim to provide the reader with an overview of TS.

Pathogenesis and Pathophysiology

Genetics

The precise pattern of transmission and the identification of a gene responsible for TS remain elusive. Studies of monozygotic twins provide the strongest support for a genetic disorder, with an 86% concordance rate with chronic tic disorder compared with 20% in dizygotic twins. A multifactorial inheritance with at least one major locus seems likely. Genetic linkage, cytogenetics, candidate gene studies, and molecular genetic studies have been used to identify the genetic site. Linkage analyses have suggested multiple chromosomal locations, but no reproducible locus or convergence of findings. An association with SLITRK1 has not been confirmed and linkage to a marker on chromosome 2p23.2 requires further investigation. Although susceptibility loci have been identified in TS, it is possible that no causative gene has been identified because of phenotypic heterogeneity. The possible effects of genomic imprinting (sex of the transmitting parent may affect the clinical phenotype), bilineal transmission (genetic contribution from both sides of the family), genetic heterogeneity, and gene–environment interactions further complicate the understanding of TS genetics. Epigenetic risk factors that have been examined include timing of perinatal care, severity of mother's nausea and vomiting during the pregnancy, low birth weight, Apgar score at 5 min, thimerosal exposure, nonspecific maternal emotional stress, and prenatal maternal smoking. Still other investigators have suggested that TS is not genetic but rather represents a common disorder in the general population.

Neurobiology

Understanding of the cortico–striatal–thalamocortical (CSTC) circuits has provided a unifying framework for understanding the interconnected relationships that exist between TS and its comorbid psychiatric disorders. The supplementary motor cortex and its projections to the putamen are believed to play a role in motor tics. The oculomotor circuit, possibly influencing ocular tics, begins principally in the frontal eye fields and connects to the central region of the caudate. Other circuits, such as the dorsolateral prefrontal circuit link Brodmann's area 9 and 10 with the dorsolateral head of the caudate and appear to be involved with 'executive functions' (flexibility, organization, constructional strategy, verbal and design fluency) and 'motor planning' (sequential and alternating – reciprocal motor tasks). Obsessive–compulsive disorders (OCD) have been linked to the lateral orbitofrontal circuit originating in the inferior lateral prefrontal cortex and projecting to the ventral medial caudate. Lastly, the anterior cingulate gyrus projections to the ventral striatum, with additional input from the amygdala, hippocampus, medial orbitofrontal cortex, entorhinal and perirhinal cortex have been linked to a variety of behavioral problems.

Although direct and indirect evidence suggests that the components of the CSTC are involved in the expression of tic disorders, identification of the primary site of abnormality (frontal cortex, striatum, midbrain) remains an active area of research. Cortical dysfunction may play a primary role in TS. Many children with TS have executive dysfunction, and volumetric MRI studies have shown larger dorsolateral prefrontal regions in children with TS, but significantly smaller volumes in adults with the disorder. Examinations of white matter have shown increased cortical white matter in the right frontal lobe and decreased white matter in the deep left frontal region in children with TS, and midsagittal measurements have shown variable changes in the size of the corpus callosum. DT-MRI studies in TS demonstrated lower fractional anisotropy of the corpus callosum, suggesting reduced white matter connectivity in this interhemispheric pathway.

Functional imaging, using glucose metabolism and blood flow studies, has identified abnormalities within the basal ganglia and cortical areas in patients with TS. Positron emission tomography (PET) showed bilateral and symmetrical increases or decreases of glucose utilization within the basal ganglia and decreased activity in frontal, cingulate, and insular cortices. Hypoperfusion of basal ganglia has been found through cerebral blood flow examination by single photon emission computed tomography (SPECT). Comparison study using 'perfusion imaging' in children with chronic motor tics and TS showed decreased perfusion primarily affecting the left hemisphere in the TS group, although the differences were thought to be related to comorbidities rather than tics. Regional blood flows were found to be significantly lower in the left caudate, cingulum, right cerebellum, and right and left dorsolateral prefrontal regions in children with TS when compared with controls; a correlation between motor tic severity and blood flow was not detected, but there was a positive correlation between the severity of vocal tics and several regions. Functional neuroimaging of tics using event-related PET combined with time-synchronized videotaping showed numerous brain regions significantly correlated with tic occurrence including medial and lateral premotor cortices, anterior cingulate cortex, dorsolateral–rostral prefrontal cortex, inferior parietal cortex, putamen, caudate, primary motor cortex, the Broca's area, superior temporal gyrus, insula, and claustrum. Which of these regions accounts for initiation, rather than execution, of motor and vocal behaviors, remains unknown.

The presence of dopaminergic, glutamatergic, GABAergic, serotoninergic, cholinergic, noradrenergic, and opioid systems within the CSTC circuits raises the possibility that various transmitters may be involved in the pathophysiology of TS. Because many transmitter systems are interrelated in the production of complex actions, it is indeed possible, if not probable, that imbalances exist within several transmitter systems.

Dopamine dysfunction continues to receive attention as playing a primary role in TS because of its therapeutic response to neuroleptics and the results from various nuclear imaging protocols, CSF, and post-mortem studies. There are increases in the number of dopamine receptors, high concentrations of dopamine transporters, and increased intrasynaptic dopamine release within the striatum. An association has been identified between a polymorphism of the dopamine transporter gene DAT *Dde*I and TS. One unifying hypothesis is that an overactive dopamine transporter results in the increase of phasic dopamine release that, in turn, results in a hyperresponsive spike-dependent dopaminergic system in the prefrontal cortex. This hypothesis is supported by clinical findings including (1) the exacerbation of tics by stimulant medication, likely secondary to enhanced dopamine release; (2) tic exacerbation by events shown to increase phasic bursts of dopamine, such as stress, anxiety and medications; and (3) tic suppression with very low doses of dopamine agonists, likely due to presynaptic reduction of phasic dopamine release.

Other neurotransmitter systems have been implicated as well. Glutamate plays an essential role in pathways of CSTC circuit. Reduced levels of glutamate have been identified in the globus pallidus interna, globus pallidus externa, and substantia nigra pars reticulata of four TS brains. Serotonin interacts with the CSTC circuit via fibers projecting from the median raphe to the basal ganglia and cortex. Decreased levels of serotonin and tryptophan were noted in serum samples of children with TS. Levels of 5-HIAA, a serotonin metabolite, were lower in the CSF and basal ganglia of TS subjects, but were normal in cortical tissue.

Epidemiology

TS affects people world-wide and its common features are evident in all cultures and races. The prevalence of tics in childhood is about 6 to 12% (range 4–24%). The precise prevalence of TS is unknown, with estimates ranging from 1 to 10/1000 children and adolescents. If mild cases that may not be identified are included, the prevalence can rise to 10–30/1000 children and adolescents. TS is more common in males than in females (more than 3:1), and the mean age of onset is typically between 5 and 7 years, with most developing tics before their teenage years. Children with autistic spectrum disorders including Asperger syndrome and fragile-X have a high incidence of TS, but it is unrelated to the severity of autistic symptoms.

Clinical Presentation

Tics, the cardinal features of TS, are involuntary, sudden, rapid, repetitive, nonrhythmic stereotyped movements or

vocalizations. Tics may take a variety of forms, with different durations and degrees of complexity. Simple motor tics are rapid movements that often involve only one muscle group (e.g., eye blink, head jerk, shoulder shrug). Complex motor tics may involve a cluster of simple movements or a more coordinated sequence of movements. These can be nonpurposeful (facial or body contortions) or can be integrated into more purposeful movements (e.g., touching, jumping, obscene gestures). Sterotypies and compulsions are often confused with the complex motor tics of TS. Stereotypic movements, such as head nodding, rocking and arm flapping/waving, tend to appear before age 3 years, involve a fixed and prolonged movement and stop abruptly with distractions. Compulsions, such as touching or tapping, occur in association with other obsessive–compulsive symptoms and are often preceded by a conscious desire to perform the action in a particular way or number of times, or until it feels 'just right.' Vocal tics can also be simple (e.g. sniffing, grunting, yelping, and throat-clearing) or complex (syllables, phrases, echolalia, palilalia, or coprolalia). Although coprolalia is one of the most distressing and recognized symptoms of TS, it occurs in only about 10% of patients.

The frequency of tics is quite variable. Tics are commonly exacerbated during periods of anticipation, anxiety, anger, or fatigue. It is controversial whether tic severity worsens during times of perceived life stress. In one study of children with TS, higher scores on the Daily Life Stressors Scale correlated positively with the total tic score on the Yale Global Tic Severity Scale. In another study, however, only a minority of patients indicated that changes in tic severity (over the course of 1 week) correlated with stressful events. Tics may also worsen during inquiries about specific movements or after the observation of a movement or sound (echophenomena). They decrease in frequency when the person is absorbed in activities, concentrating, or asleep. However, polysomnograms of people with TS have shown an increased rate of tics during rapid eye moments (REM) sleep. Patients can actively suppress tics; usually associated with a growing inner tension that resolves when the tic happens. Premonitory sensations, often described as an urge, impulse, tension, pressure, or itch may take place before a motor or phonic tic typically localized to discrete anatomical regions. In TS, premonitory sensations occur in about 90% of adults, but only in 37% of young children. Misdiagnoses of tics are common: eye blinking tics are often thought to represent eye problems and throat clearing or involuntary sniffing tics attributed to sinusitis or allergic conditions.

Tic Disorders

The diagnosis of a tic disorder is based solely on the historical features and a clinical examination confirming their presence and ruling out other conditions. There is currently no blood test, brain scan, or genetic screen to assist in diagnosis. TS represents only one entity in a spectrum of tic disorders. A classification system endorsed by the Tourette Syndrome Association defines tics as 'transient' (present for <12 months) or 'chronic' (present for more than 12 months).

The mildest and most common tic disorder is transient tic disorder, found in about 24% of school children. There is no way to predict whether an individual will have resolution of tics, addition of other tics, or persistence of tics; thus, the use of the term tic disorder – 'diagnosis deferred' is preferred for individuals with ongoing tics present for <1 year. 'Diagnosis deferred' is included, since it is impossible to predict whether an individual's tics will persist for the requisite 1-year time interval required for a 'chronic' designation or fall into the transient category. Chronic (motor or phonic) tic disorder requires that the tics be either entirely motor or, less commonly, vocal.

Formal criteria for the diagnosis of TS is similar to Tourette disorder, as outlined by the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, except for minor differences. Requirements for TS according to the Tourette Syndrome Classification Study Group are as follows: the presence of multiple motor and at least one vocal tic (not necessarily concurrently); a waxing and waning course with tics evolving in a progressive manner; the presence of tic symptoms for at least 1 year; the onset of symptoms before age 21; the absence of a precipitating illness (e.g., encephalitis, stroke, or degenerative disease) or medication; and the observation of tics by a knowledgeable individual. The DSM-IV-TR criteria for Tourette disorder requires that tic-free intervals not be greater than three consecutive months and reduce the age of onset to <18 years.

Tourette-like (or secondary) disorder includes tic syndromes that do not meet the formal criteria for TS; for example, tics associated with a variety of acute and chronic neurological disorders including head injury, stroke, cardiac surgery with by-pass and hypothermia, peripheral trauma, infectious disease, medications and degenerative disorders including neuroacanthocytosis, Huntington's disease, Creutzfeldt–Jakob disease, and pantothenate kinase deficiency. Although the diagnosis is controversial, also included in this category are children with the abrupt onset and repeated rapid worsening/exacerbation of tics associated and with evidence of group A β hemolytic streptococcal infections, known as PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection). 'Tardive' Tourettism is the de novo appearance of motor and vocal tics in patients being withdrawn from chronic neuroleptic treatment. Adult onset tic disorders have been reported and are often associated with potential environmental triggers, severe symptoms, greater social morbidity, and a poorer response to medications.

Neuropsychiatric Comorbidities

Multiple psychopathologies are associated with TS, and their clinical impact can be more significant than the tics. For example, the quality of life is predicted by the coexisting conditions such as ADHD and OCD rather than tic severity. Further, the presence of a child with TS in the home, especially one with a behavioral comorbidity, has a significant negative impact on parents. It is essential that the physician caring for an individual with TS should be aware of associated psychiatric disorders and differentiate them from tics.

Obsessive–compulsive disorder

Obsessive–compulsive behaviors are common in individuals with TS. Obsessions are recurrent ideas, thoughts, or impulsions that intrude on conscious thought and are persistent and unwelcome. Compulsions are repetitive, purposeful behaviors usually performed in response to an obsession, or according to certain rules, or in a repetitive fashion. Obsessive–compulsive behavior becomes a disorder when these activities cause marked distress, occupy inordinate time, or have a significant impact on normal function or relationships. The incidence of obsessive–compulsive behavior in TS is typically reported to be in the range of 45%, though some studies report up to 89%. Compulsive behaviors emerge during adolescence, typically several years after the onset of tics. A genetic association between OCD and TS has been identified.

The obsessive–compulsive symptoms in persons with OCD alone appear different as compared to those with OCD and TS. In patients with TS, obsessive–compulsive behaviors usually include a need for order and 'symmetry' and typically involve arranging, ordering, hoarding, touching, tapping, rubbing, counting, checking for errors, and 'evening-up' rituals.

Attention-deficit hyperactivity disorder

Attention-deficit hyperactivity disorder (ADHD) is defined by impulsivity, hyperactivity, and a decreased ability to maintain attention to a degree that impairs function. Approximately, 50% of TS cases in a referral population are affected by ADHD. ADHD typically precedes the onset of tics by 2–3 years in TS patients, beginning at age 4–5 years. The severity of ADHD in children with tics, rather than the severity of tics themselves, predicts the behavioral and social problems. In children with TS, ADHD is the primary contributing factor in impairments of school performance. The existence of a genetic relationship between TS and ADHD remains unclear. Studies showed that children with ADHD are more likely to have a family history and increased incidence of tics while others suggest that ADHD is not genetically related to TS.

Anxiety and depression

Several studies have found an increased incidence of anxiety and depression in patients with TS. A history of mood disorder of any type (based on DSM-IIR criteria) was found in 76% of children and adolescents with TS evaluated in a psychiatric specialty clinic, and 64% met criteria for any type of nonobsessive–compulsive anxiety disorder. Separation anxiety, agoraphobia, and panic disorder are all more common in TS patients. Severe anxiety was found in 25% of patients with TS and found that 17–23% were clinically depressed. Bipolar disorder was also over-represented in a community sample of TS patients. Depressive symptoms were more severe in TS patients who were female, older (adults), and who had echo phenomena (echolalia or echopraxia). It remains unclear, however, whether depressive symptoms are related to the severity of tics. Ratings on the Yale Children's Global Stress Index directly correlated with clinician depression ratings in children and adolescents with TS and/or OCD and this population also experienced more psychosocial stress than controls.

Other problems

Many other behavioral disorders have been associated with TS. Migraine headaches are observed more frequently in patients with TS compared with the general population. On the basis of migraine questionnaires, 25% of patients with TS have migraine, exceeding the general estimates of migraines in adults and in children. Problems associated with sleep have been reported in up to 50% of children and young adults with TS. The most difficulties are in falling and staying asleep and parasomnias. Polysomnographic studies have shown multiple abnormalities including disturbed sleep quality with increased sleep latency, reduced sleep efficiency, prolonged wakefulness after sleep onset, and altered slow-wave sleep. Tics can be seen in all sleep stages, along with frequent arousals, periodic limb movements, and sleep apnea. It is also known, however, that associated neuropsychiatric comorbidities, such as ADHD and anxiety can contribute to the sleep deficits. There is significant clinical and pathological overlap between patients with TS and restless-legs syndrome. Both desire to move the limbs in association with a preceding urge or sensation, worsen over the course of the day; occur with sleep, and share pathological associations with dopamine and frontal-striatal cortical circuits. A study of children with TS in a French-Canadian population demonstrated that 10% had restless-legs syndrome. Furthermore, the true prevalence of restless leg syndrome may be underestimated because of confusion with ADHD, complex tics, and compulsions. Rage attacks and difficulty with aggression have been described in patients with TS.

Treatment

Treatment of TS should be individualized based on the analysis of tics, presence of comorbiddisorders, assessment of severity, as well as the resulting impairment and the support system available. Prioritization based on the degree of impairment is an important guide for the treatment of TS patients with comorbidities. Reassurance and education of families about TS, its predicted outcome, and underlying pathophysiologic mechanisms are essential and often beneficial in permitting a conservative course.

Nonpharmacological Treatments

Behavioral treatments (conditioning techniques, massed negative practice, awareness training, habit reversal, relaxation training, biofeedback, and hypnosis) have been proposed as complementary and alternative therapeutic approaches, but their efficacy is not well evaluated. Habit reversal training substantially improved tics as compared to a supportive therapy group, with the beneficial effect persisting to follow-up 10 months later. In a small cohort study, habit reversal therapy also reduced the severity of vocal tics. Scientific evidence is scant for the use of dietary therapies, including vitamins, protein supplementation and elimination diets, or acupuncture.

Pharmacotherapy

As there is no cure for tics, all pharmacotherapy must be regarded as symptomatic therapy. Typically, medication is recommended if there are significant psychosocial disturbances (bullying, interference with schooling) or physical harm secondary to the tics. If a tic-suppressing drug is indicated, a two-tiered approach is recommended: (1) nonneuroleptic drugs for mild tics and (2) typical or atypical neuroleptics for more severe tics. Although multiple medications are used for tic suppression, the only FDA approved drugs are haloperidol and pimozide. The goal of treatment is not to completely suppress all motor and phonic tics, but to reduce to a level in which they no longer cause substantial psychosocial or physical disturbance.

Tier one drugs include clonidine, guanfacine, baclofen, and clonazepam. Both clonidine and guanfacine are α-2-adrenergic receptor agonists, primarily acting on presynaptic receptors to regulate norepinephrine release. The efficacy of anticonvulsants is unclear: the use of levetiracetam is controversial and topiramate has been beneficial in case reports.

In tier two, classic neuroleptics, such as D2 dopamine receptor antagonists, are effective tic-suppressing drugs, but side effects may restrict their use. Pimozide or fluphenazine have a lower occurrence of side effects and are preferable to haloperidol. The atypical neuroleptics (risperidone, olanzapine, ziprasidone, quetiapine) have the potential for fewer extrapyramidal side effects, likely due to a greater affinity for 5-HT2 receptors than for D2 receptors. Risperidone has been examined in randomized double-blind trials and shows efficacy against tics. Although several neurosurgical approaches have been tried, evidence that deep brain stimulation may be beneficial is accumulating.

Prognosis

The history and evolution of tics in TS remains poorly understood. Tics persisting into adulthood do not differ from those in children. Tics have a waxing and waning course. The outcome of TS is no longer thought to be lifelong, but remains quite variable, with some patients experiencing a spontaneous remission or marked improvement independent of tic-suppressing medication. In a study of 58 young adults, tics virtually disappeared in 26%, diminished considerably in 46%, remained stable in 14%, and increased in 14%. Investigations have suggested that maximum tic severity occurs between ages 8 and 12 years, and is then followed by a steady decline in symptoms. In a longitudinal study of patients first seen as children and reevaluated in adulthood, tic disability and severity were significantly reduced over time. Interestingly, 90% of patients still had some tics documented on videotape including half of those who thought they were tic-free. The severity of tics early in the course of TS is not a good predictor of later tic severity. People with chronic tic disorder and coexisting disorders are more impaired than those chronic tics alone.

Conclusion

TS remains a challenge for both the clinician and researcher. For the treating physician, patients have complex intertwined neuropsychiatric problems that can be challenging to treat. For researchers, numerous questions remain about the genetics, neuroimmunology, and neurobiology of TS.

See also: PANDAS; Tics; Tics, Complex; Tics, Simple; Tourette Syndrome: Animal Models; Yale Global Tic Severity Scale (YGTSS).

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Tourette Syndrome: Animal Models

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Glossary

Animal model – An experimental paradigm in laboratory animals designed to understand issues of relevance to human biology, e.g., anatomy, physiology, pathophysiology, and therapeutics.
Deep brain stimulation – A therapeutic modality achieved by delivering controlled electrical current to selective brain regions to reduce symptoms of specific brain disorders.
Nucleus accumbens – Literally, 'the nucleus that leans against the septum': a specialized region of the ventral striatum that is the forebrain terminal field of the mesolimbic dopamine system, and which is heavily innervated by limbic-associated cortical and subcortical regions.
Sensorimotor gating – The automatic inhibition of motor responses by a weak sensory event, operationalized in the laboratory by prepulse inhibition of the startle reflex.
Tic – A rapid, repetitive, nonrhythmic stereotyped motor, phonic, or sensory event, generated either involuntarily or in capitulation to a state of psychic or somatic discomfort.
Tourette syndrome – A tic disorder of childhood onset, characterized by multiple motor and at least one phonic tic, and typically accompanied by premonitory urges or sensory tics.

Introduction

Perhaps the most important point to understand about animal models of Tourette syndrome (TS) is that there are no adequate examples. Anyone who has experienced TS personally or is a clinician or family member involved with TS subjects knows that the symptoms of TS are far too complex and far too 'human' to be captured in the twitching of a mutant mouse or the sniffing of a rat. For the majority of individuals with TS, tics are preceded or accompanied by premonitory sensory or psychic urges that have only recently been quantified by reliable self-rating instruments in humans. These attributes of tics cannot be measured in infrahumans, even by the most sophisticated laboratory apparatus. Likewise, there are complex social and family dynamic aspects to TS that shape the expression of tics and their psychological consequences, and these features cannot be modeled in laboratory animals. Added to this, TS is a heterogeneous syndrome, with many phenotypic variations and combinations of comorbidities, and no single 'model' could possibly capture this diversity. Several investigators have written about the pitfalls of trying to develop animal models of TS or most other neuropsychiatric disorders and have argued that the most appropriate uses of animal models in neuropsychiatry are to develop and test hypotheses about the biology of brain function. In this context, animal models can lead to discoveries on neuroanatomy, neurochemistry, neuropharmacology, neurodevelopment, or genetics and

may help to suggest etiologies or treatments of disorders affecting the brain. The quest for homology in animal models is generally misguided, and as Millan aptly writes, these are 'models for, not of,' brain disorders.

Good animal models are nonetheless important, and perhaps indispensable, to understand TS and other complex brain disorders. At a basic level, animal models teach us about the organization of forebrain neural circuitries and how genes and the environment interact to regulate their development, organization, and ongoing function. Even if we posit a notion now broadly dismissed – that TS is a disorder of very simple genetics – we will never understand TS simply by finding TS genes. As Landis and Insel suggest, 'we cannot hope to understand how genomic variation influences behavior without understanding how genomic variation influences neural circuitry.'

We and others have previously written about the value of animal models and their predictive and construct validity in relationship with TS and other disorders. Predicting effective treatments and understanding their mechanisms of action have clearly been valuable for animal models of brain disorders. Animal models have also been important for testing constructs for the etiologies of disorders like TS. Here, we will describe the state of several models that may be informative about TS-related treatments and the pathogenesis of TS.

Models Related to Therapeutic Insights

Therapeutic approaches to TS include medications, behavioral therapy, and in extreme cases, neurosurgery. Animal models are being used to advance each of these approaches.

A New Target for TS Drug Development

It is generally believed that central abnormalities of dopamine (DA) function contribute to the pathogenesis of TS, or at least, to the mode of therapeutic action of anti-TS treatments. Neuroimaging studies suggest both DAergic hyperinnervation and volumetric reduction in the ventral striatum/nucleus accumbens (NAC) in TS, within a region that regulates sensorimotor gating processes that are deficient in TS, and which may also serve as a target for therapeutic effects of deep brain stimulation (DBS) in TS. Drugs that block D2-family (D2,3,4) receptors (e.g., haloperidol and pimozide) reduce tic severity; it has been hypothesized that these drugs exert at least some of their therapeutic effects via D3 receptor antagonism, while their major side effects, including extrapyramidal effects and hyperprolactinaemia, reflect widespread forebrain D2 receptor antagonism. Compared to D2 receptors, D3 receptors have a much localized expression, with very high levels in the NAC. It is thus conceivable that drugs that selectively antagonize D3 receptors might target a restricted forebrain field, and thereby offer a preferable therapeutic index.

Several studies have demonstrated the ability of D3 agonists (as well as D2 agonists and mixed D2/D1 agonists) to reproduce in rats the loss of sensorimotor gating detected in TS patients. More recently, we demonstrated that this model can be used to identify novel compounds that act as selective, functional D3 antagonists. While it is clearly premature to suggest that functional D3 antagonists will offer therapeutic benefit in TS, there is reason to believe that they might selectively oppose DA hyperfunction in TS within a relatively restricted forebrain DA field that is linked closely to identified pathology in TS. Further, they might also be relatively free from the adverse effects of existing neuroleptic agents. One advantage of the sensorimotor gating model in TS drug discovery is that it can be studied in humans in advance of clinical trials; we anticipate that future D3 antagonists will be studied in clinically normal humans to test the ability of these compounds to oppose effects of D3 agonists on sensorimotor gating, and in TS subjects, to test their ability to normalize sensorimotor gating after acute challenge. A similar strategy appears to be showing promising results in studies of fragile X syndrome. In some disorders, sensorimotor gating deficits are exhibited not only by affected probands, but also by asymptomatic first-degree relatives; this allows the use of healthy, medication-free relatives, rather than more complex patients, in early phase drug development for compounds designed to normalize disorder-related gating deficits. Studies of gating deficits in TS relatives should clarify whether this strategy could be applied toward TS drug development.

Neural Mechanisms of Habit Reversal Therapy (HRT) and Relationships to Therapeutic Effects in TS

One approach to treating TS involves therapies, including HRT, that are designed to help patients systematically 'unlearn' tics, or to learn competing response to tics. The utility of these therapies in TS was suggested by the effectiveness of related therapies in the treatment of obsessive compulsive disorder (OCD), and the fact that symptom reduction in OCD after behavior therapy is accompanied by the normalization of metabolic patterns within corticostriato–pallidothalamic (CSPT) circuitry. Controlled studies have now demonstrated the efficacy of these treatments in TS. While it is not likely that animal models will be useful for predicting the effectiveness of HRT or other behavioral therapies for TS, animal models can be quite valuable for elucidating the neural basis of implicit learning within CSPT circuitry, and potentially predicting pharmacological strategies for

augmenting HRT-induced tic suppression; similar strategies are being used in attempts to produce the pharmacological augmentation of extinction in the treatment of phobias.

Studies combining behavioral and electrophysiological measures in rats have identified probabilistic response patterns within specific caudate cell types that may be a neural substrate of 'habit' formation, 'switching' in advance of the behavioral changes that follow shifting reinforcement contingencies. The caudate and prefrontal cortex appear to respond differently to these reinforcement shifts, and to contribute differently to the subsequent behavioral change. For example, one focus of animal models of operant behavior has been the neural adaptations responsible for the shift from response acquisition, in which behavior is controlled by an expectation of the future consequences of that behavior, to habit formation, when behavior is relatively insensitive to the reduction in reward. During acquisition, responses (and their underlying neural circuitries) are plastic and easily shaped by reward contingencies; with sustained practice, responses become controlled by more complex contingencies, and the underlying neural substrates appear to diversify among distributed corticostriatal circuits. Ultimately, these types of animal models may help us understand which circuits are most culpable in disorders where habits 'stick' and may help predict what neurochemical levers will be most effective at making this circuitry amenable to response 'unlearning.' Importantly, the neurobiology of habit formation will have relevance to disorders well beyond disorders of overt tics and compulsions, perhaps including substance dependence and eating disorders, among others.

Our group is exploring a different approach to develop an animal model to understand the neural basis for therapeutic responses to HRT. In TS patients, positive responses to HRT correlate significantly ($p < 0.02$–0.008) with both deficient inhibitory priming and excessive facilitatory priming in a visuospatial priming (VSP) paradigm. Conceivably, this linkage between VSP deficits and treatment response in TS may reflect a common underlying circuitry that would make this measure particularly sensitive to predicting therapeutic potential in novel compounds. We are currently developing a VSP task suitable for rats using a 5-hole operant chamber, with the goal of using this model for both to understand the neural basis for VSP abnormalities in TS, and to predict therapeutic efficacy of novel compounds.

Animal Models for Understanding the Neural Consequences and Therapeutic Mechanisms of DBS in TS

Electrical DBS is an effective therapy in relieving some symptoms of Parkinson's disease and dystonia, and its use in treating psychiatric disorders such as OCD is being investigated in large studies. A small number of limited case series have identified both therapeutic effects and morbidities associated with the use of DBS in TS patients. The optimal stimulation sites and parameters for therapeutic effects in TS are still unclear, as are the mechanisms of action. In these areas, animal models may help inform clinicians, who can then be left to grapple with the more difficult ethical issues associated with this potential therapeutic modality.

Animal models used to understand DBS range from in vitro studies of membrane responses to electrical stimulation, to studies of intact neural circuits in both infrahuman primates and rodents. Tremblay and colleagues have studied basal ganglia subterritories responsible for the genesis and suppression of abnormal movements in infrahuman primates. Stereotyped motor responses (e.g., licking) stimulated in monkeys after microinfusion of the GABA antagonist, bicuculline, into basal ganglia regions are evaluated after systematic variations of electrical stimulation within specific portions of basal ganglia output circuitry. These studies identify both sites where DBS leads to cessation of generated abnormal movements, and sites where stimulation triggers significant adverse effects. Electrophysiological studies of DBS in rodents have primarily targeted nuclei associated with therapeutic effects in Parkinson's disease, but more recently, Grace and colleagues have been studying the effects of NAC DBS on circuitry of more relevance to TS and OCD, including the orbitofrontal cortex and more 'limbic' thalamocortical connections.

Models Related to Pathophysiological and Etiological Insights

The predominant pathophysiological constructs implicated in the etiology of TS include some combination of genetics, neurodevelopment, and autoimmune-induced neuropathology. As it stands, there is little agreement on, or compelling empirical evidence for, specific mechanisms underlying any of these constructs. Nonetheless, animal models are being used to explicate features of general relevance to genetic, neurodevelopmental, or immunologic etiologies of TS.

Animal Models of TS Genetics

Genetic models have been used in several ways to understand TS. First, a number of candidate genes of TS have been identified in human studies, though replication of many findings remains elusive. In some cases, such as the dopamine transporter (DAT) genes, mutant mouse models exist and are being studied to understand the physiological, neurochemical, and behavioral impact of DAT perturbations. For example, DAT knockout mice exhibit hyperactivity and sensorimotor gating deficits and have been used to model pathology in numerous

disorders, including schizophrenia, bipolar disorder, attention deficit disorder, and TS. As a predictive model for TS therapeutics, this mouse clearly has failings: for example, clozapine normalizes gating in DAT knockout mice but is not an effective anti-tic medication, and neither is valproate, which can normalize hyperactivity in this mouse. On the other hand, studies of gating deficits in DAT knockout mice have shown that they can be opposed by drugs that target the norepinephrine transporter; this model has some appeal in TS, where – unlike many other disorders – symptoms of a proposed underlying hyperdopaminergic state can be controlled effectively in many patients by drugs (e.g., clonidine, guanfacine) that target noradrenergic transmission. Thus, studies of a model based on this TS candidate gene might help us to understand the basis for therapeutic medication effects in TS.

Another use of genetic models to understand TS has focused on the neural basis for heritable gating deficits, like those exhibited by TS patients. Here, the glaring omission in logic is that gating deficits in TS have not yet been demonstrated to be heritable. Nonetheless, as they clearly distinguish individuals with the TS diagnosis from those without the TS diagnosis, they at least appear to be associated with the larger heritable phenotype. Freudenberg, Schwabe, and colleagues have demonstrated that selective breeding for low levels of sensorimotor gating results in substrains that not only 'breed true' for reduced gating, but also exhibit perseverative cognitive and motor patterns. Understanding the neural basis of these heritable phenotypes will at least yield some testable hypotheses for the neural basis of gating deficits and cognitive or motor disturbances in TS. Along this line of inquiry, we have reported that heritable differences in the ability of DA agonists to disrupt sensorimotor gating in rats are associated with differences in key elements of DA-linked signal transduction pathways in the NAC, and with highly significant differences ($p < 10^{-7} - 10^{-18}$) in the expression of a number of DA-linked genes in this same region. By pursuing these models, we hope to identify targets within DA signaling pathways that might serve as novel therapeutic targets in TS.

Neurodevelopmental Abnormalities in Parvalbumin-Positive GABAergic Neurons

Evolving hypotheses in TS (as well as other disorders) suggest that either genetic events, or epigenetic events, or both lead to aberrant forebrain development by altering neuronal migratory patterns within specific cell populations, including the parvalbumin (PV)-positive GABAergic neurons. Abnormal distributions of PV+ cells in cortical and subcortical regions in schizophrenia and TS have been interpreted to suggest a developmental delay or arrest in the early rostral migration of these cells, and shifts in these distributions will certainly alter the dynamics of CSPT circuits. Some of these patterns of abnormally-distributed or regionally reduced cortical and striatal PV+ cells can be recreated in animal models ranging from isolation rearing to focal cortical ischemia, and models are being developed to understand the impact of such regional and distributed circuit changes on the expression of tics and other symptoms.

Models of Autoimmune Pathology in TS

A hypothesis that has created great interest, intense study, and some degree of controversy links TS and related conditions to autoimmune mechanisms triggered by group A beta-hemolytic streptococcus or other pathogens. 'Definitive' studies are regularly published that either support or fail to support this hypothesis. Undeterred by this disagreement, many groups are pursuing animal models of relevance to the 'immune hypothesis' of TS. Three groups have reported evidence that infusion of sera from TS patients into the striatum of rats triggered the expression of TS like behaviors, including repetitive stereotyped movements and vocalizations; in one report, some of these behaviors were elicited by intrastriatal infusion of immunoglobulins isolated from TS sera, and in another report, behaviors were opposed by intrastriatal implantation of rat neural stem cells. Others have failed to detect these behavioral effects after intrastriatal infusion of TS sera, prompting the difficult search for methodological differences that might account for these contradictory reports. Of course, others have also failed to detect differences in autoantibodies in sera from controls, TS subjects, and patients with pediatric autoimmune neuropsychiatric disorders associated with Streptococcus (PANDAS).

Future Directions

Animal models are being used to understand evolving therapeutic avenues in TS, including pharmacotherapy, HRT, and DBS, and to clarify biological principles associated with the primary etiological constructs of TS. The utility of animal models in TS has been limited by the dearth of definitive findings emerging from neuropathological, neuroimaging, and neuroimmune studies of TS patients. These problems are due in part to the clinical and diagnostic complexities of this disorder and to the concentrated effort placed on other scientific endeavors, including many studies designed to identify TS genes. In parallel to the development of clinical research, animal models for TS are highly informative on issues related to the structure and function of the brain. These studies provide insights into the biological factors that control behavior, and the regulation and dysregulation of this control by genes and the environment.

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See also: Deep Brain stimulation; Dopamine Receptors; Obsessive-Compulsive Disorder; PANDAS; Tics; Tics, Complex; Tics, Simple; Tourette Syndrome; Yale Global Tic Severity Scale (YGTSS).

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Relevant Websites

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www.tsa-usa.org – Tourette Syndrome Association.

Transplantation

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Glossary

Human embryonic stem cells – Primitive undifferentiated cells derived from the inner cell mass of the blastocyst of a preimplanted embryo that can divide for long periods without differentiating and can develop into cells or tissue from the three primary germ layers.

Pluripotent – The ability of cells to give rise to various cells or tissue types of the body, except embryonic tissue.

Stem cells – Unspecialized cells that are capable of self-renewal through cell division and have the potential to be induced (differentiate) into specific cells of an organ or tissue with a particular function.

Definition and History

In the context of Movement Disorders therapy, cell transplantation can be defined as a surgical procedure in which human cells or tissue are implanted into a specific site(s) in the brain to relieve the symptoms or stop the progression of the movement disorders in a patient by either

repairing, regenerating, or restoring function to the defective area(s). The first recorded neural tissue transplants dates back to the late 1800s, when W.G. Thompson transplanted frontal cortical tissue from felines into the brain of canines. Surprisingly, some animals and grafts, he believed, survived for seven weeks, which encouraged him and other investigators to move forward in this field of study.

Early on high quality investigations were also performed by Elizabeth Dunn (1917), Le Gros Clark (1940) and R.M. May (1955). However, not until after the early 1970's did this field begin to grow with euthanasia and with the support of the scientific and medical communities. This slow start may have been related to the work of the prominent histologist Santiago Ramón y Cajal (1852–1934), who was convinced by his own research that central nervous system tissues are 'fixed and immutable' and cannot regenerate. However, eventually this hypothesis came into question, as researchers demonstrated axonal sprouting in damaged brain areas and survival of transplanted neural tissue grafts in the 1970s, thus marking the era of a new research field that would develop expeditiously neural transplantation.

Rationale for Cell Transplantation in Movement Disorders

Unlike other neurosurgical interventions for movement disorders, in which there are accepted guidelines for patients undergoing such surgeries, cell transplantation guidelines have not been established, as this is developing therapy, and patients receiving cell transplants are considered on a case by case basis. In this discussion, Parkinson's Disease (PD) is used as the disease of reference, because most clinical trials for cell transplantation have been performed in PD patients and deep brain stimulation (DBS) is the treatment of choice when drug therapy fails in PD patients. While several factors have motivated the need for neurosurgical intervention, the strict criteria for these surgeries tend to exclude a large number of patients. Statistical reviews have approximated that only 2% of PD patients evaluated are considered suitable for DBS, of the subthalamic nucleus. Consequently, cell transplantation may be the suitable alternative for patients not meeting the standards for DBS surgery.

DBS therapy has two additional criteria, the disease should be present for at least five years and there should not be any significant cognitive impairment in patients with PD. This modality also results in excluding a large subset of patients. Although the 5 year set point is to ensure the diagnosis is correct and the restriction on cognitive impairment is to confirm compliance and tolerance with surgical or postoperative procedures, this may be to extensive of await for cell therapy and earlier intervention may prove to be more beneficial. The premise of cell therapy is to stop the progression of the disease and the patient should have less cognitive impairments in the earlier stages of the disease vs. later stages.

Another factor instrumental in the development of neurosurgical and cell transplantation therapies for movement disorders is the inadequacy of oral medication, such as low or variable efficacy, low tolerability, intolerable side effects, and nondisease specific drugs, like those for dystonia and essential tremors. Patients are considered for neurosurgery when oral medication fails to relieve symptoms or when the side effects are so insufferable that the medication cannot be tolerated. In general, cell transplantation would allow more patients with PD to be treated overall compared to the other treatment modalities. The combination of medication, DBS, and cell therapy is a possible alternative for movement disorders not responding to one specific treatment alone. Co-therapies may be useful with a multifaceted disorder, such as Huntington's disease (HD), which has a complex pathology with several cell types included in the disease process. Therefore, the first criterion for cell transplantation is a meticulous and comprehensive understanding of the disease's pathology, which includes affected areas, cell type(s) and pathway (**Figure 1**). While we have focused on PD, similar arguments can be made for other movement disorders. Thus, cell therapy will likely be applicable to more patients than any other neurosurgical treatment.

Cell Transplantation for Movement Disorders

No longer is cell transplantation considered science fiction for the treatment of CNS disorders. In fact, on January 23, 2009 Genron Corp. (Menlo Park, CA) received the first approval for the transplantation of human embryonic stem cells (hESCs) from the FDA. In their application Genron states they will direct the hESCs to spinal cord progenitor cells and transplant these cells into patients with a complete spinal cord injury. Since the first human fetal tissue transplants in PD patients and the isolation of hESCs, there has been tremendous controversy surrounding their use for research and clinically. Although the ban on the use of non-Federally approved hESCs in research supported by Federal monies (grants) was lifted in March 2009, the ethical controversy and the previous 7-year ban compelled scientists to acquire other sources of pluripotent stem cells. Stem cells have now been isolated and characterized from several human tissues/organs, including bone marrow, umbilical cord blood, peripheral blood, skin, adipose, most major organs, and tumors. However, these cells do vary in their ability to differentiate into a cell or multiple cell types, even when cultured with similar methods for induction.

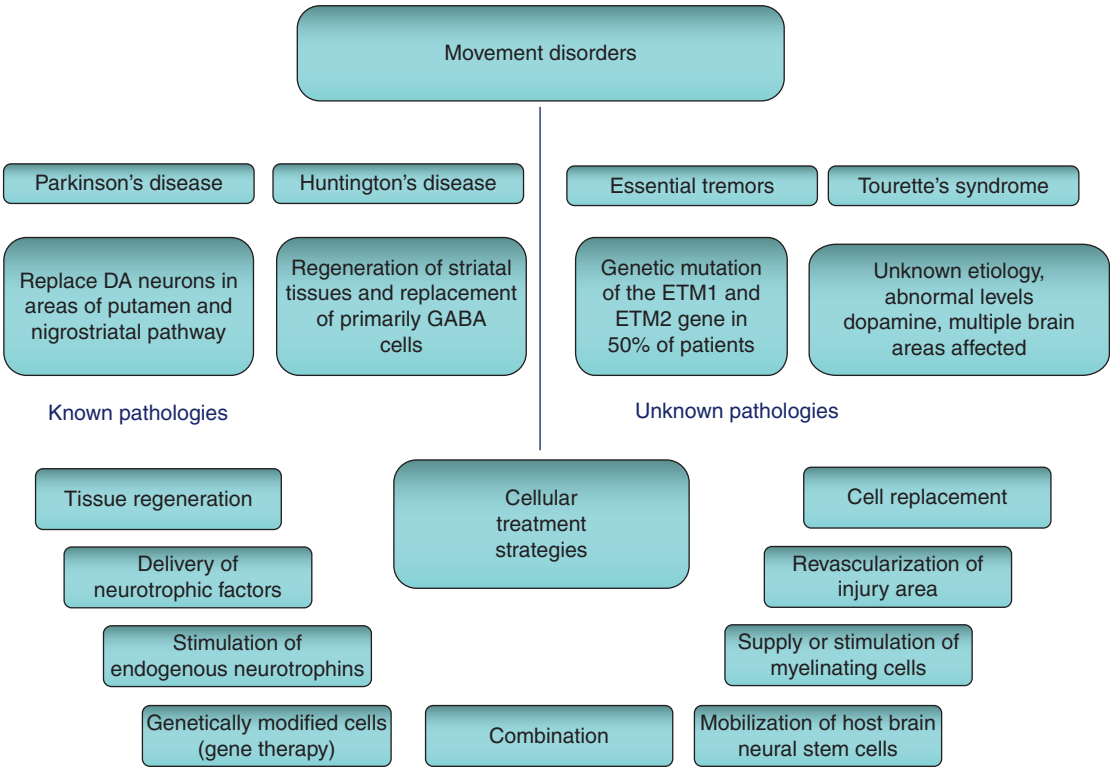

Figure 1 The schematic represents the multiple strategies of cell therapy that may be applicable to movement disorders, overall. However, the pathology of the disorder needs to be well understood before the cellular therapy is selected. Depending on the disease different strategies may be chosen, and a greater therapeutic benefit may realized by combining two or more treatment strategies, resulting in a synergistic effect. The combination of treatment strategies may be actually be necessary. For example there is a genetic mutation, damage to striatal tissue, and a loss of GABAminergic cells in HD in which a single cell type and a single strategy simply would not be enough to overcome this complex disorder. More than likely a HD patient would benefit from gene therapy, cell replacement, and neurotrophic factor support. GABA, gamma-aminobytyric acid; ETMI1 & 2, essential tremor.

Brief History of Cell Transplantation

The earliest report of fetal tissue for transplantation was in 1904, by Elizabeth Dunn from the University of Chicago who showed the survival of fetal grafts in adult animals. However, like other significant research contributions there was a long interval, approximately 85 years, before human fetal tissue was again used in transplantation of the CNS. In the 1980s, a brief flurry of enthusiasm occurred over adrenal medullary cell transplants to the caudate nucleus, but replicate studies of original observations were less impressive in light of serious operative–postoperative morbidity. Lindvall and colleagues (1989) were the first to report the successful transplantation of human fetal ventral mesencephalic tissue into the putamen of PD patients and to show graft survival with dopamine synthesis by positron emission tomography (PET). Clinical trials using improved protocols for achieving fetal dopaminergic neurons from mesencephalon tissue helped provide 'proof of principal' that cellular regeneration can be a viable treatment. Over 600 PD patients have now received human fetal ventral dopaminergic mesencephalic tissue transplants and the successes of these transplants are being evaluated clinically, through PET scans and at autopsy.

Pivotal Trials in Parkinson's Disease

Two central clinical trials for patients with PD occurred in the early 2000s. Freed and colleagues (2001) were the first to include a surgical control group in their clinical PD trial for cell transplantation. This was a double-blind, sham surgery-controlled study, with patients between the ages of 34 and 75 that were either transplanted with cultured mesencephalic tissue from four embryos or they received sham surgery (with a hole drilled in the skill, but the dura is not penetrated), and no immunosuppression treatment was administered. The results indicated the younger population had significant beneficial improvements as analyzed with scores from Unified Parkinson's Disease Rating Scale and the Schwab and England Scale. A new type of off-stage dyskinesias also recurred in 15% of the patients after the first year. A more recent analysis of this data set revealed that the early-stage-disease patients actually had improvements in motor function, and not necessarily the 'younger' patients.

The second PD clinical trial by Freeman and colleagues (2003) was a randomized placebo-controlled study, in which the transplanted recipients were randomized to receive either a 'low dose' (one donor per side) or 'high

dose' (four donors per side) of fetal dopaminergic tissue that were transplanted into the postcommissural putamen. Significant improvements in motor function were seen in the group that received four donors per side at 6 months after transplantation, but this benefit was short lived. However, the role in discontinuation of cyclosporine, an immunosuppressant, may have played in the loss of these improvements is unsettled. There have been no reported clinical studies that have tested the affects of withdraw or continuation of immunosuppression therapy for the long- or short-term outcome of movement function. However, post hoc stratification based on disease severity demonstrated a treatment effect with patients receiving four donors per side, which showed motor improvements at 2 years in milder (stage of disease) patients. More importantly, 56% of transplanted patients developed off-stage dyskinesias that persisted following withdrawal of dopaminergic medication. In addition, there was significant striatal fluoro-dopa uptake following the transplants and robust graft survival was observed postmortem in both studies.

Although both trials failed to achieve their primary outcome measure, the lessons from these two pivotal placebo-controlled trials should be applied to future trials, and other issues that were brought forth should be addressed before moving forward with additional larger trials. Most importantly, the studies demonstrated the necessity of utilizing sham surgery controls in testing all reconstructive therapies. Subsequently, the off-time dyskinesias generated by the grafts in both studies must be better understood before cell transplant trials go forward, especially because there does not appear to be a dose-related phenomena, as the dyskinesias occurred in patients that received both 'low' and 'high' doses of dopaminergic tissue. Furthermore, the withdrawal of the immunosuppressant was followed by a loss of benefits or a further loss in motor function, which generates the possibility that graft rejection may be a subclinical process. However, the patients in Freed's study were not administered an immunosuppressant and some patients showed improvements and the grafts were present at autopsy. The role of the immune system's interaction with the CNS in graft rejection or in cell transplantation, in general, is not well known. In addition, some donor solid tissue grafts (as opposed to suspension grafts/cells) may contain mesenchymal vasculature that may induce a stronger immunologic response from the graft's recipient, which can considerably influence the graft's survival, the interaction of the graft with the host tissue, and the overall host immune response. Recent autopsy studies of grafts over 10-year posttransplantation demonstrated classic lewy body degenerative changes in some of the transplanted cells suggesting possible transfer of the pathology to the graft cells.

Although there has been considerable controversy over the results from open clinical trials, with some studies reporting beneficial outcomes, others reporting innervation of graft and host tissue, while other studies showed limited behavioral recovery with untoward effects, and still others reported only effects in certain subpopulations of patients, the overall findings are still considered promising and research in this area is moving forward. Given the limited availability of fetal tissue and the ethical implications in using this tissue, other sources, particularly stem cells, are being investigated for the clinical use in cell transplantation for movement disorders.

Cell Transplantation Studies in Huntington's Disease

Several clinical trials using cell transplantation for the second major movement disorder, HD, have also been performed. Although these started much later than PD trials, the first HD clinical trial was reported in 1990 from Mexico, with others taking place even later in California, Cuba, the United Kingdom, and Czechoslovakia, in which fetal striatal tissue was transplanted into the striatum of patients without reports of any major complications. There were also reports of recipients with graft survival, as measured by MRI, within the striatum with no disruption of surrounding tissue and some cognitive improvements symptoms associated with HD were noted. However, there were no reports of cortical or subcortical improvements in these patients, which was likely due to the location of transplanted tissue and the lack of cell migration from the graft. Unlike in PD, tissue repair in other brain regions besides the striatum is imperative for the treatment of HD. The pathology of HD is widespread and characterized by affecting numerous areas within the brain, with initial atrophy of the caudate nucleus and putamen, where there is the loss of γ-aminobutyric acid (GABA)-mediated medium spiny neurons, and a secondary degeneration of globus pallidus, frontal cortex, thalamus, locus ceruleus, and subthalamic nucleus, which is due to the loss of pre- and postsynaptic neurons. Therefore, the transplantation of either fetal tissue or cells only to the striatal region may be insufficient to produce the needed improvements, given degeneration occurs in multiple brain areas, and cell transplants may need to correspond with these multiple sites. The clinical trials for HD have used the fetal tissue that came from elective abortions and spontaneously aborted fetuses, as in the PD studies. However, the tissue collected and transplanted typically is from the lateral ganglionic eminence, which is where most medium spiny neurons are derived. There were a few more clinical trials in the early 2000s, and results of some transplants have been reported postmortem. However, there has been no evidence of the fetal tissue grafts stopping or slowing down the progression of HD and a lack of graft integration with host parenchyma in patients has been reported by several scientist, which could be responsible for the in

consistant results thus far. In addition, the same ethical concerns and the lack of available fetal tissue for transplantation that plagues PD research, also affects HD research. This is true for all movement disorders that would benefit from fetal tissue or fetal cell suspension grafts, which further necessitates the need and search for alternative sources of pluripotent stem cells.

Together these findings suggest that a reliable and consistent source of human stem cells that are standardized along with improved methods of cell engraftment and graft survival are important factors in minimizing the variability of transplantation outcomes. In addition, a more thorough understanding of the immune system's capabilities and the interactions of graft and host tissues with immunosuppression is required to advance the future of cell therapies in movement disorders.

Beyond Cell Replacement Transplantation – To Repair, Regenerate, Restore, or Arrest Progression

Therapeutic effects and the survival of grafted cells are influenced by several factors; however, as discussed, there are no established criteria for cell-based therapies. **Table 1** provides a broad set of criteria we feel are important concerning cell therapies, and has been assembled from eminent reviews and prominent original scientific articles (see Further Reading). While the definition of cell therapy has changed considerably over the years, one thing that has not changed is the cell(s) utilized is highly dependent on the type of disease. Furthermore, what once was a rather simple definition of a 'stem cell' has become complex, as our characterization and study of these cells has grown. There is still unanimous agreement on the two main properties a cell must possess to be classified a 'stem cell.' First, a stem cell must be able to self-renew, that is during cell division they must produce at least one identical daughter cell. Second, at some point during one of their cell divisions one cell must further differentiate into one or more cell types, depending on their linage. In addition, a clear understanding of the terms embryonic stem cells (ESC), neural stem cells (NSCs), and neural progenitor cells (NPC) is required when discussing cell transplantation for movement disorders, because the majority of transplants discussed are concerned with the CNS and these cells have typically been used in the hope that they will integrate and communicate with the host tissue. Briefly and for the purpose of this article: (1) ESCs are from embryonic tissue and are pluripotent – meaning they will give rise to derivatives from each of the three primary germ layers, can establish a stem cell line without the use of immortalizing agents, can be propagated as a homogeneous culture, symmetrically amplified for an extended period while maintaining stability, and will develop normally when returned to a developing organism; (2) NSCs are multipotent stem cells, meaning they are more restricted in the types of cells they may give rise to, they can differentiate into one of the three neural cell types, can be expanded (self-renew) to produce clinically significant

Table 1 Criteria for cell transplantations in movement disorders

Identification of movement disorder
Complete pathology
- (a) Stage of disorder/disease of recipient
- (b) Affected areas in brain identified
- (c) Identification of pathway(s)
- (d) Degree of tissue damage

Selection of cell type(s) for transplantation
Source of cells
- (a) Source of cells known and accessible
- (b) Cells and source free of infections, diseases, and mutations
- (c) Purity of cells or purity of multiple cell types
- (d) Cells need to be consistent and renewable
- (e) Stage, maturity, and age of cells known or identified

Properties of cells once selected
- (a) Cells before grafting can be induced into required phenotype(s)
- (b) Cells differentiate to appropriate phenotype(s) upon grafting
- (c) Cells have the potential to differentiate according to host environment
- (d) Population of cells is sufficient
- (e) Cells can proliferate into needed quantities
- (f) Cells remain terminally differentiated – do not revert back to early cell stage
- (g) No potential for tumorigenicity of grafted cells

Selection of transplantation strategy
- (a) Replacement of single cell type in one or multiple brain areas
- (b) Replacement of multiple cell types in one or multiple brain areas
- (c) Transplantation of cells that produce neurotrophic or growth factor(s)
- (d) The delivery of cells to stimulate endogenous neurotrophic or growth factors, cytokines, proteins, etc.
- (e) The delivery of cells to stimulate endogenous neural stem cells
- (f) Delivery of genetically modified neural stem cells to the host that will replace damaged cells
- (g) Delivery of genetically modified cells that will produce neurotrophic or growth factors
- (h) A combination of strategies
- (i) Co-therapies – cell transplantation with therapeutic drugs, neurosurgical procedure, or gene therapy

Additional issues to consider
- (a) The selection and use of immunosuppressant drugs
- (b) Immune matching between host and donor – genotyping
- (c) Influence of culturing conditions before transplantation
- (d) Transplanted cells' ability to respond to endogenous signals
- (e) Transplanted cells' ability to integrate and form functional connection within host environment
- (f) Atypical circuit reconstruction
- (g) Standardization or reproducibility of transplants
- (h) Cost of cell transplantation procedure
- (i) Cost of clinical trials

Note: Depending on the particular disease or disorder more specific issues may arise. Individual recipient issues that may effect choice and utilization of cell-based therapy also need be recognized.

numbers of cells for transplantation, and they are cultivated from the brain at either the embryonic or the adult stage or these may be derived from ESCs; (3) NPCs have the same origin of NSCs and are typically derived from NSCs, but they have a more restricted repertoire.

There are several cell transplantation strategies that have been investigated in addition to the replacement of loss or dead cells; however, replacement of homogenous cells is still a viable approach for certain movement disorders. The current strategies are: (1) the replacement of specific cell types in a specific area or areas of the brain, such as dopaminergic neurons into the striatum for PD, (2) the replacement of multiple cell types and transplantation of cells into specific areas within the brain, as in HD, (3) the transplantation of cell that produce growth or neurotrophic factor(s) that are known to aid in repair or recovery of damaged tissue (instead of ones that produce and release neurotransmitters) and can be delivered to single or multiple areas of the brain, (4) the delivery of cells targeted to stimulate the endogenous neurotrophins and neurotrophic growth factors, proteins, or cytokines that aid in the repair of damaged tissue, (5) the delivery of cells targeted to stimulate the endogenous NSCs to proliferate and/or repair damage tissue, (6) the use of gene therapy by the delivery of genetically modified NSCs to the host that will replace damaged cells and/or delivery of genetically modified cells that will produce neurotrophic growth factors, (7) induced pluripotent stem (iPS) cells is a newer technology that uses cells extracted from adult tissue and induces them into embryonic-like stem cells; in this strategy a person's own cells may be used and made into iPS cells that could be directed to the cell type(s) needed and transplanted into target area(s) of the brain, and (8) a combination of strategies may be used, which may prove to be the most successful transplantation strategy. Most of these same strategies can apply to systems outside of the CNS. Cells that are transplanted in the brain are not isolated from affecting other systems that are not involved with the movement disorder. In fact, for most movement disorders, there is the potential for systems outside the CNS to aid in repairing the disorder. For example, the bone marrow continually releases stem cells into peripheral blood when needed. Cells transplanted into the brain could be programmed to home to the bone marrow to stimulate new stem cells that would migrate to the injured brain area to aid in the repair. Because these stem cells are from the host's bone marrow signaling and communication within the brain would be effortless and these cells would pass the body's immune defenses leaving only the transplanted cells for the host's immunological response as a concern. In addition, immune rejection would not be a concern when iPS cells, derived from the patient, are used for transplantation. Patient-specific stem cell therapies may be the direction for future cell transplantation in movement disorders. However, those movement disorders caused by a gene mutation would not be eligible for patient-specific stem cells transplants, because the mutation would still be present in the gene of the individual cells.

Single or multiple cell types transplantations?

Furthermore, single or two or more cell transplantation strategies may be necessary depending on the movement disorder identified. A single cell type might not be able to perform all the functions required of a particular disorder, and more than a single cell type would be necessary. More than likely greater therapeutic benefits would be realized from a transplantation strategy that provides a synergistic approach. For example, when cells are co-transplanted with other cell types or cells that produce growth factors there would be a combination of factors at work thus creating a synergistic effect. The transplanted cells may be releasing the needed neurotransmitter for movement, while the growth factors are aiding in repairing the damage tissue. This type of synergistic effect has been observed in clinical and preclinical studies. Meyer and colleagues (1995) co-transplanted fetal ventral mesencephalic dopaminergic neurons with embryonic striatal cells, in a PD trial, and observed that the co-grafted cells survived and integrated within the host tissue. In preclinical studies, the survival enhancement of grafted cells has been achieved when cells were co-treated with glial-derived neurotrophic factor (GDNF), and when the grafted dopamine neurons were co-transplanted with testis-derived sertoli cells. Thus, the utilization of more than one transplantation strategy may allow for a synergistic environment, which may prove to be more beneficial for movement disorder patients and their recovery.

The transplantation strategies outlined on the surface seem relatively uncomplicated, but when considering the best therapy for movement disorders that will not only treat the symptoms, but also repair the damage and stop the progression, there are multitudes of factors to consider. While the transplantation of a cell type(s) into the target site is straightforward, complications emerge when the target site(s) is not the site where most of the damaged tissue is located or where the cells are needed the most. As in the case of PD, the most damage occurs from the loss of dopaminergic neurons in the substantia nigra and these neurons' axons project to the striatum where dopamine is released and controls motor functions. The striatal tissue would be the more beneficial site to transplant dopamine replacement cells that will release the dopamine once transplanted. Here we know three factors of this disease: the pathology, the cell type to use, and the area in the brain in which to transplant. However, while this strategy has worked well in animal models and has shown potential in PD patients, progression of the disease is not stopped. We know from other animal models of disease that tissue regeneration does occur and this might be what is needed to stop the progression in PD; that is to regenerate the substantia nigra tissue and its pathway to the striatum. In animal

models of stroke, when neural-induced human SCs or ESCs are transplanted directly into the infarct area, regeneration of the damaged tissue and improvement in motor functions are seen. Published studies have suggested that the transplanted human NSCs may be assisting (stimulating) endogenous SCs, neurotrophic factors, cytokines, or other endogenous factors that are aiding in repairing the damaged tissue. Because of the inherent difficulty in measuring and verifying in vivo secondary actions, this supposition has not been fully proven, but is highly suggestive as a mechanism of action in producing regeneration of the damaged tissue. The enhancement of any biological function, by co-factors, that the transplanted cells stimulate or provide support for could be one of the first clinical treatments.

Engineered cells

Similar to the transplanted cells stimulating endogenous factors is the transplantation of engineered cells, which is a relatively new and exciting area of research especially for movement disorders. There have been a few clinical trials with neurotrophic factors, such as glial cell line-derived neurotrophic factor (GNDF) for PD, HD, and progressive supranuclear palsy, brain-derived neurotrophic factor (BDNF) for HD, and the cytokine granulocyte colony stimulating factor for Amyotrophic Lateral Sclerosis. However, most of these clinical studies had significant problems related to the delivery method employed, in which implantation of a catheter was used to target an area of brain and the infusion pump was placed under the skin. With gene therapy, the cells can be engineered to produce and release protein(s), neurotrophic or neurotrophin factor (s), or an essential amino acid that is lacking. There have been two clinical studies for Alzheimer's disease that use gene therapy to deliver human nerve growth factor to the basal forebrain. The first clinical trial for advanced PD, using the strategy of gene therapy, was the delivery of glutamate decarboxylase (GAD) by viral vector infusion to the subthalamic nucleus. Phase I study has been completed for safety and Phase II study has been started for safety and efficacy with reports thus far showing promise. Other Phase I trials have been or are being conducted for PD using adeno-associated virus as the vector and delivering either human aromatic L-amino acid decarboxylase or neurturin, which is structurally related to GDNF. There are numerous advantages to delivery of neurotrophic factors using this method of gene therapy. These include: no catheters to implant, no concerns for refilling infusion pumps, no threat of infections from external/internal catheter, long-term treatment cost should be less due fewer office visits, and the viral vectors can be implanted directly into deficient brain areas or different vectors can be implanted into appropriate areas within the brain.

There are unique concerns for any one of the strategies chosen, and there are general concerns that apply to the methods of cell transplantation. General concerns consist mostly of the concentration of cells, neurotrophic factors or other factors used, the assurance that the correct area(s) of the individual brain is reached, the acceptance of the grafts or vectors by the host system, the mechanism selected for the gene therapy or transduction method of the cells, what long-term effects this method may have on the host system, and whether cells or neurotrophic factors remain localized or become dispersed and the effects this may have on the host. Taken together with the issues that must be considered for surgery and for the patients' health, what seems to be a simple transplant is in fact very complex. The need for cell transplantation guidelines, criteria, protocols, and an open exchange of vital information between clinical trials and research is seriously needed.

New Directions

There is a genuine potential for cell therapy, in the near future, to treat or possibly cure age-related diseases and even the most debilitating movement disorders and neurodegenerative diseases. While the etiology of the disease or disorder may not be known, cell transplantation could be the provisional therapeutic strategy that improves the symptoms until the underlying cause of the disorder is found, progression is stopped and regeneration or replacement of the damaged tissue occurs. Successful cell and organ transplantations are increasing yearly, however, the number of patients needing or waiting for treatment is much greater than our current resources allow. Movement disorders is one of the major health problems and one that has led scientists and physicians to focus on new techniques, new cell sources, ways to create standardize protocols, and on means of bringing new treatments to the clinic quickly, safely, and efficiently. There are new technologies that could assist with ensuring the safety of cell transplantations such as epigenetic analysis, gene profiling, and proteomics. These technologies, as well as others, should be used whenever possible to assure safe procedures are used and to avoid clinical adversities.

See also: Deep Brain stimulation; Huntington's Disease; Parkinson's Disease: Definition, Diagnosis, and Management; Surgery for Movement Disorders, Overview, Including History.

Further Reading

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Relevant Websites

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Tremor

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Glossary

Action tremor – Tremor that occurs during any voluntary contraction of skeletal muscle.
Intention tremor – Crescendo tremor that occurs when a limb or other body part approaches a target.
Isometric tremor – Tremor that occurs during a muscle contraction against a rigid stationary object.
Kinetic tremor – Tremor that occurs during a voluntary movement.
Postural tremor – Tremor that occurs during an attempt to hold a body part motionless against the force of gravity.
Rest tremor – Tremor that occurs when skeletal muscle contraction is neither intended nor necessary.
Tremor – An involuntary oscillatory movement of a body part.

Definition and Classification of Tremor

Tremor is an involuntary oscillation of a body part. Tremor is categorized as rest, postural, kinetic, isometric, or action tremor according to whether the tremor occurs during voluntary muscle activation, steady posture, or movement (**Table 1**). The term static tremor (tremor at rest or in steady posture) is no longer used because of its ambiguous definition and usage.

The classification schema in **Table 1** is often expanded to include subtypes of tremor with unique characteristics. For example, pill-rolling rest tremor is a rest tremor in which the fingers and wrist move in a manner reminiscent of a rhythmic voluntary manipulation of small objects or pills in the hand, and is a hallmark of idiopathic Parkinson's disease. Some kinetic tremors are called task specific or focal, because they are solely limited to a specific task, movement, or body part. Postural tremors may be limited to or greatly exacerbated by specific postures, and these tremors are sometimes referred to as position-specific or position-sensitive postural tremors.

Several tools are available for the electrophysiologic quantification and characterization of tremor. Miniature accelerometers, gyroscopic angular velocity transducers, and video photogrammetry are useful in measuring the motion of a body part. Pen motion during writing and drawing can be quantified with commercially available digitizing tablets that are used in computer graphics.

Table 1 Classification of tremor

Type of tremor	*Definition*	*Example circumstances*
Rest tremor	Occurs when skeletal muscle contraction is neither intended nor necessary	The patient is recumbent on a bed or seated on a couch, with the body part supported. Tremor is often enhanced by the performance of cognitive tasks or motor tasks with other body parts, and it is often suppressed, at least temporarily, by voluntary muscle contraction
Postural tremor	Occurs in an attempt to hold a body part motionless against the force of gravity	Extending the upper limbs horizontally, pointing at objects, sitting erectly without support for the upper body, protruding the tongue
Kinetic tremor	Occurs during a voluntary movement	Finger–nose–finger testing, heel–knee–shin testing, reaching, writing, drawing, pouring water into a cup, drinking from a cup, eating with utensils, speaking
Intention tremor	Crescendo tremor that occurs when a limb or other body part approaches a target; generally greater when the movement to a target is visually guided	Finger–nose–finger testing, heel–knee–shin testing, reaching, writing, drawing, pouring water into a cup, drinking from a cup, eating with utensils
Isometric tremor	Occurs during a muscle contraction against a rigid stationary object	Pushing against a wall, flexing the wrist against a table, making a fist
Action tremor	Occurs during any voluntary contraction of skeletal muscle	Any combination of postural, kinetic, and isometric tremors

Muscle activity is measured electromyographically, using skin electrodes for gross motor activity and needle electrodes for single motor-unit activity. Motion transducer signals and electromyographic signals are recorded digitally with a computer and analyzed with spectral (Fourier) techniques. With these methods, tremor amplitude and frequency are easily quantified, and coherence (linear correlation squared) between any two digitized signals is also readily computed. These methods are also useful in quantifying the effect of mass (inertial) loading on tremor frequency (see Physiologic Tremor section) and the effect of distraction and voluntary rhythmic motor tasks on tremor amplitude and frequency (see Psychogenic Tremor section).

Physiologic Tremor

Physiologic tremor consists of two distinct oscillations: mechanical reflex and central neurogenic. All normal people exhibit the *mechanical-reflex component*, which is a passive mechanical oscillation that occurs in response to irregularities in subtetanic motor-unit firing and to the ejection of blood at cardiac systole. The cardioballistic forcing accounts for nearly all of physiologic tremor at rest. The frequency and amplitude of mechanical-reflex tremor are governed by the underdamped inertial, viscous, and elastic properties of the body. Consequently, normal elbow tremor has a frequency 3–5 Hz that is lower than the frequency (7–10 Hz) of wrist tremor, because the forearm has much greater inertia than the hand as a whole. Similarly, the fingers have even less inertia, and therefore, the frequency of metacarpophalangeal joint tremor is 17–30 Hz. Voluntary co-contraction of the muscles about a joint produces a slight increase in tremor frequency due to the increased joint stiffness. Conversely, a gradual relaxation of the joint causes the frequency of mechanical-reflex tremor to fall.

Under normal circumstances, the response of somatosensory receptors (e.g., muscle spindles) to the mechanical oscillations of physiologic tremor is too weak to entrain motoneurons at the frequency of tremor. Consequently, the electromyogram (EMG) exhibits a normal interference pattern, with no evidence of motor-unit entrainment at the tremor frequency. Additional limb inertia I decreases tremor frequency, and additional stiffness K increases frequency according to the equation $\omega = \sqrt{K/I}$. Limb ischemia sufficient to suppress the stretch reflex causes a slight reduction in normal mechanical-reflex tremor. Therefore, the stretch reflex appears to contribute little to the control of physiologic postural tremor. However, the reflex-induced modulation of EMG increases when perturbations to the limb increase the amplitude of mechanical oscillation or when stretch-reflex gain is enhanced by fatigue, anxiety, thyrotoxicosis, or β-adrenergic drugs. The increased participation of the stretch reflex is associated with increased tremor amplitude, and the resulting tremor is referred to as *enhanced physiologic tremor*. Enhanced physiologic tremor is primarily an enhanced mechanical-reflex oscillation, because the frequency of tremor is proportional to the square root of the stiffness and inversely proportional to the square root of the inertia ($\omega = \sqrt{K/I}$). However, greater central-neurogenic tremor may also occur, as in patients taking tricyclic antidepressants.

In contrast to normal mechanical-reflex tremor, the *central-neurogenic component* of physiologic tremor is always associated with a modulation of motor-unit activity at 8–12 Hz, even when this tremor is much smaller than

Table 2 Properties of tremor in healthy people

	Mechanical reflex	*Enhanced mechanical reflex*	*Central neurogenic*
Amplitude	Invisible or barely visible, not disabling	Less than 1 cm, may be disabling	Invisible or barely visible, not disabling
Frequency	A function of joint stiffness and inertia. Reduced by adding inertia to the limb	A function of joint stiffness and inertia. Reduced by adding inertia to the limb. Influenced by reflex arc length	8–12 Hz, does not vary with limb inertia or reflex arc length
Electromyogram	No motor-unit entrainment or synchronization	Motor-unit entrainment at the frequency of tremor	Motor-unit entrainment at 8–12 Hz
Treatment	Robotic aids	Robotic aids, β-adrenergic blockers	Robotic aids, β-adrenergic blockers

the mechanical-reflex oscillation. Participating motor units are entrained at 8–12 Hz, regardless of their mean firing frequency. Furthermore, the frequency of central-neurogenic tremor exhibits little or no change when inertial or elastic loads are attached to the limb, and the frequency of central-neurogenic tremor is independent of stretch-reflex loop time and muscle twitch properties. There is now fairly convincing evidence that the central-neurogenic tremor originates from an oscillation in the cerebello-thalamo-cortical loop.

Intention Tremor

Gordon Holmes noted that cerebellar 'tremor, which is sometimes apparent during the whole range of movement, is usually more prominent toward its end.' Holmes observed that 'the irregular oscillations in the intended direction result from failure of uniform deceleration, but this is complicated by secondary or correcting jerks when the object has not been accurately reached in the first attempt.' Consequently, distinguishing tremor from other features of ataxia (dysmetria, overshoot) is difficult and somewhat arbitrary in patients with cerebellar lesions.

The frequency of cerebellar tremor is commonly in the range of 3–5 Hz and is influenced by reflex arc length and by the inertia and stiffness of the body part. This influence of reflex dynamics and limb mechanics on tremor frequency is consistent with the notion that cerebellar tremor emerges from abnormal mechanical-reflex oscillation in somatosensory long-loop reflex pathways.

Intention tremor in the ipsilateral extremities occurs with lesions in the deep cerebellar nuclei or in their outflow tracts to the contralateral ventrolateral thalamus via the superior cerebellar peduncle. Thach and colleagues performed selective muscimol injections in the deep cerebellar nuclei of monkeys and found that inhibition of interpositus (globose emboliform in man) is the critical nuclear lesion in the production of tremor.

Normal limb movements toward a target are decelerated with a burst of antagonist muscle contraction so that the target is reached with little or no overshoot (dysmetria). This anticipatory deceleration is an example of feedforward motor control and is accomplished by cerebro-bulbo-cerebello-thalamo-cortical pathways. Loss of cerebellar feedforward control leads to delayed and inappropriately sized antagonist activity, resulting in target overshoot and limb oscillation. The cerebellum, based on prior experience (motor learning), is capable of predicting the amount and timing of deceleration (antagonist contraction) needed to land precisely on target. Cerebellar tremor appears to be due to an excessive reliance on feedback control, which results in abnormal mechanical-reflex oscillation in segmental and 'long-loop' transcortical and transcerebellar sensorimotor feedback pathways. The amplification of this oscillation by excitatory thalamocortical loops seems likely and would explain the dramatic reduction in cerebellar tremor that occurs with ventrolateral thalamotomy and deep brain stimulation (DBS).

Holmes Tremor (Rubral Tremor)

Holmes tremor is a striking combination of 2–5-Hz rest, postural, and intention tremor of an extremity. This unusual tremor is caused by lesions in the vicinity of the red nucleus: an observation that led to the name rubral tremor. However, isolated lesions in the red nucleus are not tremorogenic, and animal studies and clinicopathological studies in man have shown that combined damage to the neighboring cerebellothalamic and nigrostriatal fiber tracts is required. Consequently, Holmes tremor has become the preferred name for this tremor.

Holmes tremor usually begins weeks to months after brainstem trauma or stroke, and therefore, compensatory or secondary changes in nervous system function probably participate in tremorogenesis. Olivary hypertrophic degeneration is frequently present in patients with rubral tremor, due to the interruption of cerebello-olivary fibers. Thus, olivocerebellar oscillation may also play a role in tremorogenesis.

Reduced striatal ^{18}F-fluorodopa uptake is found in some patients with Holmes tremor. This finding explains why levodopa and dopaminergic agonists are occasionally beneficial. However, additional studies are needed to

determine if rubral tremor is merely a combination of parkinsonian rest and cerebellar intention tremors, or if rest tremor is produced by some other mechanism. Holmes tremor has been described in patients with cerebellar stroke and no apparent damage to the nigrostriatal pathway, and rest tremor and Holmes tremor have been reported in patients with thalamic strokes. Consequently, the rest tremor in some cases may be primarily due to compensatory changes in motor networks and is not the direct result of nigrostriatal deficiency. This notion is in keeping with the observation that other signs of parkinsonism are usually absent in patients with Holmes tremor.

Holmes tremor responds to stereotactic thalamotomy and DBS in ventralis intermedius (Vim), but its response to pharmacotherapy is usually nil. There have been no controlled trials, but there have been anecdotal reports of patients responding to dopaminergic drugs, clonazepam, propranolol, and levetiracetam.

Tremor Associated with Ventrolateral Thalamic Lesions

The development of tremor subsequent to a thalamic stroke has been known since the writings of Dejerine and Roussy in 1906, but the occurrence of tremor without other motor and sensory signs is rare. Lee and Marsden reviewed the published reports of 33 patients with movement disorders following isolated thalamic lesions. Only seven patients exhibited tremor in repose, posture, or movement, and all these patients had coexistent dystonia. However, there are case reports of rest tremor, intention tremor, and Holmes tremor following small ventrolateral strokes.

The development of tremor subsequent to a ventrolateral thalamic stroke seems paradoxical when one considers the efficacy of ventrolateral thalamotomy and DBS in the treatment of most forms of tremor. Of course, surgical thalamotomy and DBS are far more selective than thalamic infarction, and tremor following thalamic infarction is admittedly rare. In most instances, tremor developed weeks or months after thalamic infarction, and this delay suggests that neuroplasticity and network reorganization play an important role in tremorogenesis. The loss of cerebello-thalamo-cortical influence might lead to the excessive participation of cerebellobulbospinal loops, or surviving corticothalamic loops could become overactive, resulting in tremor. Furthermore, the extension of an infarct into the neighboring H fields of Forel could damage cerebellothalamic and nigrostriatal fibers, thus producing a variety of tremors.

Palatal Tremor (Palatal Myoclonus)

Palatal tremor was originally categorized as a form of myoclonus, but its rhythmicity clearly establishes that it is a form of tremor. In this condition, there is a repetitive elevation of the soft palate at 1–3 Hz. There are two forms of palatal tremor, symptomatic and essential, which differ clinically and pathophysiologically. *Essential palatal tremor* usually causes an annoying ear click but no other neurological signs or symptoms. The palatal movement and ear click are produced by a rhythmic contraction of the tensor veli palatini and are suppressed with botulinum toxin injection into the tensor veli palatini. Essential palatal myoclonus is not associated with the structural abnormalities of the brain. *Symptomatic palatal tremor* is produced primarily by a rhythmic contraction of the levator veli palatini and is frequently accompanied by synchronous movements of the eyes, face, pharynx, larynx, and diaphragm, and less commonly by movements of the extremities. It is usually associated with other signs of brainstem or cerebellar damage. It rarely causes ear clicks and is otherwise an asymptomatic sign of brainstem or cerebellar damage.

Symptomatic palatal tremor is produced by lesions, usually vascular, in the dentato-olivary pathway, which causes the secondary hypertrophic degeneration of the inferior olive. This olivary hypertrophy is visible with magnetic resonance imaging (MRI). The occurrence of olivary hypertrophy and palatal myoclonus usually follows a stroke by several weeks or more, although microscopic vacuolization of olivary neurons can be seen within 12–20 days.

The superior cerebellar peduncle contains dentate and globose-emboliform axons that project to the contralateral olive directly and indirectly, via several midbrain nuclei that include the parvocellular red nucleus. The nuclear axons in the indirect pathway are excitatory, while the axons in the direct pathway are inhibitory (GABAergic). These GABAergic neurons synapse near the electrotonic synapses between dendrites of olivary neurons, and the activation of GABAergic synapses probably decreases the coupling between olivary neurons. Since lesions in the superior cerebellar peduncle and dentate produce olivary hypertrophy, it seems likely that the loss of the direct pathway plays a major role in the pathophysiology of this condition. The loss of this pathway could produce increased neuronal coupling and could cause the olivary neurons to fire rhythmically at 1–3 Hz. However, this olivary hypothesis of palatal tremor is unproven and will probably remain so until a suitable animal model is developed and studied.

Essential Tremor and Familial Tremor

In classic essential tremor (ET), the upper limbs (>95% of patients), and less commonly, the head (at least 34%), face/jaw (~7%), voice (~12%), tongue (~30%), trunk (~5%), and lower limbs (~30%) exhibit a mixed postural and kinetic tremor without other neurologic abnormalities.

Patients with advanced ET exhibit intention tremor and impaired tandem walking. ET seems to be dominantly inherited in many large families, but there is increasing suspicion that polygenic inheritance (multiple genetic risk factors) may be more common than true autosomal dominant inheritance. A gene for ET has not been identified despite linkage studies of many large families with apparent autosomal dominant inheritance. In the cases of clear autosomal dominant inheritance, the term familial tremor is often used, but the characteristics of the tremor are the same as ET. Pharmacologic and electrophysiologic abnormalities are suggested by the variable response to ethanol, β-adrenergic blockers, primidone, and topiramate. The elucidation of these abnormalities, probably, will not occur until the underlying genetic defects or risk genes have been identified.

The fundamental electrophysiologic abnormality of ET is an abnormal entrainment of motor-unit firing at the frequency of tremor, which is typically 4–8 Hz. Many observations suggest that motor-unit entrainment emerges from oscillation in thalamocortical and olivocerebellar pathways. Lesions of the cerebellum, basis pontis, and thalamus have abolished or reduced ET. These observations are consistent with the notion that ET depends critically on the corticospinal tract and on cerebellar pathways projecting via the ventrolateral thalamus (Vim) to motor cortex. Louis and coworkers have found abnormally high numbers of axonal torpedoes in the deep cerebellar white matter and reduced numbers of Purkinje cells in the cerebellar cortex of patients with ET. PET studies of patients with ET revealed increased olivary glucose utilization and increased blood flow in the cerebellum, red nucleus, and thalamus. Finally, harmaline and related β-carboline alkaloids enhance the inhibition-rebound properties of olivary neurons and other neurons, causing increased rhythmicity and neuronal entrainment. The tremor produced by harmaline resembles ET.

Primidone, topiramate, and propranolol reduce tremor in many patients. Response to one does not predict response to the others, and their mechanisms of action in tremor reduction are unclear (see Beta Blockers, Essential Tremor).

Stereotactic thalamotomy and DBS in Vim are beneficial in the treatment of ET, but they are also beneficial in the treatment of Parkinson, cerebellar, rubral, and task-specific tremors. Vim receives inputs from the contralateral cerebellar nuclei and possibly from ascending somatosensory pathways, and it makes abundant reciprocal connections with motor cortex, from which tremor-correlated electroencephalogram (EEG) activity has been recorded. The Vim thalamocortical loop could amplify tremor of any origin.

Patients with ET and with ET combined with Parkinson's disease have responded to DBS in the subthalamus (STN). The critical target in this anatomically compact area is unclear, but is possibly the neighboring H field of Forel, which carries cerebellar and somatosensory afferents to the ventrolateral thalamus. Thalamic and subthalamic DBS probably suppress tremor by driving motor circuits at high frequencies to prevent pathologic low-frequency tremorogenic neuronal firing.

Parkinson Tremor

Rest tremor in the upper or lower extremities is the most specific feature of Parkinson's disease. Action tremor is common and is often an asymptomatic 8–12 Hz tremor, indistinguishable from an enhanced central-neurogenic component of physiologic tremor. Disabling action tremor is usually a re-emergent rest tremor or a coexistent ET. Recent magnetoencephalography (MEG) data by Timmermann and coworkers suggest that the 4–6 Hz oscillation of rest tremor is a subharmonic of the 8–12 Hz oscillation in sensorimotor cortex. Both forms of tremor have neurophysiological properties that are consistent with a central source of oscillation.

The principal site of tremorogenic oscillation is unknown. The cortical–basal ganglia–thalamocortical loop is prone to oscillation when dopaminergic nigrostriatal input is lost. Recent PET studies revealed an inverse correlation between presynaptic raphe 5-HT_{1A} binding and tremor severity, suggesting that the degeneration of the raphe nuclei may contribute to the expression of Parkinson rest tremor. Recordings during stereotactic surgery in Parkinson's disease reveal oscillatory neuronal firing in the ventrolateral thalamus, globus pallidus, and STN. Tremor-related oscillation in lateral premotor cortex, cingulate motor area, supplementary motor area, somatosensory cortex, and thalamus has been demonstrated with MEG.

The cerebellum is active in patients with Parkinson tremor, and MEG activity from the cerebellum is correlated with tremor in EMG and sensorimotor cortex. However, the cerebellum appears to be active in all forms of tremor, and the cerebellum is not necessary for the production of rest tremor.

Vim is the most effective stereotactic surgical site for treating Parkinson tremor, even though Vim receives inputs from cerebellum and ascending spinal sensory tracts and only a sparse input from the internal pallidum. The destruction of the posteroventrolateral internal pallidum or the STN is an effective treatment for tremor, but the thalamic receiving nucleus of the internal pallidum, ventralis oralis posterior (Vop), is not an effective target. These paradoxical surgical and anatomical data can be reconciled, to some extent, by noting that Vim and Vop are not completely segregated, and both nuclei project to and receive considerable input from supplementary and primary motor cortices. These over-lapping

corticothalamocortical projections could facilitate the entrainment of the pallidothalamic and cerebellothalamic pathways. Furthermore, spinothalamic inputs to VL overlap with the cerebellothalamic projections in Vim, and therefore, this thalamic nucleus could easily become entrained by any tremor, through sensory and cerebellar inputs. Finally, amplification within the thalamocortical loop in Parkinson's disease could contribute to the tremorogenic oscillation and entrainment of neurons throughout the cortical-basal ganglia-thalamocortical loop. Vim thalamotomy may simply preclude this amplification more effectively than Vop thalamotomy, because Vim projects more abundantly to motor cortex and receives somatosensory feedback from the periphery.

This discussion of Parkinson tremor illustrates the difficulty and perhaps futility in ascribing the origin of any tremor to a single nucleus of oscillating neurons. In Parkinson tremor, all parts of the cortical-basal ganglia-thalamocortical loop are involved, facilitated perhaps by their intrinsic oscillatory properties and interconnections. There is increasing evidence that Parkinson tremor emerges from the altered dynamics of this loop such that lesions in many locations are capable of suppressing tremor.

Neuropathic Tremor

Patients with acquired and hereditary peripheral neuropathies occasionally exhibit symptomatic 3–10Hz action tremors. Some patients with hereditary neuropathy have tremor that is indistinguishable from 6- to 8-Hz ET. Other patients exhibit an abnormal mechanical-reflex tremor that resembles enhanced physiologic tremor or cerebellar tremor. The frequency and amplitude of many neuropathic tremors bear little or no relationship to the degree of sensorimotor loss or the velocity of nerve conduction. Therefore, compensatory changes in the central nervous system, in response to distorted sensory input, are possibly tremorogenic. The cerebellum, in particular, has been implicated, but the details are far from clear. Central reorganization in response to altered peripheral sensorimotor function is hypothesized to cause the rare heterogeneous tremors that occur weeks to months after peripheral nerve trauma.

Focal, Dystonic, and Task-specific Tremors

Patients with *primary writing tremor* exhibit severe tremor during the act of writing, but there is no tremor during other activities. Isolated *tremors of the voice, chin, tongue, head, and smile* have also been described. These focal and task-specific tremors are analogous to focal and task-specific dystonias, and the prevailing opinion is that these focal and task-specific tremors are tremor-predominant dystonias with little or no dystonic posturing. Dystonic muscle contractions are commonly tremulous.

Orthostatic Tremor

Orthostatic tremor is an unusual postural tremor that develops in the lower extremities and torso within seconds of assuming erect stance, producing a sensation of unsteadiness. Electromyography of the lower extremities and torso reveals rhythmic bursts of motor-unit activity at 14–18 Hz, which is a uniquely high tremor frequency. This activity begins almost immediately upon standing and is usually symptomatic to the patient, but barely visible to the examiner. With continued standing, the frequency of body tremor may change into a 7–9 Hz subharmonic oscillation that is more symptomatic and visible. The same synchronous tremor occurs in the upper limbs if the upper limbs are used for support while standing (e.g., leaning on a table).

Patients may benefit from clonazepam, primidone, gabapentin, and possibly dopaminergic medications, but the response is often disappointing. The patient's complaints often exceed the visible signs of unsteadiness and tremor, and the disabling sensation of unsteadiness may be due to the tremulous disruption of somatosensory feedback.

A central source of oscillation is certain, given the high tremor frequency and synchrony of oscillation among the involved body parts. No other tremor exhibits bilateral synchrony in the upper and lower limbs.

The anatomy of this oscillator is unknown. Oscillation in the cranial musculature has been demonstrated, and therefore, a supraspinal source of oscillation is certain. Like many other tremors, orthostatic tremor is associated with increased cerebellar blood flow as measured with $H_2{}^{15}O$ PET, and the phase of orthostatic tremor is reset by transcranial electrical stimulation over the posterior fossa, but not by transcranial magnetic stimulation over the motor cortex. Thus, the cerebellum and bulbospinal pathways appear to play an important role in tremorogenesis.

Cortical Tremor (Rhythmic Cortical Myoclonus)

Cortical tremor is an irregular 7–14 Hz action tremor that resembles ET and occurs in patients with cortical myoclonus. Many patients also exhibit major motor seizures and myoclonus, and have a family history of these disorders with tremor. The tremor in asterixis is probably a form of cortical tremor, and therefore, cortical tremor is common in patients with metabolic encephalopathies. Enhanced C-reflexes and giant sensory evoked potentials

occur in many patients and are consistent with the presence of enhanced cortical excitability. An EEG transient preceding the EMG bursts of cortical tremor has been demonstrated with EEG back averaging. Therefore, cortical tremor is actually a rhythmic cortical myoclonus at 7–14 Hz. Clonazepam and other medications for cortical myoclonus are often beneficial (see Cortical Myoclonus).

Drug-induced Tremor

Many drugs produce parkinsonian rest tremor (neuroleptics, metoclopramide, dopamine-depleting drugs), action tremor (β-adrenergic agonists, valproic acid, lithium, thyroxin, tricyclic antidepressants, and methylxanthines), and combinations of rest, postural, and kinetic tremors (lithium, amiodarone, and valproate). Parkinsonian tremor is produced by dopaminergic blockade (neuroleptics, metoclopramide) or depletion (reserpine). Extrapyramidal toxicity underlies amiodarone-induced tremor, and enhanced mechanical-reflex oscillation occurs with β-adrenergic agonists, valproic acid, lithium, thyroxin, tricyclic antidepressants, and methylxanthines. Enhanced cortical irritability is considered the primary mechanism underlying lithium and valproate-induced tremors. Amiodarone- and lithium-induced tremors are particularly noteworthy, because they are occasionally irreversible. Persistent lithium-induced tremor and ataxia are caused by neuronal loss and gliosis of the cerebellar cortex and dentate nuclei.

Drug-induced tremor must be distinguished from an undiagnosed tremor disorder (e.g., ET, Parkinson's disease) that is exacerbated by a drug. A complete withdrawal of the drug and long-term follow-up are often needed to make this determination.

Psychogenic Tremor

There are two basic types of psychogenic tremor: co-contraction type and coherent type. These two forms of psychogenic tremor are equally common, and electrophysiology is useful in their diagnosis.

In the co-contraction type, patients consciously or subconsciously coactivate the muscles of the affected body part. In the hands, one typically sees a 7–10 Hz tremor that is independent (not synchronous) of tremor in the contralateral limb. This tremor is associated with an abnormally increased tone that is produced by the coactivation of the forearm muscles. A passive manipulation of the wrist reveals that the amplitude of tremor is proportional to the degree of coactivation ('coactivation sign'), and the tremor stops during interruptions in coactivation.

The coherent type is produced by a conscious or subconscious rhythmic movement of the affected joint. The tremor frequency is usually about 6 Hz or less, because voluntary rhythmic movement at higher frequencies is extremely difficult and exhausting. People with this form of psychogenic tremor cannot rhythmically move the same or contralateral extremity at a different frequency, except at subharmonics of the tremor frequency. Attempts to do so result in an abrupt change in the tremor frequency to the frequency of voluntary movement (entrainment), or the tremor abruptly stops during the voluntary movement. During entrainment, the tremor and voluntary movement become synchronous (coherent).

See also: Accelerometry; Postural Tremor; Primary Orthostatic Tremor; Rest Tremor; Tremor, Essential (Syndromes); Tremor, Holmes; Tremor: Drug-induced.

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Tremor, Essential (Syndromes)

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Glossary

Familial tremor – This term for inherited tremor is often used interchangeably with 'essential tremor (ET),' or combined as in 'familial ET'; however, ET cases with no clear tremor family history are well reported (generally 30% of study cohorts), and a positive family history is not required for ET diagnosis, so this frequently used term does not capture a current movement disorders entity.
Intention tremor – Intention tremor implies a distinct increase in tremor amplitude at the endpoints of targeted visually guided movements; this is a subtype of kinetic tremor by Movement Disorders Society consensus definitions.
Kinetic tremor – Tremor occurring with any type of voluntary movement including nontargeted, visually guided or nonvisually guided.
Physiological tremor – Tremor that occurs normally in any area/joint that can oscillate, and may enhance in many conditions (medications, pregnancy, metabolic disorders) or situations (anxiety, stress); the low amplitude high frequency (8–12 Hz) upper extremity form, especially enhanced physiological tremor, can be indistinguishable from mild ET.
Postural tremor – Tremor occurring with voluntarily held postures against gravity.

Definition and History

Tremor descriptions date back to Ecclesiastes XII:3, and ancient India and Egypt. Galen's writings specifically describe kinetic tremor. The term 'essential tremor' (ET) was developed in the 1800s to describe kinetic, usually familial tremor; the medical term 'essential' indicated unknown cause.

Tremor is an involuntary rhythmic oscillatory movement. ET is defined as persistent bilateral hand/arm tremor occurring with voluntary action or posture. The head/neck (most commonly), voice, legs, or other areas may also be affected. Head tremor without limb tremor is accepted as ET, although this definition remains uncertain as isolated head tremor is a manifestation of cervical dystonia among other disorders. Definite, probable, possible ET categories are used in research, not clinically. Duration over 3 years, positive family history, and positive alcohol response are considered supporting criteria.

This deceptively simple definition belies the diagnostic challenges. Mild or even severe ET is often incorrectly dismissed as normal aging. The old conception of tremor as a trait rather than a treatable pathologic state persists in ET families and the medical community. Tremor self-reporting and community diagnosis rates are notoriously low. These issues impact all ET aspects, from epidemiology to management.

Tremor Characteristics

Kinetic tremor is the most recognized ET form. Postural tremor may also define ET. Intention tremor implies an amplitude increase at targeted movement endpoints; this kinetic tremor subtype occurs in ET, but is not required for diagnosis. Tremor amplitude may vary with posture or movement trajectory. Frequency ranges from 4 to 12 Hz, typically 4–8 Hz, especially in older individuals and with tremor progression.

Rest tremor without Parkinson's disease (PD) occurs in ET, notably in long-standing severe ET: rest tremor is less severe than kinetic/postural.

ET is usually slowly progressive. Longstanding mild hand tremor may rapidly change into significant ET later in life. Tremor can progress in amplitude, plus spread to more areas. While current definitions stress bilateral tremor, severity may be asymmetric, and many ET descriptions note unilateral onset with subsequent spread to both upper extremities.

Severity and Disability

ET tremor severity may vary by day or hour, and can create significant disability. Kinetic limb tremor can compromise eating, drinking, and handwriting (**Figure 1**). Vocal tremor may limit communication or social activities. Even mild limb tremor affects work skills, causing job loss or preventing promotions. Functional impairments, from objective skill change to social embarrassment, are important factors in ET treatment decisions.

Age of Onset and Family History

ET manifests at any age, including childhood and (rarely) infancy. In population-based studies, onset peaks in later decades. Patients often reported the age tremor became

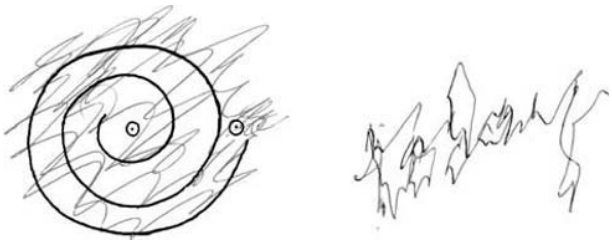

Figure 1 Writing sample from an ET research participant on maximum medical therapy for tremor. Attempt to draw within the lines of a spiral figure using right (dominant) hand, and write 'today.'

bothersome as age of onset, noting 'nervousness' or mild tremor from a younger age. Familial ET has generally earlier onset than sporadic, but onset varies widely within families. About 60% of ET subjects self-report positive tremor family history.

Exacerbating and Remitting Factors

Tremor increases with stress, fatigue, anxiety, and excitement. Caffeine may increase tremor, although a formal study of caffeine in ET showed no effect.

Ethanol ameliorates tremor in up to 75% of ET patients. Alcohol response is heterogeneous within families. Ethanol likely decreases tremor through a central mechanism. The effect, while more common than in other disorders, is not sensitive or specific enough for diagnosis.

Nontremor Features

ET is defined as a monosymptomatic tremor disorder. Still, some nontremor signs are long recognized. ET causes measurable, sometimes significant balance and gait impairments, independent of tremor site (head or not) and severity. Alcohol ingestion improves, not worsens, ET gait.

Minimal parkinsonian signs without PD are frequently reported – mild tone changes, cogwheel rigidity, and mild arm swing decrease. Severe kinetic tremor may break up fine motor tasks.

Controversial ET Subsets

Attempts to subclassify ET using tremor characteristics, treatment responses, and family history combinations have not yielded consistent categories, reinforcing the concept of ET as one clinical entity. However, dividing ET into classic and 'complicated,' usually ET/parkinsonism or ET/dystonia, dates back to at least the 1800s. Associations with dystonia and parkinsonism pervade ET genetics, pathophysiology, and diagnosis. Many argue for focusing on monosymptomatic classic ET to best move research forward. Alternatively, nontremor characteristics or ET subsets may indicate the range of underlying ET pathophysiology. Current evidence favors separating ET from dystonia and considering ET/parkinsonism within ET, but this is far from a consensus view. Sections below discuss classic ET, with relevant data on dystonia and parkinsonism.

The Evolving Range of ET

Cognition and mood

Cognitive symptoms in ET are increasingly recognized. Most reports focus on mild cognitive impairment, particularly in executive function and memory. Deficits closely overlap with observations in PD. One group reported increased dementia incidence and prevalence in ET, particularly tremor onset at the age of 65 and above. The extent and frequency of cognitive impairment in ET remain unclear.

Mood disorders may reflect primary ET neuropathology, secondary reaction to tremor, or shared predispositions for ET and other distinct disorders. Higher anxiety scores, harm avoidance, and social phobia rates are reported in ET versus controls. Strikingly, these findings are independent of tremor severity. Depression may be frequently comorbid in ET, as in PD.

Executive dysfunction, apathy, and depression, each predict poorer perceived health status in ET. Social phobia correlates with disability level. Thus, understanding cognitive and mood disorders in ET is crucial to improving treatment outcomes.

Special senses

ET subjects in one cohort had higher hearing disability than PD or controls. In another, hearing-impaired subjects were 30% more likely to have ET than controls. Families with coinherited sensorineural hearing loss and ET are reported.

Unlike in PD, olfaction is usually normal in ET. Olfaction testing scores in ET, even ET with rest tremor, are higher than in PD. However, one group observed mild olfactory deficits in ET versus controls, an intriguing, but disputed finding.

Potential comorbid conditions

Most proposed associations of ET with other common conditions have not held up. Currently, restless legs syndrome and migraine are each strongly associated with ET in isolated prospective studies. There are reports of clearly coinherited ET and migraine.

There are case series describing frequent ET within Klinefelter's syndrome. A recent controlled study observed a strong association between Klinefelter's syndrome and self-reported tremor. A high rate of intention tremor is also reported in XYY males.

Epidemiology

Prevalence, Incidence, and Mortality

The reported ET prevalence range is huge, narrowing to 0.4–4% when confined to community-based studies that specify ET definition. The highest estimates occur when neurologists directly examine all subjects – 4% at the age of 40 and above and up to 22% at the age of 95 and above.

Incidence and mortality data are scarce. One retrospective study (US) reported 23.7 cases per 100 000. The only prospective study (Spain) observed 616 cases per 100 000 person-years; the higher number is likely due to undiagnosed cases missed retrospectively. ET is assumed to have no impact on lifespan; however, limited prospective data suggest a mildly elevated mortality risk in ET.

Age and Gender

Age is an ET risk factor; prevalence increases with increased age.

ET prevalence and incidence are roughly equal in men and women, although some studies observe a higher prevalence in men. Voice and head tremor occur more often in women. Some studies report an association between childhood onset and male gender.

Ethnicity

ET is reported in many ethnic groups worldwide. Widely variable methodologies hinder comparisons across studies. Very few studies report on different ethnicities within a geographic population. A large Singaporean study observed higher ET prevalence in ethnic Indians than Chinese, and no Malay ET cases. A US survey (23 842 persons, 49% black, 50% white) found a slightly higher age-adjusted prevalence ratio for ET in whites versus blacks. One other US study observed some tremor characteristic differences between small groups of white, African–American and Hispanic ET subjects, and higher odds of ET in Hispanics.

Environmental Risks

Data on ET environmental risks are limited. One case-control study observed an association between ET and agricultural work; however, unlike in PD, a correlation between pesticides and ET is not observed. Blood lead concentrations were higher on average in ET versus controls in two small studies.

Mean log blood concentrations of the β-carboline alkaloid harmane were higher in ET than controls in one cohort. β-Carbolines are endogenous in brain; exogenous sources include dietary meats. Elevated plasma harmane levels are also reported in PD and alcoholism. Tobacco smoke is a β-carboline source, and plasma norharman is elevated in smokers. However, one group reported lower ET incident risk among heavy smokers and an inverse association between ET and smoking level. Harmaline toxin model use (below) lends importance to clarifying β-carbolines' roles, if any, in ET.

Genetics

There is varied and convincing evidence that much of ET is inherited in an autosomal dominant fashion. Twin studies support a large role of genes over environment in ET. In one study, pairwise concordance in monozygotic twins (0.60) was about double than that in dizygotic twins (0.27). In another, including only probable and definite ET cases, concordance rates were 0.93 monozygotic and 0.29 dizygotic, putting the heritability for potential ET development at up to 99%.

There are three distinct reported susceptibility loci linked to autosomal dominant ET: ETM1, chromosome 3q13, identified in Icelandic families with definite classic ET; ETM2, 2p24, first linked in a US family; and a 6p23 region linked in North American families with ET and dystonia, but not families with classic ET alone. More loci await identification: ETM1 and ETM2 have been excluded in other genetically informative families.

The first reported ET-associated genetic variation, 828C→G in the HS1 binding protein 3 gene (*HS1-BP3*), is within ETM2. Subsequent negative data argue for a restricted role (close linkage disequilibrium with a causative mutation) or no association.

Within ETM1, the dopamine D3 receptor gene (*DRD3*) 312A→G variant was associated with the age of onset and disease severity in French and US samples. Several replication studies did not observe an association between *DRD3* variants and ET risk or onset age, or linkage with *DRD3* in ET families. *DRD3* is probably not involved in ET genetic pathophysiology.

A recent genome-wide analysis observed association with markers in the leucine-rich repeat neuronal 6A gene (*LINGO1*) using an Icelandic plus multiple confirmatory ET cohorts. LINGO1 has possible links to ET cerebellar pathology (see text below).

Several candidate mutations were considered based on ET phenotypic overlaps. Fragile X associated tremor ataxia syndrome causes intention tremor, gait ataxia, and parkinsonism. However, studies show no role for the *FMR1* premutation in ET. Spinocerebellar ataxia type 12 (SCA-12) presents with kinetic tremor; indeed, affected SCA-12 family members are often initially misdiagnosed as ET. Kinetic tremor occurs less frequently in other SCAs. ET cohort screens have not yielded unexpected SCA mutation rates. Linkage to DYT1 (autosomal dominant dystonia) was negative in two independent studies, and the dystonia-causative 946–948delGAG deletion was absent in other ET families.

There are reports of ET (not PD) phenotypes observed with PD-causative *LRRK2* (encoding leucine-rich repeat kinase 2/dardarin), *SNCA*, and *parkin* mutations; however, these observations do not occur in larger ET surveys. ET/parkinsonism is reported in some kindreds, while PD and ET are linked to separate loci in others. One study observed an association between the length of a mixed dinucleotide repeat sequence (REP1) in *SNCA* (α-synuclein gene) and both ET and PD. However, we detected only a mild association for REP1 allele lengths with ET in our US cohort. The only other reported ET *SNCA* study did not observe an association between ET risk and *SNCA* haplotypes.

Inherent ET features complicate genetic studies. High age-related prevalence and multiple susceptibility loci both increase possible phenocopies. Inaccurate tremor and family history self-reporting impact phenotype assignments. Current data still indicate that clinically defined ET is a genetically heterogeneous disorder: multiple genetic loci contribute to similar phenotypes.

Pathophysiology

Electrophysiological data support a central tremor generator in ET. Early speculation on ET neuropathology suggested cerebellum and basal ganglia. The current consensus strongly favors cerebellar pathway dysfunction, but evidence continues to implicate both. Until recently, neuropathology data were surprisingly scarce.

Intention tremor, while not always present, is a classic cerebellar finding. ET gait abnormality is similar to cerebellar-based ataxia. Some authors see the pattern of cognitive findings in ET as evidence for cerebello-thalamo-cerebral dysfunction. Functional imaging ET studies show increased activation of and metabolism in cerebellar pathways, most consistently cerebellar cortex and red nucleus. An olivocerebellar tremor generator remains the popular hypothesis based on the preponderance of data.

Anatomical imaging techniques argue against gross cerebellar degeneration, but suggest cerebellar damage. Gross brain pathology is generally normal; however, most ET cases have cerebellar neuropathology including Purkinje cell loss and torpedos.

Other data suggest ties to basal ganglia disorders. Although dystonia is a classic ET exclusion criterion, the 6p23-linked families have affected members with tremor and dystonia or ET without dystonia. Rest tremor and mild parkinsonian signs are accepted in ET. Overlaps between ET and PD cognitive deficit patterns argue for similar underlying neuroanatomy.

A significant minority of ET cases is reported with Lewy bodies (non-PD distribution, locus ceruleus). α-Synuclein is the major component of Lewy neurites and bodies, the PD pathological hallmarks. *SNCA* variants represent a biologically plausible way to confer altered α-synuclein disease susceptibility; however, ET genetic studies yield mixed results (see earlier text). One pathological series reported locus ceruleus degeneration in noncerebellar ET but no significant difference in Lewy body pathology between ET and controls.

A phenotypic continuum of dystonia, ET, and parkinsonism may reflect the relative degree and type of underlying cerebellar versus brainstem/basal ganglia pathology, in completely distinct or mechanistically related disorders. The strongest ET data implicate cerebellar dysfunction but, taken together, recent findings demonstrate that ET may be pathologically as well as genetically heterogeneous.

Model Systems

There is no clear ET animal model. γ-Aminobutyric acid A receptor α1 knockout mice have alcohol-responsive tremor and cerebellar dysfunction; however, there are no corresponding genetic mutations in human ET.

Harmaline toxicity in mammals is a cerebellar tremor model; however, studies indicate direct effects on basal ganglia as well. Harmaline acts on many different neurotransmitter and ion channel systems, with unknown primary tremorogenic mechanism. Screening ET therapeutics against harmaline rodent models yields mixed results. Propranolol, ethanol, and 1-octanol improve harmaline tremor, but primidone does not. Mefloquine suppresses harmaline tremor in mice, but not humans. Harmaline model data should be interpreted cautiously.

Differential Diagnosis

Other Causes of Similar Tremor

Some level of involuntary oscillation, physiological tremor, is normal. It may be impossible to distinguish mild ET from enhanced physiological tremor. This is of limited clinical concern, but crucial for research. Electrophysiological data from young individuals at risk for ET support the concept that mild ET and physiological tremor are distinct entities; physiological tremor is not a precursor of ET.

Many drugs can cause or exacerbate ET-like tremor, including antidepressants, antiepileptics, antiarrhythmics, immunosuppressants, chemotherapeutics, hormones, antiasthma agents, and stimulants. Common causes (high percentage of tremor in users) include lithium, valproic acid, amiodarone, tacrolimus, and β-adrenoceptor agonists. Withdrawal of drug may be necessary to distinguish between medication-induced tremor and exacerbated ET. If this is not practical, the time line for tremor versus

medication is crucial, and supporting ET criteria (e.g., family history) may be useful.

Multiple systemic metabolic disorders cause tremor. Hyperthyroidism is particularly common, especially in older populations. Thyrotoxicosis often causes tremor indistinguishable from enhanced physiological tremor, and thus, mild ET.

Isolated action-specific tremors such as primary writing tremor and orthostatic tremor are considered separate from ET.

Misdiagnoses Versus Clinical Overlaps

Psychogenic disorders and ET

Tremor is a common purely psychogenic entity. Sudden onset, disappearance with distraction, and spontaneous remissions favor a psychogenic tremor diagnosis. However, ET patients may present with ET symptoms plus psychosomatic overlay. Clearly defining which symptoms represent ET versus psychogenic is critical to successful treatment. Our center has successfully treated ET with medications or even surgery while addressing psychosomatiform symptoms with psychology (panic-like tremor attacks), physical therapy (knee-buckling, cautious gait), and speech therapy (nonphysiological voice changes).

Diagnostic controversies: Dystonia and PD

ET is a misdiagnosis in up to 30–50% of cases (depending on ET definition). The most common alternative diagnoses are PD and dystonia. Conversely, ET is frequently misdiagnosed as PD.

Nonclassic ET with dystonia is currently thought to represent dystonia (although see Genetics and Pathophysiology above). In contrast, ET plus PD, PD/ET misdiagnoses, and disputed ET/parkinsonism subsets are all possibilities. Views on dystonia, parkinsonism, and ET will likely shift with future data.

There are numerous reports of ET preceding PD onset, and higher than expected frequencies of ET in PD patients' relatives and PD patients themselves, but the data are inconclusive. Whether ET/parkinsonism subsets exist will be debated until defining biomarkers are available. Current practice accepts ET with mild parkinsonism as ET, but recognizes patients can have both ET and PD. Diagnoses of ET, parkinsonism, and PD will necessarily overlap and should be skeptically, frequently reassessed.

Diagnostic Work up

The interview includes tremor characteristics, tremorogenic medication exposures, treatment responses, and functional impact. Probing for full duration may reveal longstanding 'nervousness.' Nonresponse to dopaminergic agents helps uncover PD misdiagnosis. Family history includes specific questions for ET, tremor, PD, and dystonia. Clinical and family history for alcoholism are prudent to distinguish mild self-medication with alcohol from abuse.

Tremor examination includes rest, postures (arms outstretched and wing-beating, knee extended/ankle dorsiflexed), and action (finger-to-nose, foot floor-to-hand, jaw clench, head turn). Writing and drawing are key exam components. ET spirals and writing demonstrate tremor but not micrographia. Bias of kinetic/postural tremor over milder rest tremor also distinguishes ET from PD. Voice is assessed with speaking and sustained vowel sounds.

Tremor rating scales provide reproducible exam structures, albeit subjective and nonlinear ones. Interrater reliability is good for upper extremity tremor but poor for writing/drawing. An objective tremor measurement like digitized spiral analysis may, therefore, be of particular value. Detailed electrophysiological tremor characterization may best classify ET versus others, but is impractical in most settings.

Attention to nontremor features is important. Tandem gait testing best reveals ET-related imbalance. A check for unrelated conditions (e.g., peripheral neuropathy) that further impair balance helps assess functional severity of gait impairment. Questioning for neuropsychiatric and cognitive symptoms, and consideration of formal neuropsychologic testing, are recommended.

Abnormal posturing of the head/neck, scalloping hands, or any other dystonia signs is exclusionary for ET. Use of a geste antagonistique (sensory trick) argues for dystonic head tremor, not ET.

A possible ET diagnosis generally assumes toxic/metabolic conditions are eliminated. Laboratory and other tests may eliminate alternative causes of nonclassic presentations, such as sensory ataxia, Wilson's disease, and stroke-induced tremor. There are no tests for ET, a clinical diagnosis. There are no ET genetic tests, and features vary widely within families; there are no prognostic algorithms for at risk subjects.

Management

There are no ET disease-modifying agents. Treatment plans center on weighing ET functional impact against tremor suppression treatment downsides. Management, therefore, requires attention to patient and family education. Education about clinical diagnoses is also crucial; many patients carry a misdiagnosis for years.

Tremor Suppression

Medications

Primidone and propranolol

Propranolol and primidone are the most widely used tremor suppressants, and the only level A evidence agents for ET. Both can reduce limb tremor by 60% or more, but

each is effective in ~50% of cases. Response of vocal tremor to either agent is mixed at best.

Primidone is well tolerated chronically, but can produce acute severe vertigo, nausea, ataxia, and confusion at initial doses of 50 mg or more. To avoid: start primidone at an extremely low dose, 12.5 or 25 mg, at bedtime for a week, and increase slowly to effect, intolerance, or a low initial 150 mg dose. Further increases can split doses two or three times a day, biasing larger doses to evening to avoid sedation. Maximum dose is 250 mg three times a day, with little symptomatic gain over 250 mg twice a day.

Long acting (LA) propranolol may be more effective than short acting. Start at 80 mg LA once a day or 10 mg a day for short acting, then slowly increase as needed and tolerated. Most patients benefit at 120 mg a day or lower. Side effects often relate to lowered pulse rate and blood pressure: fatigue, orthostatic hypotension. Patients should be altered to infrequent, but possible side effects of depression and impotency. Relative contraindications include heart block, heart failure, asthma, and diabetes mellitus.

Primidone and propranolol appear equally effective compared to placebo. They are frequently combined to increase tremor suppression, although combination efficacy is untested. There is no evidence for choosing one over the other to start. Given the range of propranolol contraindications, primidone may be easier initially (with care to avoid acute side effects). Propranolol's anxiolytic or antihypertensive effects may add benefit. Because ET treatments are not disease modifying, intermittent medication use to suppress tremor only when needed is an option. Short acting propranolol may be particularly effective in this setting.

Other Available Agents

Interestingly, no other β-blocker has Level A evidence for tremor suppression, despite numerous studies. β-Blockers at Level B or C include atenolol, sotalol, and nadolol. Metoprolol was a preferred alternative to propranolol, but class I data on its effectiveness are conflicting. Pindolol may actually cause tremor.

Topiramate may be effective. Adverse effects of topiramate include altered cognition. Study doses were ~300 mg total a day; many patients respond at much lower doses. Gabapentin also has Level B evidence, although with some contradictory results. There is a recent small positive report on pregabulin, now in active clinical trials.

Alprazolam is a Level B agent. Benzodiazepines may be most helpful in ET with anxiety; however, benzodiazepines worsen imbalance. Clonazepam has Level C evidence, but its long half-life is sometimes preferred.

There are numerous reports of medications improving ET tremor, with no or contradictory expanded data. For example, carbonic anhydrase inhibitors are no longer recommended in ET.

Experimental Therapeutics

The alcohol 1-octanol and dimethoxymethyl-diphenyl-barbituric acid (T2000) each improved tremor in small double-blind placebo-controlled trials. The antiepileptic carisbamate is also being tested in ET.

Ethanol

Ethanol often dampens tremor, as many patients discover; given dependency issues and other side effects, this is not a viable treatment recommendation. Most of the limited direct evidence shows no increased alcohol abuse in ET compared to the general population, although this is a recurring concern. Thus, while ethanol is not recommended as a treatment, there is no compelling reason to discourage its moderate use.

Botulinum Toxin

ET vocal tremor can be treated with botulinum toxin chemodenervation. Vocal tremor may involve a wide range of muscles; thus, flexible fiberoptic laryngoscopic exam is recommended. Efficacy varies; 40–65% show objective improvement, but up to 80% experience subjective improvement. Head tremor may also respond well to botulinum toxin. Potential side effects include dysphagia and neck weakness. Note while botulinum toxin is often used and may have a marked impact, it is a Level C agent based on aggregate data.

Botulinum toxin for upper extremity tremor yields mixed results, limited by hand and arm weakness.

Deep Brain Stimulation and Stereotactic Lesion Surgery

Thalamic deep brain stimulation (DBS) and stereotactic lesion surgeries effectively reduce limb tremor. Surgery is generally reserved for refractory tremor, when treatment benefit outweighs surgical risks. Both procedures yield immediate and sustained benefits. The established target is the thalamic ventral intermediate nucleus; new data suggest zona incerta DBS is as or more effective. DBS is now preferred over thalamotomy due to somewhat fewer side effects and stimulator adjustability, but there is little compelling evidence for one procedure over the other. Bilateral procedures control tremor in both upper extremities; there is no clear evidence for synergistic effects after bilateral procedures. There are case reports of bilateral thalamic DBS providing excellent benefit for ET vocal and head tremor, but results are mixed.

Surgical procedures carry a low risk of severe adverse events like stroke and hemorrhage. Long-term safety is generally good. Long-term side effects including dysphagia and imbalance are particular issues in bilateral procedures. These may be ameliorated in DBS with stimulator adjustment. There are few data on possible long-term nonmotor benefits or side effects.

Other Modalities

Occupational therapy, including weighted utensils and computer mouse tremor-suppression devices, is of anecdotal benefit. Physical therapy can address functional mobility and balance deficits. Walking is strongly recommended for maintaining balance. Both medication and nonmedication modalities can be effective for mood disturbances.

See also: Benzodiazepines and Movement Disorders; Beta-blockers and Movement Disorders; Botulinum Toxin; Cervical Dystonia; Cognitive Assessments and Parkinson's Disease; Dementia, Movement Disorders; Dystonia, Task-specific; Essential Tremor: Animal Models; Executive Dysfunction; Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS); Harmaline Tremor Model; Hoehn and Yahr Staging Scale; PARK1, Alpha Synuclein; Parkinson's Disease: Genetics; Postural Tremor; Primidone and Movement Disorders; Psychogenic Movement Disorders; Rating Scales in Movement Disorders; Rest Tremor; SCA12; Surgery for Movement Disorders, Overview, Including History; Thalamotomy; Tremor; Tremor, Essential: Genetics; Tremor, Holmes; Tremor: Drug-induced; Unified Parkinson's Disease Rating Scale (UPDRS) and The Movement-Disorder Society Sponsored-unified Parkinson's Disease Rating Scale (MDS-UPDRS).

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Tremor, Essential: Genetics

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Definition and History

Tremor is defined as a rhythmic oscillation of the upper extremities, or other body part, that is present at rest, the performance of an action, or during the maintenance of a posture. In addition, modern clinicians describe tremors by their oscillation frequency, aggravating factors, associated medical conditions, family history, and clinical findings on a neurological examination. These features are used to classify different types of tremor as physiological, essential, dystonic, parkinsonian, cerebellar, basal ganglia, palatal, neuropathic, toxic, or psychogenic tremor.

Tremor was recognized as a malady by the ancient Indians, Egyptians, Hebrews, Greeks, and Romans.

The distinction between a resting and action tremor is credited to the Greek physician, Galen of Pergamon, who lived between 130 and 200 AD. It was not until 1836 that C. F. Most recognized that tremor could be inherited. Half a century later, Charles L. Dana, an American physician, described the clinical characteristics and the inheritance pattern of the common type of tremor that we presently know today as hereditary or familial tremor. Two Italian medical professors, Pietro Burresi and Edoardo Maragliono, introduced the adjective 'essential' to the medical literature in 1874 and 1879, respectively. The term gained popularity at the turn of the twentieth century to delineate essential tremor (ET) from other types of tremors by its inherited, constitutional, and monosymptomatic nature.

Epidemiology

ET is a common movement disorder with prevalence rates ranging from 3.1% to 4.8% in epidemiological studies conducted between 2003 and 2005. The estimated incidence of ET is 17.5 cases per 100 000 persons annually with a higher adjusted rate of 616 cases per 100 000 persons annually in populations over the age 65. Frequency estimates of the familial aggregation of ET vary between 17% and 100%. First-degree relatives of individuals with ET have a higher risk of developing the disorder at an early age. Epidemiological studies show an association between ET and exposure to certain environmental factors such as the β-carboline alkaloids.

Clinical Features and Diagnostic Criteria

The cardinal clinical feature of ET is the presence of a postural tremor in the upper extremities with an oscillation frequency of 6–12 Hz. Other neurological abnormalities are absent in ET. A tremor is present in both upper limbs in ~95% of patients. The head (34%), tongue (30%), lower limbs (30%), voice (12%), face (5%), and trunk (5%), are involved less commonly. ET is a progressive disorder that often interferes with the quality of life by causing a functional impairment in daily living activities, social functioning, and employment.

The assignment of the correct phenotype in genetic studies is difficult because there are no validated clinical tests or scales to diagnose ET. Misdiagnoses are common because the clinical characteristics of tremor are not specific to ET. Tremor can be the presenting sign in other neurological conditions such as Parkinson's disease (PD), hereditary spinocerebellar ataxias (SCAs), dystonia, and the fragile X-associated tremor/ataxia syndrome (FXTAS). The rating scales clinicians use to evaluate ET include the criteria developed by the Tremor Investigator Group (TRIG), National Institutes of Health Essential Tremor Consortium, the Consensus Statement on Tremor by the Movement Disorder Society, and the Washington Heights-Inwood Genetic Study of ET (WHIGET). The affected phenotype in genetic studies is assigned to individuals with abnormal action tremor of both upper limbs or an isolated head tremor in the absence of abnormal posturing, dystonia, and other neurological signs. The hand tremor must be rhythmic and present in multiple activities with an amplitude of at least 1–2 cm. The accuracy of genetic studies may improve by incorporating quantitative measurements such as motion transducers into the clinical rating scales.

Inheritance

ET occurs as a sporadic or an inherited trait. The variable concordance rates between 60% and 93% in monozygotic twins with ET suggest that genetic, as well as environmental factors are operational in the pathogenesis of the disorder. An autosomal dominant (AD) pattern of inheritance is often seen in family pedigrees with ET. Transmission of ET to offspring is more than 50% that is expected for a dominantly inherited mutant allele. Incorrect phenotyping or genetic heterogeneity may explain the high ratio of affected to unaffected offspring. The disease penetrance of ET may be incomplete even at advanced ages.

Family Linkage Studies

Genetic studies on families where ET is presumably inherited as an AD trait find a high likelihood of linkage between ET and genetic loci on chromosome 3q13 (ETM1), 2p22–p25 (ETM2), and 6p23 (ETM3). The ETM1 and ETM2 loci have been excluded or have not reached statistical significance for genetic linkage in at least 13 large families with ET from the United States, Italy, and Tajikistan. Two candidate genes in the ETM1 and ETM2 regions that are involved in dopamine signaling and regulation, the *dopamine D3 receptor gene* (*DRD3*) and the *hematopoietic-specific protein 1 binding protein 3 gene* (*HS1BP3*), are identified as potential causes of ET, but are not confirmed in other studies. Genetic mutations are not found in the coding regions of 15 genes within the ETM3 candidate region. The search for a specific genetic cause for ET has been difficult due to confounding factors such as genetic heterogeneity and the presence of other conditions that mimic ET (i.e., phenocopies).

ETM1

In 1997, the ETM1 susceptibility locus for ET was mapped to chromosome 3q13 in 75 affected individuals from 16 Icelandic families. A variant (serine-9-glycine) in one of the genes [*dopamine D3 receptor gene* (*DRD3*)] within the ETM1 region is associated with ET in French and American families. Individuals homozygous for the *DRD3*

gene variant (glycine-9) are reported to have an earlier onset and a more severe ET phenotype. Experiments using cultured human embryonic kidney cells transduced with the glycine-9 *DRD3* gene variant show a greater dopamine affinity, an increased dopamine-mediated cyclic adenosine monophosphate (cAMP) response, and a prolonged mitogen-associated protein kinase signal. The *DRD3* variants reported in American and French families are not associated with ET in other family cohorts from the United States, Italy, Latvia, or Singapore. The relationship between *DRD3* homozygosity and an earlier age of ET onset and severity was not confirmed in other studies.

ETM2

In 1997, the ETM2 susceptibility locus for ET was mapped to chromosome 2p25–p22 in a large American family of Czech descent with 15 affected individuals in four generations. Genetic association studies in American, Singaporean, and Korean populations show that the ETM2 locus is in linkage disequilibrium with a disease gene for ET. A heterozygous polymorphism (alanine-265-glycine) in a gene within the candidate region, the *hematopoietic-specific protein 1 binding protein 3 gene* (*HS1BP3*), is associated with ET in 16.4% of 73 singleton families from the United States. This finding was not confirmed in other studies.

ETM3

In 2006, a third susceptibility locus for ET, ETM3, was mapped to chromosome 6p23 in one large North American family with 14 affected individuals in five generations with tremor and a form of dystonia called writer's cramp. An additional genetic disorder, malignant hyperthermia susceptibility, caused by a missense mutation in the *ryanodine receptor 1 gene* (*RYR1*) was also present in this family pedigree. This trait segregated independently from the tremor and dystonia phenotype. A second family with a pure ET phenotype was marginally linked to the same locus. Sequencing the coding regions of the 15 genes within the ETM3 candidate region did not identify mutations.

Cytogenetics

Tremor has been associated with numerical abnormalities and mutations of the X and Y chromosomes. Supernumerary X and Y chromosomes such as in the XXYY syndrome are associated with psychomotor retardation and a tremor that resembles ET. Men older than the age 50 who carry a *fragile X mental retardation 1 gene* (*FMR1*) premutation have tremor, gait ataxia, and executive cognitive deficits (i.e., the FXTAS). Intellectually disabled boys with the fragile X syndrome and *FMR1* gene mutations are not uniformly affected with tremor.

Candidate Gene Association Studies

Alcohol Dehydrogenase Genes

The ingestion of alcohol relieves tremor in two thirds of ET patients. This observation led investigators to research the possible association between alcohol dehydrogenase genotypes and ET. A study conducted in Spain that analyzed the relationship between the alcohol dehydrogenase 1B, β-polypeptide (*ADH2*) gene, and ET demonstrated no differences in the frequencies of *ADH2* genotypes and alleles between ET patients who did not drink alcohol and those who reported improvement with alcohol use.

PD Genes

James Parkinson alluded to the similarities between ET and PD in his original description titled the 'Shaking Palsy' in 1817. Some individuals have bilateral, postural tremor before they develop PD. The PD tremor differs from ET by its long latency of onset. There is no delay in the onset of tremor in ET upon the assumption of the arms in the horizontal position. Neuropathological evidence suggests that alpha synuclein-positive Lewy bodies are present in both ET and PD, but the substantia nigra is not involved in ET. These observations led to studies analyzing the association between ET and the genes that are involved in PD including the *parkin*, *α-synuclein*, *leucine-rich repeat kinase 2 (LRRK2)*, and the *cytochrome P450, subfamily IID, polypeptide 6 (CYP2D6)* genes. None of these genes are consistently associated with the ET phenotype.

Mitochondrial Genes

Mitochondria are subcellular organelles that are critical for oxidative phosphorylation and diverse neuronal signaling events. Mitochondria have an independent circular genome that encodes for five multisubunit complexes (complex I–V) involved in these processes. Electrons from Kreb cycle intermediates feed into complex I or II, and are transferred to complex III, then to complex IV, and finally to oxygen. The electrochemical gradient generated across the inner mitochondrial membrane by electron transport is ultimately utilized by complex V to produce energy in the form of adenosine triphosphate (ATP). The mitochondrial 'vicious cycle' theory hypothesizes that neurodegeneration occurs as a result of the accumulation of reactive oxygen species such as hydrogen peroxide and hydroxyl radicals, which in turn induces mutations in mitochondrial DNA. These mutations then lead to further oxidative phosphorylation dysfunction. This theory and the presence of a high burden of mitochondrial

DNA deletions in the substantia nigra of individuals with PD were the basis for a study that compared the mitochondrial DNA of nine patients with familial ET and six controls. Deletions in various mitochondrial genes including the *16S ribosomal RNA gene* (*16S rRNA*), and complex I [*nicotinamide adenine dinucleotide dehydrogenase subunit 1 gene* (*ND1*), and *nicotinamide adenine dinucleotide dehydrogenase subunit 2 gene* (*ND2*)], complex III, complex IV [*cytochrome c oxidase subunit II gene* (*COII*)], and complex V [*adenosine triphosphate synthase subunit ATPase 6* (*ATPase 6*), and *adenosine triphosphate synthase subunit ATPase 8* (*ATPase 8*)] region genes were identified in these patients. Deletions were not observed in the D-loop or in a complex IV gene [cytochrome c oxidase subunit I (COII)] in the ET patients. Currently, there is no definitive in vivo experimental evidence to support the mitochondrial vicious cycle theory. Thus, it is unclear if mitochondrial DNA deletions are directly involved in the pathogenesis of ET.

Genetics of ET 'Plus' Syndromes

The diagnosis of ET is complicated by the coexistence of phenocopies and other genetic disorders such as dystonia (*torsin-A* gene), X-linked spinobulbar muscular atrophy type I (*androgen receptor gene*), SCA types 2, 3, and 12 (*ataxin 2, ataxin 3,* and *beta subunit of the protein phosphatase 2* genes), and the FXTAS (*FMR1*). Genetic studies have not identified a specific link between these genes and individuals with ET as an isolated neurologic condition. ET-like tremor has been described in other genetic disorders including hereditary peripheral neuropathies such as Charcot–Marie-Tooth disease due to mutations in the *connexin 32,* and *peripheral myelin protein 22* genes.

Genetic and Biochemical Animal Models of ET

γ-Aminobutyric $acid_A$ receptor alpha 1 knockout transgenic mice (*gabra*1 −/−) exhibit a postural and kinetic tremor that is responsive to alcohol ingestion. This ET-like phenotype suggests that gamma-aminobutyric acid neural transmission has a role in the pathogenesis of ET. However, mutations in the human *GABRA1* gene are not found in individuals with ET.

Ecogenetics

Studies suggest that ET results from interactions between genes and the environment. Experimental data generated over four decades show that laboratory animals exposed to the β-carboline alkaloids (e.g., harmaline, harmane) exhibit a tremor similar to ET. β-Carbolines are a class of indole alkaloids which are structurally similar and biosynthetically derived from L-tryptophan, a serotonin precursor. The sources of dietary beta-carbolines are from plant-derived foods (e.g., wheat, barley, rice, and corn), beverages (wine, beer, whisky, and sake), and tobacco. Measurements of blood harmane levels in sporadic and familial cases of ET suggest that these chemicals exacerbate or even cause ET especially when there is a family history of the disorder. Blood lead levels and genetic variants in an enzyme involved in lead metabolism, delta aminolevulinic acid dehydratase, have been associated with the presence of ET in humans. Genetic variants in *glutathione-S-transferase* genes, polymorphic enzymes that participate in the metabolism of carcinogens (including those of tobacco smoke) and pesticides, are more frequent in individuals with ET.

See also: Tremor; Tremor, Essential (Syndromes).

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International Essential Tremor Foundation.

Tremor, Holmes

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Glossary

Bradykinesia – Slowness of movement.
[18F]-fluorodopa PET – Positron emission tomography (PET) scan using [18F]-fluorodopa as radioactive ligand to evaluate presynaptic dopaminergic function.
Thalamotomy – Permanent lesioning of the thalalmic nuclei as a treatment for tremor.
Tremor – Repetitive, rhythmic oscillation of a body region caused by contraction of opposing muscle groups.

Definition and History

In 1904, Gordon Holmes described nine patients with different etiologies (vascular and tumors) all having a characteristic tremor. Since his was one of the first descriptions, the tremor has been eponymously named as 'Holmes tremor.' Although, the literature is abundant with various terms such as midbrain tremor, rubral tremor, and myorhythmia, which have been used interchangeably, the term Holmes tremor (HT) is preferred to describe this specific tremor syndrome. This tremor can also be a part of a larger syndrome associated with additional signs and symptoms such as ataxia, nystagmus and ophthalmoplegia, bradykinesia, and apathy. Some characteristics of HT include

1. A tremor of a low frequency usually less than 4.5 Hz, mostly unilateral.
2. Tremor is usually of a large amplitude and has a certain irregularity to it. It is more prominently seen with action, although may be present at rest and with posture as well.
3. There is considerable delay in the onset of the tremor compared with the timing of the original insult (from weeks to months).
4. Tremor cannot be controlled by volition and only increases in severity with the attempt. It also abates during sleep.

Pathophysiology of the Tremor

It is widely accepted that HT is a symptomatic tremor, that is, secondary to a lesion. In HT, the lesions usually involve the brainstem/cerebellar and thalamic regions mostly affecting the cerebello-thalamo-cortical and dentato-rubro-olivary pathways, and the dysfunction of the nigrostriatal system may account for the rest component. Even in his original monograph, Holmes postulated that the tremor was due to the interruption of the cerebello-rubrothalamic pathways and that when the lesion was caudal to the decussation of the pathway, it resulted in an ipsilateral tremor and when rostral, a contralateral tremor. A positron emission tomography (PET) study of six patients with HT secondary to a contralateral peduncular lesion showed a significantly decreased [18F]-fluorodopa uptake in the striatum, suggestive of nigrostriatal dysfunction. Also, MRI and dopamine transporter SPECT scan in a patient with the classic HT secondary to midbrain cavernous angioma showed damage to the cerebellorubro-thalamic and nigrostriatal pathways. This also suggests a possible pathophysiological interplay between the two pathways in the production of this distinct tremor. Since the typical rest tremor from basal ganglia dysfunction usually improves with voluntary activity, Deuschl and Bergman have hypothesized that once the ipsilateral cerebellum also becomes involved, the rest tremor spills over to voluntary activity producing the high-amplitude characteristic HT. Also, the frequency of HT (~4 Hz) is typically less than the Parkinson disease rest tremor (~6 Hz) possibly because of the influence of the cerebellar circuits over the basal ganglia, which are also disrupted.

Any lesion that disrupts the aforementioned pathways can produce a HT. Some of the different lesions reported to cause a HT include tumors, vascular insults (i.e., stroke, AVMs), hemorrhages, CNS infections including abscesses, multiple sclerosis, and iatrogenic causes (i.e., surgery/gamma-knife procedures or radiation injury) damaging the midbrain, among others. Hence, the diagnostic workup in a patient with HT is directed at detecting the lesion that caused the tremor.

Management

Since HT is typically secondary to an underlying lesion, it is important to identify the underlying cause, because if the insult is reversible, tremor may have a very favorable prognosis and however if the damage is permanent, that may not always be the case, that is, demyelination secondary to multiple sclerosis.

Medical management to symptomatically treat the tremor involves the use of levodopa, anticholinergics,

and clonazepam with some response. Others have also tried propranolol, dopamine agonists, and valproate with mixed results. Although, only isolated cases of levodopa-responsive HT (~15) have been found in the literature, it may be prudent to try levodopa as a first choice medication in the treatment of HT before resorting to other medications or invasive procedures. Ferlazzo et al. report a case of successful treatment of HT secondary to head injury with levetiracetam. Reports of HT responding to dopamine agonists such as pramipexole and cabergoline also exist in the literature. Hallett et al. treated six patients with isoniazid in a double-blind, placebo-controlled, crossover trial and found improvement in the severe postural cerebellar outflow tremor, suggesting that isoniazid may have a role in the treatment of cerebellar outflow tremor.

In the recent years, surgical treatment of HT with either lesioning or stimulation (DBS) has been employed with success. Many groups have noted improvement of HT in selected patients following stimulation or lesioning of the nucleus ventrointermedius (Vim) of the thalamus as well as with pallidotomy or stimulation. A recent review of the literature comparing outcomes of thalamotomy to DBS in patients with tremor secondary to multiple sclerosis showed that both thalamotomy and thalamic DBS were comparable procedures for tremor suppression. However, functional improvement was seen only in 47.8% of those who underwent thalamotomy, as opposed to 85.2% of those who had DBS. Earlier reports of Vim stimulation suggested more improvement of the distal contralateral extremity tremor with little effect on the proximal tremor. This relatively resistant nature of the tremor to single targets prompted investigators to combine to Vim stimulation with other DBS targets or lesions in patients with Holmes' tremor. Authors have reported a synergistic improvement of the tremor when combining Vim DBS with subthalamic nucleus DBS, globus pallidus interna pallidotomy, or ventralis oralis anterior (Voa)/posterior (Vop) pallidal receiving area stimulation. However, Lim et al. did not observe any additive effect with simultaneous multiple target DBS stimulation in two patients (one with MS-related tremor and one with post-stroke tremor).

Given the limited efficacy of thalamic DBS in alleviating proximal tremor in Holmes' tremor, other targets for stimulation have been explored. Plaha et al. performed bilateral stimulation of the caudal zona incerta (cZI) in patients with Holmes' tremor and found significant amelioration of both the distal and proximal limb tremor. However, further studies to evaluate cZI are necessary before concluding its efficacy as a potential therapeutic target for DBS.

See also: Deep Brain stimulation; Postural Tremor; Rest Tremor; Tremor; Tremor, Essential (Syndromes).

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Tremor: Drug-induced

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Glossary

Intention tremor – A terminal kinetic tremor that increases in amplitude near the target.
Postural tremor – Tremor that occurs with the arms outstretched.
Rest tremor – Tremor that occurs in a limb when fully supported and typically improves with action.
Tremor – Rhythmic or semirhythmic oscillation of one or more body parts.

Tremor is a common movement disorder. While there are numerous causes of tremor, drug-induced tremor is relatively common and frequently easy to treat by stopping the causative medication. The multiple causes of tremor and the high prevalence of tremor, especially in the elderly, sometimes makes it difficult to determine if a drug is responsible for a patient's tremor. Polypharmacy also makes it difficult to identify a single drug as causative. This discussion focuses on several drugs commonly associated with the induction or exacerbation of tremors.

The major drugs associated with tremor are listed in **Tables 1** and **2**. Different drugs can cause different types of tremors varying from resting (neuroleptics) to postural (central stimulants and numerous other drugs) to kinetic (ethanol and lithium) tremors. While most drug-induced tremor occurs in the context of current use of a medication, tremor can also emerge or continue after withdrawing the drug (ethanol withdrawal, tardive tremor related to chronic drug treatment that may persist after withdrawal). In addition, comorbidities can significantly influence the expression of drug-induced tremor. For example, renal failure is known to exacerbate metoclopramide-induced tremor. Typically, drug-induced tremors are rapid in onset and dramatically improve or resolve with discontinuing the offending drug.

Antiarrhythmics

Amiodarone, mexelitine, and procainamide are all reported to cause tremor, but amiodarone-related tremor is the most commonly encountered in practice. Amiodarone-induced tremor is reported to occur in about one-third of patients on the drug, and the tremor is characterized as a postural and kinetic tremor in the 6–10 Hz range. Keeping the dose of the drug in the low range (200 mg day^{-1}) appears to provide good arrhythmia control while minimizing the risk of tremor. Stopping the causative drug usually resolves the tremor, and in patients who cannot stop the medication safely, propranolol appears helpful. Amiodarone can cause thyroid dysfunction (both hypo- and hyperthyroidism), so it is important to exclude secondary hyperthyroidism in a patient with tremor on this drug.

Antibiotics/Antivirals/Antifungals

Antibiotics, antivirals, and antifungals are widely prescribed, but there are very few reports of tremor secondary to these drugs. Trimethoprim-sulfamethoxazole (TMP-SMX) is reported to cause significant resting and postural tremor in AIDS patients undergoing treatment of *Pneumocystis carinii* pneumonia. The mechanism of TMP-SMX-induced tremor is unknown, although tremor may relate indirectly to reduced catecholamine and indolamine synthesis through inhibition of dihydrofolate reductase.

The antiviral drugs vidarabine (Ara-A) and acyclovir are associated with tremors in patients being treated for herpetic infections or undergoing bone marrow transplant. Acyclovir-related tremors often occur in the elderly and in those with renal failure. The movement disorder is typically self-limited, resolving within several days to a week after discontinuing the drug.

Antifungal agents like amphotericin B, ketoconazole, and fluconazole are also rarely reported to cause tremors.

Antidepressants/Mood Stabilizers

Tricyclic antidepressants (TCAs) are widely used for numerous conditions including depression, headaches, and neuropathic pain. The development or exacerbation of existing tremor is a known side-effect of these drugs. While clinically significant tremor interfering with activities of daily living is uncommon with these drugs, most patients have at least some postural tremor evident on neurophysiological recording. The tremor can improve over time on therapy and in the event that the movement disorder is problematic and the patient cannot use an alternative drug, β-adrenergic blocking agents may be helpful.

Selective serotonin reuptake inhibitors (SSRIs) are widely used to treat anxiety, depression, and multiple other conditions. SSRI-induced tremor is probably the most common movement disorder induced by these

Table 1 Major drugs which induce or exacerbate tremors

Drug class	*Major tremorogenic drugs*
Antiarrhythmics	Amiodarone
Antibiotics/antivirals	Trimethoprim/sulfamethoxazole (TMP-SMX)
Antidepressants/mood stabilizers	Lithium, SSRIs, TCAs
Antiepileptics	Valproic acid (VPA)
Bronchodilators	Albuterol, salmeterol
Chemotherapeutics	α-Interferon, tamoxifen, thalidomide
Drugs of abuse	Alcohol, cocaine, nicotine
Gastrointestinal drugs	Cimetidine, metoclopramide
Hormones	Epinephrine, thyroxine
Immunosuppressants	Cyclosporine, tacrolimus (FK-506)
Methylxanthines	Theophylline, caffeine
Neuroleptics	Haloperidol, thioridazine

SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants; MDMA, 3,4-methylenedioxymethamphemtamine or 'Ecstasy'

Table 2 Drugs that cause resting, postural, and action/intention tremors

Major category	*Typical examples*
Resting	
Antibiotics/antivirals/antifungals	Trimethoprim/sulfamethoxazole (TMP-SMX)
Antidepressants/mood stabilizers	SSRIs, lithium
Antiepileptics	Valproic acid (VPA)
Chemotherapeutics	Thalidomide
Drugs of abuse	Cocaine, ethanol, MDMA
Gastrointestinal drugs	Metoclopramide
Neuroleptics/dopamine depleters	Haloperidol, thioridazine, cinnarizine reserpine, tetrabenazine
Postural	
Antiarrhythmics	Amiodarone
Antidepressants/mood stabilizers	Amitriptyline, lithium, SSRIs
Antiepileptics	Valproic acid (VPA)
Bronchodilators	Albuterol, salmeterol
Chemotherapeutics	Tamoxifen, Ara-C, ifosfamide
Drugs of abuse	Cocaine, ethanol, nicotine
Gastrointestinal drugs	Metoclopramide, cimetidine
Hormones	epinephrine, thyroxine
Immunosuppressants	Tacrolimus, cyclosporine, α-interferon
Methylxanthines	Theophylline, caffeine
Neuroleptics/dopamine depleters	Haloperidol, thioridazine, cinnarizine reserpine, tetrabenazine
Intention	
Antibiotics/antivirals/antifungals	Vidarabine
Antidepressants/mood stablilizers	Lithium
Bronchodilators	Albuterol, salmeterol
Chemotherapeutics	Ara-C, ifosfamide
Drugs of abuse	Ethanol
Hormones	Epinephrine
Immunosuppressants	Tacrolimus, cyclosporine

drugs, and it is estimated that new-onset tremor occurs in ~20% of SSRI-treated patients. In a study with fluoxetine, tremor emerged at a mean latency of 54 days at an average dose of 26 mg day^{-1} and the tremor frequency was typically 6–12 Hz. The tremor was typically postural in nature, although on occasion, resting and kinetic tremor developed. In half of the SSRI-treated patients with tremor, the movement disorder remitted within 1 month after discontinuing fluoxetine, while in the remaining patients, the tremor persisted for at least 15 months. Tremor can also occur as part of SSRI withdrawal, especially in patients discontinuing SSRIs with short half-lives.

Tremor is the most common movement disorder due to lithium. While the true prevalence of lithium-induced tremor is unknown, an average of 27% of 1000 patients in several studies developed tremors that were thought to be due to the drug. One study found that 32% of patients felt that their tremor resulted in noncompliance and some disability. For the majority of patients, however, the tremor is mild and not disabling. Men and the elderly may have a higher risk of developing tremor on chronic lithium therapy.

The tremor induced by lithium is typically between 8 and 12 Hz, falling into the category of enhanced physiological tremor and affecting mainly the hands. It can occur over a range of lithium levels and other medications, especially antidepressants and valproate, can exacerbate lithium-related tremor. Treatment involves dose reduction if the underlying medical or psychiatric condition permits. Another alternative treatment is a switch to another medication such as lamotrigine. In the event that the lithium cannot be decreased or replaced, the addition of propranolol or primidone can be helpful.

Antiepileptics

Valproic acid (VPA) is widely used for migraine prophylaxis, epilepsy, and bipolar disorder. Tremor due to this drug is one of the most common drug-induced tremors in clinical practice. The clinical and electrophysiological features of VPA-induced tremor resemble essential tremor, and VPA may induce tremor in people who never had tremor before or it can exacerbate underlying tremor conditions. Whereas 25% of patients exposed to VPA complain of tremor, up to 80% of patients show evidence of tremor on accelerometry recordings. The tremor is typically kinetic and postural, although rest tremor may occur. The hands are predominantly affected, but head and truncal tremor also occur. The tremor appears dose-related and dose reduction can improve VPA-induced tremor, usually within several weeks. If dose reduction is not possible, then propranolol, amantadine, or acetazolamide appear to provide benefit for VPA-induced tremor.

There are few reports of tremor with other AEDs. In fact, multiple AEDs, including primidone, carbamazepine, gabapentin, and topiramate are often useful in treating essential and other forms of tremor.

Bronchodilators

Albuterol (salbutamol) is a β_2-adrenergic agonist widely prescribed for chronic obstructive pulmonary disease (COPD) and asthma and one of the most common drugs causing drug-induced tremor. In large clinical trials, 7–20% of patients complained of tremor due to inhaled albuterol with similar numbers of patients complaining of tremor due to inhaled isoproterenol (14%). Tremor and other side effects appear dose related with β_2-agonists. Salmeterol, a newer β_2-agonist with a significantly longer half-life, can also cause tremors. While the exact mechanism for tremor induction by β_2-agonists is unknown, there is some evidence that these drugs act through a peripheral mechanism at the level of the muscle. Tolerance develops with continued use of β_2-agonists and the tremor may occur more often with oral versus inhaled therapy.

Chemotherapeutics

There are some reports of tremor associated with chemotherapy, but most standard chemotherapic agents are not associated with pronounced tremor. Tamoxifen is an antiestrogenic agent used in the treatment of breast cancer, and in early studies, the dose-limiting toxic effects of tamoxifen included tremor. Thalidomide caused tremor in 36% (10/28) of patients when used alone and in 30% (12/40) of patients receiving combination therapy with dexamethasone in one multiple myeloma clinical trial. Tremors associated with thalidomide therapy are mild and reversible. Cytarabine (Ara-C) is used to treat various cancers and can cause intention tremor, perhaps due to damage to cerebellar Purkinje cells. Ifosfamide, vincristine, and cisplatin are also rarely associated with tremors.

Drugs of Abuse

Ethanol is reported to cause multiple forms of tremor, including postural tremor as an acute/transient disorder when discontinuing ethanol use, a 'metabolic tremor' associated with alcoholic liver disease, a 3 Hz leg tremor in the context of alcoholic cerebellar degeneration, and rarely parkinsonism associated with intoxication or withdrawal. In addition, as a withdrawal syndrome, approximately one-half of 100 alcoholics who did not use ethanol for 3 weeks or more had postural tremor, although the tremor was associated with functional disability in only 17%. Propranolol appears to provide significant benefit in this setting.

Smoking is associated with an increase in tremor amplitude by at least twofold over all frequencies. In another study, cigarette smoking increased tremor significantly independent of age, gender, and anxiety levels. This effect was documented using electrophysiology and it appears that the effect is due to nicotine.

3,4-Methylenedioxymethamphemtamine (MDMA or 'Ecstasy'), cocaine, and amphetamine derivatives are reported to cause tremor. Cocaine can cause resting tremor and parkinsonism and the tremor may not remit even after 3 months of abstinence.

Gastrointestinal Drugs

Metoclopramide is a dopamine-receptor blocking agent that remains in relatively widespread use for gastroesophageal reflux disease and gastroparesis. Metoclopramide-induced movement disorders (tremor, orobuccolingual dyskinesia, parkinsonism) are very common in the tertiary setting in our experience. This drug can induce a Parkinsonian tremor, an essential-like tremor that responds to ethanol, or tardive tremor. Metoclopramide-induced parkinsonism and tremor appears more common in patients with renal failure and the dose should be lowered in these patients. Metoclopramide may cause tremor by acting as a cholinomimetic tremorogen or due to its dopamine-receptor blocking properties.

Cimetidine (a histamine H2 receptor antagonist) was shown to exacerbate tremors in three patients in one report. Bismuth salt toxicity can cause an encephalopathy with myoclonus, ataxia and tremor.

Hormones

Excess thyroid hormone in hyperthyroidism or in the setting of ingesting excess levothyroxine can cause tremor. In one study of elderly patients with hyperthyroidism, 36% had clinical signs of tremor. Tremor is frequently noted in children or adults who overdose on levothyroxine. It appears that the peak tremor frequency in thyrotoxicosis is the same as that of physiological tremor in healthy subjects; however, the power of thyrotoxic tremor is increased. Thyrotoxic tremor responds to both β-adrenoreceptor blockade by nadolol as well as treatment of the thyrotoxicosis by carbimazole.

Epinephrine and norepinephrine are associated with tremor in patients with pheochromocytomas. Epinephrine and norepinephrine have been extensively studied in humans and appear to act by enhancing physiological tremor at the level of the muscle. Interestingly, tremor

was noted as a side effect in *all* children injected with an epinephrine injectable (for patients at risk for anaphylaxis) in one study.

Immunosupressants/Immunomodulators

Calcineurin inhibitors such as cyclosporine and FK-506 (tacrolimus) are widely used in immunosuppressive transplant regimens and in autoimmune disorders. Postural tremor is reported in up to 40% of patients on cyclosporine with intention tremor being less frequent. The tremor typically is mild and generalized in nature and higher blood levels of cyclosporine are correlated with tremor. Tremor is frequently preexistent due to hepatic or renal failure and polypharmacy in most patients. Cyclosporine can also rarely cause parkinsonism with rest tremor.

FK-506 (tacrolimus) is also commonly used in immunosuppressive regimens and was associated with tremor in the first reports of neurological toxicity related to the drug following liver transplantation. Tremor was observed in 8 of 22 pediatric liver transplant patients on FK-506 and occurred in 10 of 44 patients undergoing orthotopic liver transplantation in another study. The tremor associated with FK-506 therapy in the latter 10 patients was severe and affected the hands, interfering with handwriting and worsening with action, but improving with dose reduction. Tremor was also associated with FK-506 therapy in rheumatoid arthritis and in treatment of fistulas related to Crohn's disease.

Tremor was actually the major neurological side effect in a trial of α-interferon for metastatic melanoma. Significantly increased action tremor occurred in 22% of patients in this trial and facial myorhythmia was also reported in one patient on the drug.

Methylxanthines

Methylxanthines include theophylline, aminophylline, and caffeine. Theophylline and aminophylline are typically used in the treatment of COPD and asthma. Caffeine is widely consumed throughout the world. Aminophylline and theophylline treatment leads to increased patient complaints of tremor, not quite reaching statistical significance in a recent meta-analysis of these drugs in acute COPD exacerbation, but aminophylline does increase tremor power on accelerometry when given to patients with essential tremor. In contrast to these reports, there is evidence that theophylline (an adenosine antagonist) may improve essential tremor as much as propranolol.

Studies on caffeine and tremor have demonstrated that 2% of normal controls complained of tremor when drinking coffee. Essential tremor and Parkinson's disease patients complained that coffee worsened their tremors in 8% and 6% of patients, respectively. However, an oral caffeine dose of 325 mg did not increase physiological, Parkinsonian or essential tremor in formal clinical studies. Other accelerometry studies have shown that 450 mg day^{-1} of caffeine appears to increase finger tremor in the fasting state. In another accelerometry study, a caffeine dose equal to two or three cups of coffee increased whole-arm tremor in normal subjects.

Antipsychotics and Dopamine-Depleting Agents

Antipsychotics or neuroleptics (dopamine-receptor blocking agents) can cause resting and postural tremors. Tremor occurs most frequently as a part of drug-induced parkinsonism with these drugs, and rest tremor generally develops several days or weeks after introduction or dosage increase of antipyschotics. Tardive tremor that occurs after prolonged antipsychotic therapy with persistence even after withdrawal of the drug has been reported, although its existence as a nosographic category has been debated. Parkinsonism with tremor that continues after withdrawal of an antipsychotic in an elderly or middle-aged subject is more likely due to the unmasking of Parkinson's disease that was preclinical at the time of antipsychotic exposure. Tremor associated with drug-induced parkinsonism was particularly frequent with older typical antipsychotics affecting 35–60% of treated patients. Tremor typically began asymmetrically in one arm, similar to Parkinson's disease, although bilateral tremor is also a frequent presentation. Exposures to fluphenazine (piperzaine group) or thioridazine (piperadine group) have been reported to cause drug-induced parkinsonism more frequently than chlorpromazine (aliphatic group). Newer generation antipsychotics are associated with lower frequencies of drug-induced parkinsonism, but the potential problem exists with all available antipsychotic agents that work through dopamine-receptor blockade.

The vestibular sedatives cinnarizine and flunarizine are not prescribed in the United States; however, they are frequently associated with drug-induced parkinsonism and postural/rest tremor in treated patients. The dopamine-depleting agents, reserpine, methyldopa, and tetrabenazine, are also reported to cause tremor.

Other Miscellaneous Drugs

While most β-blockers typically ameliorate various forms of tremor, pindolol, is known to cause tremor in various settings. The tremor is mostly postural and action in nature, about 7 Hz and is usually self-limited after

Table 3 Therapy of the most common drug-related tremors

Drug	*Treatment*
Albuterol	Reduce frequency or discontinue use longer-acting inhaled β-agonist may help
Amiodarone	Screen for hyperthyroidism, reduce dose to 200 mg day^{-1} if possible, β-blocker may help
Amitriptyline/ TCAs	Allow time to see if tremor will improve discontinue use or switch to an SSRI, β-blocker may help
Caffeine	Reduce caffeine intake
Cyclosporine	Avoid toxic states and consider reducing dose, try another immunosuppressive agent
Ethanol	Abstinence β-blockers
Lithium	Check drug levels, reduce dose change medications (valproate, lamotrigine, etc.) β-blocker therapy (may worsen depression)
Metoclopramide	Discontinue use and observe consider using erythromycin for gastroparesis observe for signs of parkinsonism
Nicotine	Stop using all forms of tobacco or nicotine gum
SSRIs	Wait to see if tremor improves over time reduce dose if depression allows β-blockers (may worsen depression)
Tacrolimus (FK-506)	Reduce dose try another immunosuppressive agent
Valproic acid	Reduce dose change to another antiepileptic or mood stabilizer β-blockers

stopping the drug. This drug may cause tremor due to its partial β-agonist activity, unlike other β-blockers.

Various reports have documented tremor in patients taking ephedrine, pseudoephedrine, and phenylpropanolamine in over the counter cold preparations or when used as appetite suppressants. The tremorogenic effect of these drugs is likely due to their sympathomimetic effects. Ephedrine and phenylpropanolamine are no longer available in the United States, but pseudoephedrine remains in widespread use.

Central stimulants like amphetamines, methyphenidate, and dexedrine are also known to cause tremors in some treated patients.

Treatment Strategies

Ideally a drug-induced tremor should be treated with withdrawal of the causative agent. In many instances, however, the underlying medical, psychiatric, or neurological condition requires the use of the tremorgenic drug and in these cases other treatments must be added to the tremorgenic drug.

Table 3 lists the most widely prescribed and used tremorogenic drugs in the United States today and briefly details treatment of tremor related to these drugs. It is important to remember that many drugs exacerbate underlying tremors and an underlying cause for tremor (psychogenic tremor, essential tremor, Parkinson's disease) should be considered in each patient.

See also: Antidepressants and Movement Disorders; Benzodiazepines and Movement Disorders; Beta-blockers and Movement Disorders; Central Nervous System Stimulants and Movement Disorders; Drug-induced Movement Disorders; Neuroleptics and Movement Disorders; Nicotine; Tardive Syndromes.

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Relevant Websites

www.movementdisorders.org – Movement Disorders Society.
www.wemove.org – WE MOVE.
www.clevelandclinicmeded.org – Cleveland Clinic Med Ed.

Trinucleotide Repeat Disorders

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Glossary

Condensed chromatin – DNA that is tightly packaged in chromatin inaccessible to transcription factors. Generally, genes present within condensed chromatin are silenced. Various histone modifications are associated with condensed chromatin, for example, deacetylated histone H3/4 and histone H3 methylated at lys^9 residue.
CBP – CREB binding protein, CREB – cAMP response element binding protein; both components of a common transcription activator pathway.

Huntington's Disease (HD)

Definition and History

HD is an autosomal dominant (AD) disorder, described by George Huntington in 1872. The HD locus was localized to chromosome 4p in 1983. The causative mutation identified in 1993 is an unstable expanded CAG repeat in exon 1 of the *Huntingtin* (*IT15*/*Htt*) gene.

Pathogenesis

The expanded CAG trinucleotide repeat is translated into a polyglutamine (polyQ) tract at the N-terminus of the Htt protein. The CAG repeat is unstable expanding between successive generations, particularly with paternal transmission, resulting in a more severe and earlier disease: a phenomenon known as anticipation. Pathogenesis is complex involving multiple cellular processes. The primary pathological changes are seen in the striatal medium-sized spiny neurons and in layers V and VI of the neocortex. Common to all the polyQ repeat diseases is a toxic gain of function of the mutant polyQ containing protein and deposition of ubiquitinated neuronal intranuclear inclusions (NIIs) – in HD formed by the self association of N-terminal mutant Htt. NIIs may be directly toxic to the cell but may represent a clearance mechanism for misfolded proteins and components of the ubiquitin-proteosome pathway are found associated with inclusions. Mutant-expanded Htt itself interacts with multiple cellular proteins, including transcription factors such as CBP, which may result in gene repression and cellular toxicity. Apoptosis is important in polyQ disease neurodegeneration.

Epidemiology

The prevalence of HD is ~4–8/100 000 in Europe and North America. The *Htt* gene usually contains 8–39 repeats; 37 or more repeats are found in patients, suggesting variable penetrance in the overlap range; 40–50 are found in middle age onset (90–95% of cases); >60 usually results in juvenile HD.

Clinical Features and Diagnostic Criteria

HD typically develops in adulthood with a progressive personality change, cognitive decline, and chorea. Psychiatric features such as depression may predate the movement disorder. Additional features include extrapyramidal signs such as rigidity, bradykinesia, tremor, myoclonus, and dystonia as well as pyramidal signs and ataxia. Difficulty in initiating saccades and gaze impersistence also occurs. Juvenile HD often manifests itself as an akinetic rigid syndrome (Westphal variant).

Differential Diagnosis

Adult onset chorea has a wide differential. Other genetic conditions that may mimic (HD phenocopies) or appear similar to HD are listed in **Table 1**. The HD phenocopies known as HD-like (HDL) syndromes have become increasingly appreciated.

HDL1, 2, and 4 are AD disorders. HDL1 is due to 168 or 192 base pair in frame insertions in the *PRNP* gene, encoding additional octapeptide repeats. HDL2 occurs mostly in families of African ancestry and is due to a CAG repeat expansion in the *JPH3* gene. Pathological repeat length is 44–57 and it is unstable on maternal transmission. HDL4 is also known as SCA17. Cerebellar ataxia is the most common feature, often occurring with extrapyramidal and pyramidal signs and dementia, but a form indistinguishable from HD occurs. It is due to an expanded CAG repeat within the *TBP* gene. HDL3 is an autosomal recessive disorder and of childhood onset – its features are not reminiscent of HD.

Diagnostic WorkUp

PCR of DNA obtained from peripheral blood identifies the CAG repeat expansion. MRI imaging may show prominent caudate nucleus atrophy and atrophy of the cerebral cortex.

Table 1 Summary of hereditary disorders that may mimic or have features similar to Huntington's disease

Disorder	*Inheritance*	*Gene*	*Average age of onset*	*Clinical features*
HDL1	AD	*PRNP*	20–40	HD phenocopy
HDL2	AD	*JPH3*	25–45	HD phenocopy
HDL3	AR	Unknown		
HDL4/SCA17	AD	*TBP*	25–40	HD phenocopy/ataxia
SCA1	AD	*Ataxin-1*	30–40	Ataxia, extrapyramidal features, spasticity
SCA2	AD	*Ataxin-2*	25–45	Ataxia, extrapyramidal features, ophthalmoparesis, neuropathy, dementia
SCA3	AD	*Ataxin-3*	20–50	Ataxia, extrapyramidal features, ophthalmoplegia, neuropathy
DRPLA	AD	*Atrophin-1*	>40	Ataxia, chorea, myoclonus, dementia
Neuroferritinopathy	AD	*FTL*	40	Parkinsonsim, chorea, dystonia
Neuroacanthocytosis	AR	*VPS13A*	20–30	Dystonia with oromandibular involvement, chorea, neuropathy, self mutilation, red cell acanthocytes
McLeod Syndrome	X linked	*XK*	40–60	Similar to neuroacanthocytosis, seizures, myopathy in addition
Pantothenate kinase associated neurodegeneration	AR	*PANK2*	Childhood	Dystonia, Parkinsonism, chorea, dementia, occasionally acanthocytes
Wilson's disease	AR	*ATP7B*	20–30	Parkinsonism, dystonia, chorea, ataxia, psychiatric features, liver disease, Kayser Fleischer rings

PRNP, prion protein.
JPH3, junctophillin 3.
TBP, TATA binding protein.
FTL, ferritin light polypeptide.
VPS13A, vacuolar protein sorting 13 homolog A (encodes chorein).
XK, X-linked Kx blood group.
PANK2, pantothenate kinase 2.
ATP7B, ATPase CU^{2+} transporting beta polypeptide.

Management

Multidisciplinary management is essential. Psychiatric features may require atypical antipsychotic drugs and antidepressants. Chorea may be controlled with antipsychotic drugs and tetrabenazine can be useful. Weight loss is a common feature requiring expert dietetic advice. Speech therapy is often useful to help speech and swallowing. Predictive testing of family members is a major issue and is best carried out with a geneticist under the auspices of the expert HD clinic.

Prognosis

Generally, life span after diagnosis is 15–20 years but this is influenced by the severity of the disease, which is variable and related to CAG repeat length.

Dentatorubral–Pallidoluysian Atrophy

Definition and History

Dentatorubral–pallidoluysian atrophy (DRPLA) is an AD neurodegenerative disorder caused by an expanded CAG repeat in the *atrophin-1* gene on chromosome 12p. It shares many clinical and pathological features with HD.

Pathogenesis

Macroscopically, there is cerebellar and brainstem hypoplasia with microscopic features of degenerated denatatorubral and pallidoluysian systems. Neuronal loss in the dentate nucleus and pallidum is constant, while the red nucleus is least affected. Toxic gain of function of mutant polyQ atrophin-1 is thought to be pathogenic with ubiquitinated NIIs developing.

Epidemiology

The disease is found most commonly in Japan. The length of the repeat on the normal allele is 7–34 and on the expanded, 58–88. There is clear anticipation particularly with paternal transmission.

Clinical Features and Diagnostic Criteria

The juvenile form usually manifests itself as progressive myoclonus epilepsy (PME) with cognitive decline. In early adulthood (third decade), DRPLA may present in a similar manner to HD with prominent chorea or with prominent ataxia/myoclonus all associated with cognitive decline. Seizures may also develop. In cases developing later in life, a milder cerebellar ataxia may predominate.

Differential Diagnosis

The differential diagnosis is similar to HD (**Table 1**). In juvenile cases with PME, other conditions such as mitochondrial disease (MERRF), Lafora body disease, Unverricht Lundborg disease, sialidosis type 1, neuronal ceroid lipofuscinoses, and GM_2 gangliosidoses may need to be considered.

Diagnostic Workup

PCR of DNA obtained from peripheral blood identifies the CAG repeat expansion. Some cases may be identified in investigating HD or cerebellar ataxia. MRI imaging may show cerebellar and midbrain atrophy and high signal change in cerebral white matter.

Management

Management of the movement disorder and psychiatric manifestations is similar to HD as is the genetic counselling.

Prognosis

The prognosis for juvenile myoclonus epilepsy is poor. As in HD, prognosis is influenced by the severity of disease, which in itself is related to CAG repeat length.

Spinocerebellar Ataxia

Definition and History

There are at least 28 different AD SCAs. SCA1, 2, 3, 6, 7, and 17/HDL4 are polyQ diseases. In SCA8 and 12, a CTG and CAG expansion remains untranslated (**Table 2**).

Pathogenesis

Macroscopically, there is atrophy of cerebellum, brain stem nuclei, basal ganglia, spinal cord long tracts, and cerebral cortex varying with the specific syndrome. The pathogenesis of the polyQ SCAs shares features in common with HD, with a toxic gain of function of mutant proteins thought to be the primary pathogenic mechanism. The pathogenesis in SCA8 and 12 remains unclear.

Epidemiology

The incidence of SCA in general is ~1–5/100 000. SCA3 is the most common, worldwide (20–50% of cases), and is common in Brazil. SCA1 is more common in South Africa.

Clinical Features and Diagnostic Criteria

The clinical classification of these disorders as autosomal dominant cerebellar ataxias (ADCA) remains useful (**Table 3**). A cerebellar syndrome of progressive ataxia and dysarthria is common to all with the average onset in the third decade. The ADCA classification is not exhaustive. For example, a peripheral neuropathy is common in SCA3 and an upper limb tremor common in SCA12. Slow ocular saccades usually occur in SCA2. The polyQ SCAs exhibit anticipation except in SCA6 where the CAG repeat is short and relatively stable.

Differential Diagnosis

The differential diagnosis for cerebellar ataxia is wide. This discussion is limited to genetic causes. It can be difficult to differentiate the SCAs clinically and this often relies on genetic testing. Several SCAs have been identified that are not due to trinucleotide repeat expansions (**Table 4**). Late-onset DRPLA can appear similar to SCA. Often, a family history of SCA is not clear and recessive forms of ataxia may be considered, although these often have systemic features, which are not found in AD SCAs. However, several recessive forms are associated with cerebellar atrophy and have additional clinical

Table 2 Summary of genetic features of the trinucleotide repeat spinocerebellar ataxias

Disorder	*Gene*	*Trinucleotide repeat*	*Normal range*	*Pathological range*
SCA 1	*Ataxin-1*	CAG	6–44	40–82
SCA 2	*Ataxin-2*	CAG	14–31	32–200
SCA 3	*Ataxin-3*	CAG	12–40	61–84
SCA 6	*CACNA1A*	CAG	4–20	20–29
SCA 7	*Ataxin-7*	CAG	4–27	37–306
SCA 8	*Unknown*	CTG	15–91	>74
SCA 12	*PPP2R2B*	CAG	<29	55–78
SCA 17	*TBP*	CAG	25–42	47–63

CACNA1A = α_{1A} subunit of P/Q-type voltage gated calcium channel.
PPP2R2B = protein phosphatase 2 regulatory subunit B.
TBP = TATA binding protein.

Table 3 Harding's classification of the autosomal dominant cerebellar ataxias

ADCA I	*ADCA II*	*ADCA III*
Cerebellar syndrome with involvement of other regions within the CNS, e.g., pyramidal and extrapyramidal signs, supranuclear ophthalmoplegia and dementia	Cerebellar syndrome with pigmentary retinal degeneration	Pure cerebellar syndrome
SCA1, 2, 3, 8, 12, 17	SCA7	SCA6

Only the trinucleotide repeat SCAs are included in the table.

Table 4 Other genetically defined autosomal dominant SCAs

Disorder	*Gene*	*Clinical features*
SCA4	*PLEKHG4*	Ataxia, sensory neuropathy, pyramidal signs
SCA5	*βIII Spectrin*	Pure cerebellar syndrome
SCA10	*Ataxin10* (intronic ATTCT repeat)	Pure cerebellar syndrome with seizures
SCA11	*TTBK2*	Pure cerebellar syndrome
SCA13	*KCNC3*	Ataxia, developmental delay, onset usually in childhood
SCA14	*PRKCG*	Ataxia, myoclonus and tremor
SCA15	*ITPR1*	Pure cerebellar syndrome
SCA27	*FGF14*	Ataxia, tremor, orofacial dyskinesia, psychiatric features

PLEKHG4, pleckstrin homology domain-containing protein, family G, member 4.
TTBK2, tau tubulin kinase 2.
KCNC, A-type potassium channel.
PRKCG, protein kinase Cγ.
ITPR1, inositol 1,4,5-triphosphate receptor type 1.
FGF14, fibroblast growth factor 14.

features, including eye movement disorders and extrapyramidal features that may be reminiscent of the ADCA I disorders (**Table 6**).

Diagnostic Workup

MRI brain imaging typically shows cerebellar atrophy. There may be associated brainstem and cerebral cortex atrophy. PCR of DNA obtained from peripheral blood identifies the repeat expansion.

Management

Physiotherapy to prevent falls and to provide mobility aids should be offered. Speech therapy is also helpful. Spasticity, chorea, and dystonia may be amenable to drug treatment. Genetic counseling is important.

Prognosis

The prognosis is variable (years) and depends on disease severity, which is influenced as in other polyQ diseases by the trinucleotide repeat length.

Fragile X Tremor Ataxia Syndrome

Definition and History

Fragile X syndrome is the most common form of inherited mental retardation. It is due to a > 200 CGG repeat expansion located in the promoter region of *FMR1*, which causes complete or partial silencing of the gene. Fragile X tremor ataxia syndrome (FXTAS) was reported in 2001, affecting carriers of the CGG repeat in the premutation range (55–200).

Pathogenesis

Fragile X syndrome is associated with silencing of the *FMR1* gene on the X chromosome. In FXTAS, overexpression of *FMR1* and/or the presence of the expanded repeat may result in a toxic gain of function of *FMR1* mRNA. Eosinophillic ubiquitinated intranuclear inclusions form in neurons and astrocytes throughout the cerebral cortex, deep cerebellar nuclei, and brain stem. Inclusion number seems directly related to the number of repeats. Deep white matter change within the cerebral hemispheres and cerebellum is increasingly recognized.

Epidemiology

It has been estimated that ~1/800 males and 1/260 females carry the fragile X premutation. Up to 1/3000 males may have a lifetime risk of FXTAS. CGG repeat length appears to be directly related to disease severity and inversely related to the age of death.

Clinical Features and Diagnostic Criteria

Typical features are progressive action tremor and gait ataxia. Parkinsonism, cognitive decline, emotional problems, autonomic dysfunction, and peripheral neuropathy also occur. Cognitive problems mostly affect short-term memory and executive function. The condition typically affects older males with an average age of onset of 60. Women are less severely affected.

Differential Diagnosis

In the elderly population, acquired forms of ataxia with Parkinsonism and autonomic dysfunction may be considered, for example, multiple systems atrophy and paraneoplastic disorders. Other genetic conditions such as SCA can develop later in life. FXTAS may appear similar to

essential tremor and Parkinson's disease. Cognitive decline may predominate and with associated autonomic dysfunction, a diagnosis of dementia with Lewy bodies may be considered.

Diagnostic Workup

PCR of DNA obtained from peripheral blood identifies the CGG repeat expansion. MRI brain imaging typically shows high signal abnormality within the middle cerebellar peduncles and deep cerebral white matter change also occurs.

Management

Beta blockers and primidone may help the tremor. Standard SSRI antidepressants can be used for depression and anxiety. Physiotherapy and speech therapy may be helpful.

Prognosis

Currently, prognostic details are imprecise. However, FXTAS is a progressive disorder and over several years, the patient may become dependent on a walking aid. Swallowing problems can occur late in the disorder.

Friedreich's Ataxia

Definition and History

Nicholaus Friedreich described this autosomal recessive disease in 1863. In 1996, expanded GAA trinucleotide repeats in the first intron of the *FRDA* gene on chromosome 9q were identified.

Pathogenesis

Pathologically, there is degeneration in the spinal cord of the spinocerebellar tracts, the pyramidal tracts, and the dorsal columns as well as neurodegeneration in the cerebellum and medulla.

FRDA encodes frataxin, located on the inner mitochondrial membrane and is involved in the synthesis of mitochondrial iron–sulfur cluster containing proteins. Frataxin expression is downregulated in Friedreich's ataxia (FA) resulting in an increased mitochondrial oxidative stress and cell death. There is a correlation between the severity of some clinical features and the age of onset with the shorter of the two expanded repeats.

GAA repeat-induced *FRDA* repression may occur by the repeat impairing *FRDA* transcription and sequestering transcription factors, including RNA polymerase to the 'sticky' repeat. Recently it has been suggested that the GAA repeat affects the chromatin packaging of *FRDA*, rendering it inaccessible to transcription factors. Changes in histone acetylation and methylation found in association with inaccessible condensed chromatin have been found in association with the GAA repeat in downregulated *FRDA* genes.

Epidemiology

FA is the most common hereditary ataxia with a prevalence of ~1/50 000 and the carrier rate in the range 1/50–1/100. The normal repeat length is less than 33 with most expanded disease-causing alleles having from 67 to 1700 repeats. Most patients have repeats of between 600 and 1200. Approximately 2% of patients are compound heterozygotes for a GAA repeat expansion and a point mutation.

Clinical Features and Diagnostic Criteria

Harding's essential clinical features of FA are autosomal recessive inheritance, onset before the age of 25 (although with the advent of genetic testing onset at later ages has become apparent), progressive limb and gait ataxia, absent deep tendon reflexes in the lower limbs, and electrophysiological evidence of a sensory axonal neuropathy. Within 5 years, there should be dysarthria, areflexia, distal loss of proprioception and vibration sense, extensor plantar reflexes, and pyramidal leg weakness. There is associated cardiomyopathy, scoliosis, pes cavus, optic atrophy, hearing loss, extrapyramidal features, and diabetes in some patients. The Acadian form is milder and without cardiomyopathy. Late onset and FA with retained reflexes also occurs.

Differential Diagnosis

Disorders phenotypically similar to FA may lack (as in FA) or possess significant cerebellar atrophy, which can be a useful differentiating feature. There is a large collection of autosomal recessive cerebellar ataxias and several of the more commonly encountered conditions are summarized in **Tables 5** and **6**. Many of these conditions develop in the teens, similar to FA.

Diagnostic WorkUp

PCR and Southern blotting of DNA obtained from peripheral blood identifies the GAA repeat expansion. Sequencing of the FRDA gene may be required to look for a point mutation if only a single GAA expansion is found. An ECG and echocardiogram should be performed

Table 5 Autosomal recessive disorder with similar phenotype to Friedreich's ataxia, including minimal cerebellar atrophy

Disorder	*Gene*	*Clinical features*
Friedreich's ataxia	*FRDA*	See text
Ataxia with vitamin E deficiency	*TTPA*	Ataxia, peripheral neuropathy, cardiomyopathy, head tremor, retinitis pigmentosa, low serum vitamin E
Abetaliproteinaemia	*MTP*	Ataxia, peripheral neuropathy, lipid malabsorption, hypocholesterolaemia, acanthocytosis, retinitis pigmentosa
Refsum's disease	*PNYH, PEX7*	Cerebellar ataxia, peripheral neuropathy (can be acute), retinitis pigmentosa, anosmia, deafness, skeletal abnormalities, icthyosis, renal failure, cardiomyopathy

TTPA, α-tocopherol transfer protein.
MTP, microsomal triglyceride transfer protein.
PNYH, phytanoyl-CoA hydroxylase.
PEX7, peroxin 7.

due to the hypertrophic cardiomyopathy, present in up to two thirds of patients and blood glucose measured. These should be regularly monitored.

Management

A multidisciplinary approach with physiotherapy, occupational and speech therapy is needed. Mobility aids are required by the majority of patients. Genetic counseling should be offered. Cardiomyopathy and diabetes may require expert advice. Specific therapies used in FA include vitamin E and coenzyme Q10, which may improve cardiac function. Idebanone may improve cardiac function. Several agents have been suggested to increase frataxin expression, including erythropoietin and histone deacetylase inhibitors, but these drugs are not recommended as yet.

Prognosis

The rate of progression of FA is variable with average time from symptom onset to wheelchair dependence being about 10 years. In 1996, the average interval from symptom onset to death was ~36 years. Death is often related to cardiomyopathy or aspiration pneumonia. Improvement in the management of cardiomyopathy may prolong survival times.

Table 6 Autosomal recessive cerebellar ataxias with prominent cerebellar atrophy

Disorder	*Gene*	*Clinical features*
Late onset Tay Sach's disease	*HEXA*	Ataxia, amyotrophy, psychiatric problems, spasticity, seizures
Cerebrotendinous xanthomatosis	*CYP27A1*	Ataxia, pyramidal/extrapyramidal features, peripheral neuropathy, tendon xanthomata, diffuse high signal on MRI brain
POLG disorders (MIRAS)	*POLG*	Ataxia, dorsal column dysfunction, peripheral neuropathy, cognitive features, myoclonus and other involuntary movements, bilateral cerebellar high signal on MRI, common in Finland
Ataxia telangiectasia	*ATM*	Ataxia, oculomotor apraxia, oculocutaneous telangiectasia, extrapyramidal features, immunodeficiency, cancer susceptibility, radiosensitive, elevated serum AFP
Ataxia telangiectasia-like	*MRE11*	Similar to ataxia telangiectasia but later onset, lacks telangiectasia, later onset, slower progression, normal AFP
Ataxia with oculomotor apraxia type 1 (AOA1)	*APTX*	Ataxia, sensorimotor neuropathy, dorsal column involvement, oculomotor apraxia, gaze impersistence, extrapyramidal signs, cognitive impairment, hypoalbuminaemia, hypercholesterolaemia, normal AFP, vermian cerebellar atrophy, onset usually in childhood but can be later
Ataxia with oculomotor apraxia type 2 (AOA2)	*SETX*	Similar to AOA1 but later onset (teens), oculomotor apraxia may be less, normal albumin and cholesterol, elevated AFP, vermian cerebellar atrophy. May appear similar to Friedreich's ataxia

Ataxia telangiectasia and ataxia-telangiectasia like usually have childhood onset with the other conditions often developing in the teens or early 20s.
HEXA, hexosaminidase A.
CYP27, sterol 27 hydroxylase.
POLG, DNA polymerase γ.
ATM, ataxia telangiectasia mutated.
MRE11, meiotic recombination 11.
APTX, aprataxin.
SETX, senetaxin.
MIRAS, Mitochondrial Recessive Ataxia Syndrome.

Summary

The trinucleotide repeat diseases are individually rare but as a group are not uncommonly responsible for disabling movement disorders. One of the major challenges of the future is to develop specific treatments for these diseases.

See also: Aprataxin; Ataxia; Ataxia with Isolated Vitamin E Deficiency; Ataxia-Telangiectasia; Ataxin; ATM Gene; Atrophin-1; Cerebrotendinous Xanthomatosis; Co-enzyme Q_{10}; Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS); Friedreich's Ataxia and Variants; Huntington, George; Huntington's Disease: Genetics; Huntington's Disease-like 2; Huntington's Disease; Idebenone and Friedreich Ataxia; Junctophilin; Refsum Disease- a Disorder of Peroxisomal Alpha-oxidation; SCA1; SCA2; SCA3, Machado–Joseph Disease; SCA4; SCA5; SCA6; SCA7, Spinocerebellar Ataxia with Macular Dystrophy; SCA8; SCA10; SCA11; SCA12; SCA13, 14, 15, and 16; SCA17; Senataxin; Spinocerebellar Ataxia Type 19, 20, 21, 22, 23, 26; Spinocerebellar Ataxias Genetics; Tocopherol Transfer Protein and Ataxia with Vitamin E Deficiency; Westphal Variant.

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http://neuromuscular.wustl.edu/ – Neuromuscular home page – database of genetic disorders.

http://www.geneclinics.org – Gene Tests – database with regular reviews of genetic disorders.

TWSTRS

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Glossary

Anterior sagittal shift – Dystonic deviation of the chin forward rather than downward.

Anterocollis – Dystonic deviation of the chin downward in the sagittal plane toward the chest.

Interrater reliability – The extent to which a rating instrument yields reproducible, accurate, consistent, and stable results when scored by different observers.

Lateral shift – Horizontal displacement of the base of the neck in the absence of tilting of the ear toward the ipsilateral shoulder (unless accompanied by

laterocollis, which usually occurs in the opposite direction).
Laterocollis – Dystonic tilting of the head laterally in the coronal plane, moving the ear toward the ipsilateral shoulder.
Posterior sagittal shift – Backward displacement of the head without upward deviation of the chin.
Retrocollis – Dystonic extension of the head, producing upward excursion of the chin.
Rotational torticollis – Dystonic rotation of the nose and chin around the longitudinal axis toward the shoulder.
Sensory trick (gestes antagonistes) – A pathognomonic feature of CD characterized by the transient correction of head posture with the use of maneuvers such as touching the face, neck, or head with the hand or an object.
Tsui scale – An objective CD rating scale developed by Tsui and colleagues, evaluating the amplitude and duration of sustained movements and head tremor and the presence of shoulder elevation.
Validity – The extent to which a rating instrument accurately measures what it is designed or purports to measure. *Content validity* refers to the extent to which a scale includes all relevant dimensions of the condition being measured and whether it represents these in reasonably weighted proportions. *Construct validity* evaluates whether the rating instrument measures what it intends to measure, and does not measure what it is not intended to measure, predictably distinguishing between groups and producing results consistent with a predetermined theoretical framework. *Convergent validity* refers to the correlation with other measures of the same construct or attribute. In addition, the *responsiveness* of the rating scale to detect clinically significant change is considered an aspect of validity.

TWSTRS

TWSTRS, the Toronto Western Spasmodic Torticollis Rating Scale, developed by Consky and Lang in 1990, is a multidimensional objective and subjective rating scale for cervical dystonia (CD) with subscales for the relevant and distinct clinical dimensions of CD: impairment severity, associated disability and pain (see **Figure 1**). It has been widely accepted and used as an outcome measure in therapeutic intervention studies, including Botulinum toxin (BoNT) therapy, oral pharmacotherapy, and surgical trials for CD. It also has practical applicability in a clinical setting in the ongoing management of individual CD patients. The clinimetric properties of the TWSTRS have been defined in a number of studies that have demonstrated TWSTRS reliability, validity, and responsiveness to change following treatment. A teaching tape for the TWSTRS severity scale and a videotape protocol that contains the elements of a standardized examination for CD have been developed to promote consistent application.

The TWSTRS Severity Scale

The severity scale objectively quantifies the dynamic and varied clinical spectrum of the involuntary movements or abnormal postures of the head and neck seen in CD. The *maximum amplitude of excursion* (A) (sustained or unsustained) is determined on the basis of the standardized examination, the patient being asked to allow the head to deviate fully without resistance or the use of sensory tricks, after activating and distracting maneuvers, walking and sitting, and is determined for all dominant and minor planes of head deviation: rotational torticollis (0–4), laterocollis (0–3), anterocollis or retrocollis (0–3), lateral shift (0–1), and sagittal shift (0–1). The *duration factor* (B) (0–10) for the dominant deviation quantifies the dynamic and variable character of CD, which may change significantly with posture and activity. To account for this variability, the duration factor assesses first the proportion of time for which there is any deviation from a neutral position and second the proportion of time for which the amplitude of the deviation is either predominantly maximal or submaximal. The *efficacy of sensory tricks* (C) (0–2) is a reflection of CD severity. The effectiveness of sensory tricks may vary considerably among patients, may wane over time, and may change following therapeutic intervention. Intermittent or sustained *elevation or anterior displacement of the shoulder* (D) (0–3) is frequently present, commonly ipsilateral to the direction of the turn or tilt. Examination of the *range of active motion* (E) (0–4) in each of the three axes rotational, lateral tilting, and flexion and extension, without the aid of sensory tricks, is also determined. CD severity is also quantified by determining the average *time* (F) (0–4) on two attempts for whcih the patient is able to maintain the head within 10° of a neutral position with active resistance but without the use of sensory tricks. The total TWSTRS Severity Scale score is a summation of items A–F with a maximum score of 35.

The TWSTRS Disability Scale

Disability is task-specific and is not necessarily directly proportional to the clinical severity of the abnormal postures and movements of CD. The direction of head deviation, coexisting dystonic involvement of other sites, pain,

depression, sleep impairment, coping strategies, the availability of support, and the effectiveness of treatment may all significantly influence the level of disability experienced by an individual CD patient. The TWSTRS Disability Scale consists of a broadly based assessment of the performance of daily activities that may be affected by CD. General as well as specific activity categories are assayed, including work performance (employment or domestic work), activities of daily living (hygiene, dressing, feeding), reading, television viewing, driving, and leisure activities outside the home. The extent to which social embarrassment rather than head deviation or pain specifically contributes to disability was initially included as an inverse item but was deleted following initial testing of the scale. The maximum TWSTRS Disability Scale score is 30.

The TWSTRS Pain Scale

Cervical pain is a frequent and prominent feature of CD that often significantly contributes to disability and impairment of quality of life. It is a separate and distinct aspect of CD that may not be directly correlated with

The toronto western spasmodic torticollis rating scale (TWSTRS)

I. TWSTRS Severity Scale

A. Maximal excursion

Rate maximum amplitude of excursion asking patient not to oppose the abnormal movement; examiner may use distracting or aggravating maneuvers. When degree of deviation is between two scores, chose the higher of the two

1. Rotation (turn: right or left)
0 None
1 Slight (<1/4 range) (1–22°)
2 Mild (1/4–1/2 range) (23–45°)
3 Moderate (1/2–3/4 range) (46–67°)
4 Severe (>3/4 range) (68–90°)

2. Laterocollis (tilt: right or left) (exclude shoulder elevation)
0 None
1 Mild (1–15°)
2 Moderate (16–35°)
3 Severe (> 35°)

3. Anterocollis/retrocollis (a or b)
a) Anterocollis
0 None
1 Mild downward deviation of chin
2 Moderate downward deviation (approximates 1/2 possible range)
3 Severe (chin approximates chest)

b) Retrocollis
0 None
1 Mild backward deviation of vertex with upward deviation of chin
2 Moderate backward deviation (approximates '/z possible range)
3 Severe (approximates full range)

4. Lateral shift (right or left)
0 Absent
1 Present

5. Sagittal shift (forward or backward)
0 Absent
1 Present

Figure 1 (Continued)

the severity of motor impairment. The TWSTRS Pain Scale includes an assessment of pain intensity, pain duration, as well as the affective components of pain resulting in disability. A weighted dimensional severity score (0–10) for the patients usual, best, and worst pain, a second-scale item which evaluates the duration of pain typically experienced during the preceding week (0–5), and a third-scale item which assesses the contribution of pain to the disability (0–5) are scored with a maximum TWSTRS Pain Scale score of 20.

The TWSTRS (total) score is the sum of the TWSTRS Severity Scale score (0–35), the TWSTRS Disability Scale score (0–30), and the TWSTRS Pain Scale score (0–20) with a maximum score of 85.

Reliability and validity and comparative testing of TWSTRS

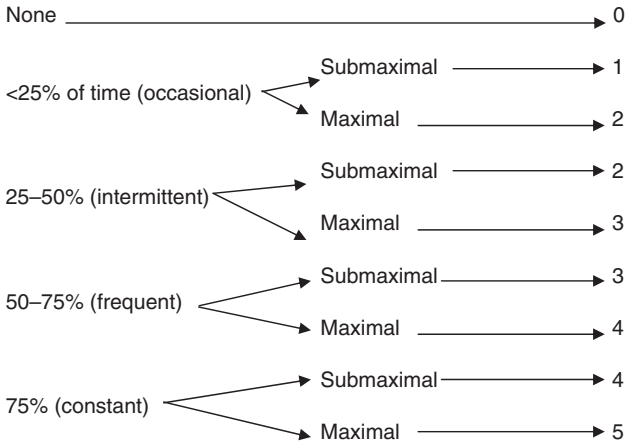
Initial evaluation of TWSTRS by Consky, Lang, and colleagues showed substantial interobserver agreement for each component of the TWSTRS Severity Scale, for the whole Severity Scale, and for the TWSTRS Disability and Pain Scales. The average severity component of the TWSTRS Pain Scale was added subsequently and was not included in the initial testing. High interrater reliability for the change in patients' scores prior to and 6 weeks following BoNT treatment was demonstrated, indicating the responsiveness of the scales for objectively detecting clinical change in severity. Convergent validity of TWSTRS was evidenced by the high correlation of changes in TWSTRS

B. Duration factor

Provide an overall score estimated through the course of the standardized examination after estimating maximal excursion (exclusive of asking patient to allow head to deviate maximally). Weighted × 2 (see schematic representation of scoring duration)

0 None
1 Occasional deviation (<25% of the time), most often submaximal
2 Occasional deviation (<25% of the time), often maximal or intermittent deviation (25–50% of the time), most often submaximal
3 Intermittent deviation (25–50% of the time) often maximal or frequent deviation (50–75% of the time), most often submaximal
4 Frequent deviation (50–75% of the time), often maximal or constant deviation (>75% of the time), most of ten submaximal
5 Constant deviation (>75% of the time), often maximal

Schematic representation*



**The rater determines the proportion of time that the dystonic head posturing is present (left column) and then decides whether the deviations are most often maximal or submaximal, having previously determined the maximal excursion score (A).*

Figure 1 (Continued)

Severity Scale scores from videotape raters with patients' self-reported overall percent improvement. There was also substantial agreement between changes in total TWSTRS Severity Scale scores of videotape raters with changes in patient self-reported TWSTRS Disability and Pain Scale scores following BoNT treatment. The utility of the standardized TWSTRS Videotape Protocol was reflected by the substantial agreement between blinded videotape raters and a direct live examiner.

Further reliability testing of the TWSTRS severity subscale was undertaken by Comella and colleagues in the process of developing a teaching tape for scoring the TWSTRS Severity Scale. There was statistically significant interrater agreement for all individual components as well as for the complete TWSTRS Severity Scale based on the standardized videotape protocol.

Goertelmeyer and colleagues also demonstrated high interrater reliability and high sensitivity to change following BoNT as indicated by the mean change in TWSTRS Severity score, and recently a study by Kaji and colleagues confirmed the high interrater reliability of the TWSTRS Severity Scale

Tarsy compared TWSTRS to the Tsui scale and to a physician-rated subjective global improvement scale in CD patients treated with BoNT. There was a significant correlation between the posttreatment reduction of the Tsui scale and total TWSTRS scores as well as the TWSTRS Severity Scale scores. Both the TWSTRS and the Tsui score reduction rates also correlated with the global improvement scale. However, the TWSTRS Disability and Severity Scale score reduction rates showed a relatively weak correlation. TWSTRS Pain Scale score reduction also showed a weak or no correlation with the TWSTRS Severity scores or the Tsui scale scores, with some patients experiencing a significant reduction in pain scores despite the absence of objective improvement in either the TWSTRS Severity score or the Tsui scale score. The lack of correlation further

C. Effect of sensory tricks

0 Complete relief by one or more tricks
1 Partial or only limited relief by tricks
2 Little or no benefit from tricks

D. Shoulder elevation/anterior displacement

0 Absent
1 Mild (<1/3 possible range), intermittent or constant
2 Moderate (1/3–2/3 possible range) and constant (>75% of the time) or severe (>2/3 possible range) and intermittent
3 Severe and constant

E. Range of motion (without aid of sensory tricks)

If limitation occurs in more than one plane of motion use individual score that is highest

0 Able to move to extreme opposite position
1 Able to move head well past midline but not to extreme opposite position
2 Able to move head barely past midline
3 Able to move head toward but not past midline
4 Barely able to move head beyond abnormal posture

F. Time (*up to 60 s*) for which patient is able to maintain head within 10° of neutral position without the use of sensory 'tricks' (*mean of two attempts*)

0 0 > 60 s
1 46–60 s
2 31–45 s
3 16–30 s
4 <15 s

Total severity score = sum of A–F. Maximum score = 35

Figure 1 (Continued)

emphasizes that the clinical severity, disability, and pain subscales of TWSTRS measure distinct and importantly different attributes of CD.

Lindeboom and colleagues evaluated the extent to which the therapeutic effectiveness of BoNT is captured by various rating instruments. Changes in objective motor impairment evaluated with the Tsui scale correlated poorly with the TWSTRS Pain Scale, TWSTRS Disability Scale, and handicap and quality-of-life (HRQoL) as measured by subscales of the Medical Outcome Study Scale. The decision to continue BoNT treatment in this study correlated with a meaningful improvement to the patient as reflected by changes in TWSTRS Disability and HRQoL scale scores rather than changes in motor severity Tsui scores. These findings further indicate that each TWSTRS subscale assesses different aspects of the disorder and its effect on patients.

Comella and colleagues investigated the internal consistency of TWSTRS, determined the factor structure of TWSTRS, and assessed whether the identified factors form rational domains. High internal consistency was demonstrated for the TWSTRS scale as a whole. Factor structure analysis showed three clinically distinct factors: a motor severity factor, a disability factor, and a pain factor, again indicating that the severity, disability, and pain subscales of TWSTRS form rational domains that assess independent, different features of CD. Items found to contribute least to the factor structure included the effect of sensory tricks and the dichotomous items for anterior and sagittal shift.

Grafe and Goertelmeyer undertook a study to demonstrate the construct validity of the TWSTRS Severity Scale and examine the responsiveness of the factorial scores in a trial comparing different BoNT brands.

II. TWSTRS Disability Scale

1. Work (occupation or housework/home management)

0 No difficulty
1 Normal work expectations with satisfactory performance at usual level of occupation but some interference by torticollis
2 Most activities unlimited, selected activities very difficult and hampered but still possible with satisfactory performance
3 Working at lower than usual occupational level; most activities ham peers, all possible but with less than satisfactory performance in some activities
4 Unable to engage in voluntary or gainful employment; still able to perform some domestic responsibilities satisfactorily
5 Marginal or no ability to perform domestic responsibilities

2. Activities of daily living
(e.g., feeding, dressing, hygiene, includes washing, shaving, makeup, etc.)

0 No difficulty with any activity
1 Activities unlimited but some interference by torticollis
2 Most activities unlimited, selected activities very difficult and hampered but still possible using simple tricks
3 Most activities hampered or laborious but still possible; may use extreme 'tricks'
4 All activities impaired; some impossible or require assistance
5 Dependent on others in most self-care tasks

3. Driving

0 No difficulty (or has never driven a car)
1 Unlimited ability to drive but bothered by torticollis
2 Unlimited ability to drive but requires 'tricks' (including touching or holding face, holding head against head rest) to control torticollis
3 Can drive only short distances
4 Usually cannot drive because of torticollis
5 Unable to drive and cannot ride in a car for long stretches as a passenger because of torticollis

Figure 1 (Continued)

Factorial analysis revealed a clinically meaningful four factor solution. Factor one was primarily loaded by rotation, duration, range of movement, and time in midline; factor two by laterocollis and shoulder elevation/anterior displacement; factor three by lateral shift and sensory tricks; and factor four by retrocollis/anterocollis and sagittal shift. The total TWSTRS Severity Scale score as well as the factorial subscores was sensitive to change due to

4. Reading

0 No difficulty
1 Unlimited ability to read in normal seated position but bothered by torticollis
2 Unlimited ability to read in normal seated position but requires use of 'tricks' to control torticollis
3 Unlimited ability to read but requires extensive measures to control torticollis or is able to read only in nonseated position (e.g., lying down)
4 Limited ability to read because of torticollis despite tricks
5 Unable to read more than a few sentences because of torticollis

5. Television

0 No difficulty
1 Unlimited ability to watch television in normal seated position but bothered by torticollis
2 Unlimited ability to watch television in normal seated position but requires the use of tricks to control torticollis
3 Unlimited ability to watch television but requires extensive measures to control torticollis or is able to view only in nonseated position (e.g., lying down)
4 Limited ability to watch television because of torticollis
5 Unable to watch television for more than a few minutes because of torticollis

6. Activities outside the home

(e.g., shopping, walking about, movies, dining, and other recreational activities)

0 No difficulty
1 Unlimited activities but bothered by torticollis
2 Unlimited activities but requires simple 'tricks' to accomplish
3 Accomplishes activities only when accompanied by others because of torticollis
4 Limited activities outside home; certain activities impossible or given up because of torticollis
5 Rarely if ever engages in activities outside the home

Total disability score = sum of 1–6. Maximum score = 30

Figure 1 (Continued)

the therapeutic intervention with the exception of factor three (lateral shift and sensory tricks). The latter finding is consistent with the study of Comella and colleagues, which found a lack of variability of scale items for shift and sensory tricks. There were no compensation effects between the single items. The study's findings provide further support that the TWSTRS Severity Scale is a valid and responsive tool for assessing change following therapeutic intervention.

Several deficiencies and ambiguities of TWSTRS have been identified by Comella and others, including the absence of a scale component to assess the presence and severity of associated dystonic head tremor, the lack of the specification of midline and the full range of active motion in each of the three planes, and the absence of specification of the duration of relief provided by the use of sensory tricks. Elimination or modification of the dichotomous items for lateral and sagittal shift as well as the item for the effect of sensory tricks has been suggested because of the lack of variability of these items. Further data-driven refinement and testing of TWSTRS are required.

Substantial evidence for TWSTRS reliability and validity as well as its responsiveness to detect a clinically significant change following treatment has steadily accumulated. TWSTRS encompasses the heterogeneity and variability of the clinical features of CD, and the subscales for severity, disability, and pain evaluate distinct aspects of CD. Consistent application of TWSTRS is promoted by the standardized examination contained in the TWSTRS Videotape Protocol as well as the availability of a teaching

III. TWSTRS Pain Scale

1. Rate the severity of neck pain during the last week on a scale of 0–10 where a score of 0 represents no pain and 10 represents the most excruciating pain imaginable

Best 0–10
Worst 0–10
Usual 0–10

Severity = [(2 × usual) + best + worst]/4

Maximum score = 10

2. Rate the duration of neck pain

0 None
1 Present <10%' of the time
2 Present 10%–<25% of the time
3 Present 25%–<50% of the time
4 Present 50%–<75% of the time
5 Present >75% of the time

3. Rate the degree to which pain contributes to disability

0 No limitation or interference from pain
1 Pain is quite bothersome but not a source of disability
2 Pain definitely interferes with some tasks but is not a major contributor to disability
3 Pain accounts for some (less than half) but not all disability
4 Pain is a major source of difficulty with activities; separate from this, head pulling is also a source of some (less than half) disability
5 Pain is the major source of disability; without it most impaired activities could be performed quite satisfactorily despite the head pulling

Total pain scale score = sum of 1–3. Maximum score = 20

TWSTRS score = Severity + disability + pain Maximum score = 85

Figure 1 (Continued)

TWSTRS videotape protocol

1. **Standing-viewed from front, side, and back x 10 s each**

2. **Walking-20 feet back and forth**

   a) Without instructions × 2
   b) With instructions not to resist deviation (i.e., allow head to deviate to maximum)× 2

3. **Sitting-in preferred or most comfortable position**

   a) Without instructions × 30 s
   b) With instructions not to resist deviation × 30 s

4. **Distracting or activating maneuvers: (sitting) (R and L separately) each× 10 s**

   a) Finger tapping
   b) Opening and closing fist
   c) Pronation and supination forearm
   d) Arms outstretched, held under nose, finger to nose × 3
   e) Foot tapping

5. **Time in midline**

   With active resistance to deviation but without aid of sensory tricks or support. Patient asked to maintain head in midline for as long as possible-maximum 60 s× 2 attempts. Patient instructed not to talk.

6. **Effect of 'tricks'**

   Including touching side of face, holding chin, holding back of neck or head, pressing against wall behind head, and other preferred tricks used by patient

7. **Active range of movement (× 2 each time)**

   Rotation, lateral flexion, forward flexion, extension

8. **Writing name, sentence, repetitive words or phrase × 10 s**

9. **Lying supine × 20 s**

Figure 1 The Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS).

tape for the TWSTRS Severity Scale. TWSTRS has gained widespread acceptance and is the outcome measure most commonly used in CD intervention studies.

See also: Botulinum Toxin; Cervical Dystonia; Dystonia; Fahn–Marsden Rating Scale.

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www.mdvu.org/library/ratingscales/dystonia/ – TWSTRS rating scale, TWSTRS examination and injection record.
www.movementdisorders.org/publications/audio_visuals.php – TWSTRS training videotape.

U

Unified Parkinson's Disease Rating Scale (UPDRS) and The Movement-Disorder Society Sponsored-unified Parkinson's Disease Rating Scale (MDS-UPDRS)

C G Goetz

The UPDRS

The Unified Parkinson's Disease Rating Scale (UPDRS) was originally developed in the 1980s and has become the most widely used clinical rating scale for Parkinson's disease (PD). In almost all instances, for clinical trials assessing new treatments for PD, the UPDRS has been the scale used to determine the treatment-related benefits. The original scale was composed of four parts: part I assesses behavioral problems such as intellectual decline, hallucinations, and depression; part II assesses patients' perceptions of their ability to carry out activities of daily living, including dressing, walking, and eating; part III covers the motor evaluation of disability and includes ratings for tremor, slowness (bradykinesia), stiffness (rigidity), and balance; part IV covers a number of treatment complications including ratings of involuntary movements (dyskinesias), painful cramps (dystonia), and irregular medication responses (motor fluctuations). The goal of the UPDRS was to provide a comprehensive, practical, and easy to administer scale that can be used across all patients regardless of severity, medication treatment, or age. Clinimetric testing was performed on components of the original UPDRS; recommendations were published on enhancing uniform application of the scale, and a teaching video-tape was formulated.

Needs for Changes to Reflect Scientific Advances

Over its 20 years of usage, the UPDRS has been lauded as the best available rating scale for rating PD. Nonetheless, over time, many investigators have commented on some weaknesses of the scale, including a number of unclear questions or answers. Further, many current research trials increasingly focus on very early PD, and the scale was not designed to detect patterns of changes that occur particularly in mildly disabled patients. Finally, with scientific advances, experts now recognize several aspects of PD that are not assessed with the original UPDRS.

In 2001, the Movement Disorder Society (MDS) sponsored a critique of the UPDRS, and the summary document recommended the development of a new version of the UPDRS. According to the published recommendations from this critique, the new version should retain the core four-part structure of the original scale, but resolve identified ambiguities, provide clear instructions, and incorporate the clinically pertinent PD-related problems poorly captured in the original version. The effort resulted in a new scale, termed the MDS-sponsored UPDRS revision (MDS-UPDRS). This version was presented in a full format in June 2008 and has undergone clinimetric testing in its original English version. Official foreign translations and introduction of the scale into clinical trials are anticipated.

How is the New Scale Different?

Patient/Caregiver Involvement

The new scale has direct patient and caregiver involvement, and many questions as a patient-based questionnaire are formulated in standard language. This questionnaire can be filled in the waiting room or after the physician visit. These questions focus on the activities of daily living and several behaviors such as fatigue and anxious mood. The new scale is organized so that all questions have a consistency that is anchored in the concept that a zero means normal or no problems; one slight problems; two mild problems; three moderate problems; and four severe

problems. In all instances, descriptive language is added for each question so that the patient and rater have clear explanations.

New Questions

The MDS-UPDRS contains more questions than the UPDRS (**Table 1**), but because of the questionnaire methodology for many items, the time estimate for the entire scale is estimated to remain ~30 min for the physician.

More Emphasis on Rating Mild Impairment/Disability

The original UPDRS placed considerable emphasis on marked and severe disabilities or impairments. The scientific advances since the original scale's development, along with the growing emphasis on neuroprotection and early therapies, prompted a strong recommendation in the published critique to adapt the scale so that it measured more mild deficits and allowed detection of small changes in early disease. In order to respect the limitation of five rating options for each item, this decision necessarily collapses impairments that separated severe versus marked impairments in favor of allowing a wider range of differentiation among the lower ranges of disability.

Cultural Sensitivity and Official Non-English Translations

The published critique identified cultural biases in the original scale and considered some questions to be restrictive to developed countries. Further, the original scale focused on specific activities and was not tailored to assess the impact of PD on activities (hobbies, personal interests) that are particularly important to an individual subject. The MDS-UPDRS addresses these issues first by focusing on the experiences (e.g., feeding) rather than tasks (e.g., handling utensils). Second, a new question addresses the impact of PD disability on the performance of tasks related to areas of personal interest, without specifying a given activity. This question allows patients to sculpt their response to consider areas of personal importance, remaining bias-free, applying to piano playing, ping-pong, or raising snakes with equal specificity. This question is aimed to relate to different activities for different patients, but allows each subject to choose a key activity of interest for a focused response. Finally, though the first phases of testing use only an English version, official translations in multiple languages will be prepared and tested.

Table 1 MDS-UPDRS

Part I: Nonmotor aspects of experiences of daily living (13 questions)
- Cognitive impairment
- Hallucinations and psychosis
- Depressed mood
- Anxious mood[a]
- Apathy
- Features of dopamine dysregulation syndrome[a]
- Sleep problems
- Daytime sleepiness[a]
- Pain and other sensations
- Urinary problems[a]
- Constipation problems[a]
- Lightheadedness on standing
- Fatigue[a]

Part II: Motor experiences of daily living (13 questions)
- Speech
- Saliva and drooling
- Chewing and swallowing
- Eating tasks
- Dressing
- Hygiene
- Handwriting
- Doing hobbies and other activities[a]
- Turning in bed
- Tremor impact on activities
- Getting in and out of bed
- Walking and balance
- Freezing

Part III: Motor examination (18 questions)
- Speech
- Facial expression
- Rigidity
- Finger tapping
- Hand movements
- Pronation–supination movements of hands
- Toe tapping[a]
- Leg agility
- Arising from chair
- Gait
- Freezing of gait
- Postural stability
- Posture
- Global spontaneity of movement (body bradykinesia)
- Postural tremor of hands
- Kinetic tremor of hands[a]
- Rest tremor amplitude
- Constancy of rest tremor[a]

Part IV: Motor complications (6 questions)
- Dyskinesias: time spent with dyskinesias
- Dyskinesias: functional impact of dyskinesias
- Dykinesia: painful off-state dystonia
- Motor fluctuations: time spent in the off state
- Motor fluctuations: functional impact of fluctuations
- Motor fluctuations: complexity of motor fluctuations

[a]Are domains not previously assessed.
The unmarked items are newly written, but were covered in some capacity in the original UPDRS.

Clinimetric Testing Program

The MDS-UPDRS has been tested in a direct comparison with the original version and found to have a very strong clinimetric profile. This effort involved over 800 patients with Parkinson's disease and had both Caucasian and minority racial/ethnic representation. The factor structure of the new scale favors utilizing each of

the four parts separately rather than collapsing all values into a final 'total' score. For official non-English translations, a centralized clinimetric program exists within the MDS so that each translation effort meets standardized clinimetric criteria. A teaching tape is also part of the training program so that standardized methods of application are utilized.

See also: Parkinson's Disease: Definition, Diagnosis, and Management.

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Unverricht–Lundborg's Disease

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Glossary

Action myoclonus – Myoclonic jerks provoked by the intentional movements.
Cystatin B – Its function is to ensure protection of cells against the proteolytic activity of lysosomal peptidases that are released occasionally during normal cell death or activated by proliferating cancer cells.
Progressive myoclonus epilepsies (PME) – Represent a heterogeneous group of often familial, sometimes sporadic, diseases that are characterized by the occurrence of epileptic seizures, prominent myoclonus, and a progressive course.
Sensitive-myoclonus – Myoclonic jerks provoked by light, touching, noise, especially emotion.
Unverricht–Lundborg disease – PME characterized by stimulus-sensitive action myoclonus, clonic–tonic–clonic epileptic seizures, and ataxia.

Introduction

ULD, first described by Unverricht in 1891 and by Lundborg in 1903, is a progressive myoclonus epilepsy (PME) type 1 (EPM1) characterized by myoclonus, epilepsy, and ataxia, without major cognitive decline.

The disease is inherited in an autosomal recessive manner and it is caused by an unstable expansion of a 12-nucleotide (dodecamer) repeat 5-CCC-CGC-CCC-GCG-3t in the promoter region of the cystatin B (CSTB) gene, mapping on CR 21q22.31.

Cystatin B is an inhibitor of cysteine proteases that are thought to be involved in the initiation of apoptosis. With mutation in cystatin B gene and loss of inhibition of cysteine proteases, apoptosis proceeds uncontrolled.

Although ULD occurs worldwide, its prevalence is increased in certain populations, for example, in Italy, southern France, and in the North African countries of Tunisia, Algeria, and Morocco. The age of onset is between 6 and 16 years and the symptom(s) at onset can be either myoclonic jerks and/or generalized tonic–clonic seizures. The most incapacitating symptom is stimulus-sensitive action myoclonus, exacerbated by light, noise, physical exertion, and emotions. Tonic–clonic seizures, often preceded by massive myoclonic jerks, are the most common type of epileptic seizures in ULD patients. EEGs show normal or mildly slow background activity (BA), brief bursts of generalized spike-wave discharges (GSWD) both spontaneous and provoked by intermittent photic stimulation (IPS). Classic treatment includes Valproate usually in combination with

Clonazepam. Levetiracetam and Zonisamide have been recently reported to be efficacious in ULD. Although the disease is progressive, the condition of patients affected by ULD appears less serious than reported in the past. The intensity of myoclonus is mild at the disease onset and worsens only during the first 5 to 10 years of illness, to stabilize thereafter; epilepsy has an active phase in the early 10 years of illness and remits in most patients thereafter.

Pathogenesis

The pathogenesis by which a deficit of CSTB leads to ULD has not yet been elucidated. CSTB knock-out mice display a behavioral phenotype similar to that shown by human patients affected by ULD, and the analysis of the CSTB-deficient brain reveals the presence of apoptosis mainly involving cerebellar granular cells and cerebellar atrophy.

CSTB knock-out mice show an increased susceptibility to seizures and a greater degree of neuronal damage after seizures than WT mice. It has been hypothesized that the lack of CSTB, besides playing an etiological role in triggering neurodegeneration and seizures in ULD, may also worsen brain damage after the disease onset, when seizures and epileptic events recur persistently.

Epidemiology

Although ULD occurs worldwide, its prevalence is increased in certain countries, for example, in Italy, southern France, and North Africa (Tunisia, Algeria, and Morocco), where the exact prevalence figures are not available. The incidence of ULD in Finland is about 1:20 000 births per year. Patients with ULD have been observed also in the Reunion Island, North America, The Netherlands, the Arabian peninsula, the Galilee region of Israel, Cuba, Southern India, and the Congolese Africa.

Clinical Features and Diagnostic Criteria

The age of onset is between 6 and 16 years and the symptom(s) at onset can be either myoclonic jerks and/or generalized tonic–clonic seizures.

Myoclonus

The most incapacitating symptom is stimulus sensitive action myoclonus, exacerbated by light, noise, physical exertion, and emotions. Its severity changes at different times in the same day, being usually more pronounced in the morning upon wakening, and varies from day to day (good day, bad day). Handwriting, drinking, standing up from a sitting position, walking, and speaking are performed with difficulty. Myoclonic jerks are asynchronous, may be focal or multifocal, and are not related to epileptiform discharges on the EEG. They may generalize to a massive myoclonic seizure, which can lead to a fall or a tonic–clonic seizure. Negative myoclonus is often found in association with positive myoclonus. The worsening of myoclonus is observed between the first and the fifth years of illness and thereafter stabilizes.

A great variability of the myoclonus severity exists among patients, even among siblings.

Epilepsy

Tonic–clonic seizures are the most common type of epileptic seizures in ULD patients. They can be preceded by a series of massive myoclonic jerks (clonic–tonic–clonic seizures). Absence, simple motor, or complex focal seizures may be present, but they are not common. Epilepsy has an active phase in the first 10 years of illness and remits in most patients thereafter.

Other Neurological Findings

Ataxia, incoordination, and dysarthria are usually observed some years after the onset of the disease.

It is difficult to assess whether they represent independent cerebellar signs or just the effect of action myoclonus.

Neuropsychological Profile

A progressive cognitive decline of about 10 points of total IQ every 10 years of disease, reported by Koskiniemi et al. in ULD patients of Finnish origin, has been later attributed by the same authors to the use of high-phenytoin regimen in Finnish patients. Indeed, no significant cognitive decline has been observed in patients from Mediterranean areas. In a recent study performed in 20 patients from Italy, France, and North Africa, with a mean duration of disease of 22 years, a mild to moderate cognitive impairment, in particular of memory abilities, was found in 11 patients.

Depression, anxiety, aggressiveness, and mood lability are frequently observed, especially in patients seriously handicapped by severe myoclonus. These symptoms often make the patient interrupt education, cause major problems in interpersonal relations, and sometimes, produce suicide attempts.

Diagnosis

Diagnosis may be difficult at the beginning of the disease, when myoclonus is very mild or even absent and

tonic–clonic seizures are rare and easily controlled by antiepileptic drugs.

Parental consanguinity and the presence of affected siblings may rouse the suspicion for ULD.

Diagnosis is easier 1–2 years after the onset, when action myoclonus becomes evident, stimulus sensitive, and progressively worsens.

Photoparoxysmal responses (PPRs) and the features of GSWD, showing an irregular pattern and very rapid spikes, can lead an expert electroencephalografist to differentiate them from the more regular GSWD observed in the idiopathic generalized epilepsy (**Figure 2**) and suspect the diagnosis of ULD.

MRI is not contributing to the diagnosis, being very often normal, especially in the early stage of the disease.

The diagnosis must be confirmed by genetic test, with the detection of the cystatin B gene mutation.

Workup

EEG

At the disease onset, background activity (BA) is normal or mildly slow (BA at 6–7 Hz).

Superimposed slower activity at 4–5 Hz can be present, resulting in an irregular appearance of BA. BA keeps stable during the course of the disease.

During the initial years of the disease, EEGs show spontaneous brief bursts of GSWD, characterized by very rapid spikes (**Figure 1**). Focal epileptiform abnormalities can be observed over the central and posterior regions of the scalp. Intermittent photic stimulation (IPS) provokes the appearance of GSWD and increases myoclonus, both generalized and focal.

During sleep, a normal representation of physiological sleep patterns and a reduction of GSWD during nREM and REM sleep, along with the presence of fast spikes and polyspikes over the central and the vertex regions during REM sleep, were observed.

Long-term evolution of EEG in ULD is characterized by no relevant deterioration of BA, a gradual reduction of GSWD and PPR, correlating with good seizure outcome, and a progressive disappearance of physiological sleep patterns 10–20 years after the disease onset.

Neuroimaging

MRI, recorded during the early stage of the disease, is usually normal. MRI of the brain and MRS of the pons and dentate, obtained in 10 patients at a later stage of the disease, showed decreased bulk of the basis pontis, medulla, and cerebellar hemispheres. Cerebral atrophy was present in six patients.

The *N*-acetylaspartate/creatine and choline/creatine ratios were reduced in the pons but not in the dentate. Brainstem involvement could play a role in the pathophysiology of ULD.

Differential Diagnosis

In the early stage of the disease, ULD can be misdiagnosed as Juvenile Myoclonic Epilepsy (Janz syndrome) due to

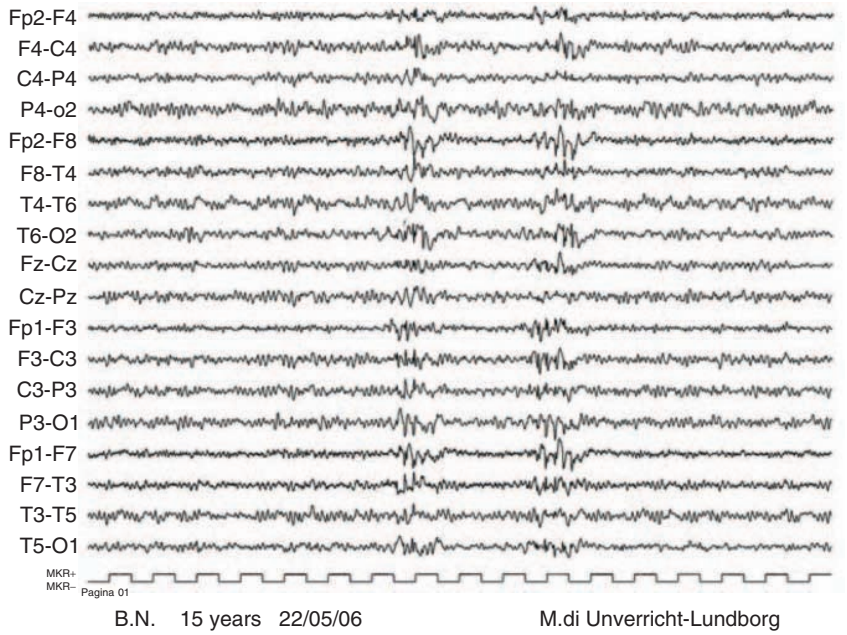

Figure 1 EEG in a 15-year-old ULD patient, showing normal background activity and brief bursts of irregular generalized spike – wave discharges, characterized by very rapid spikes.

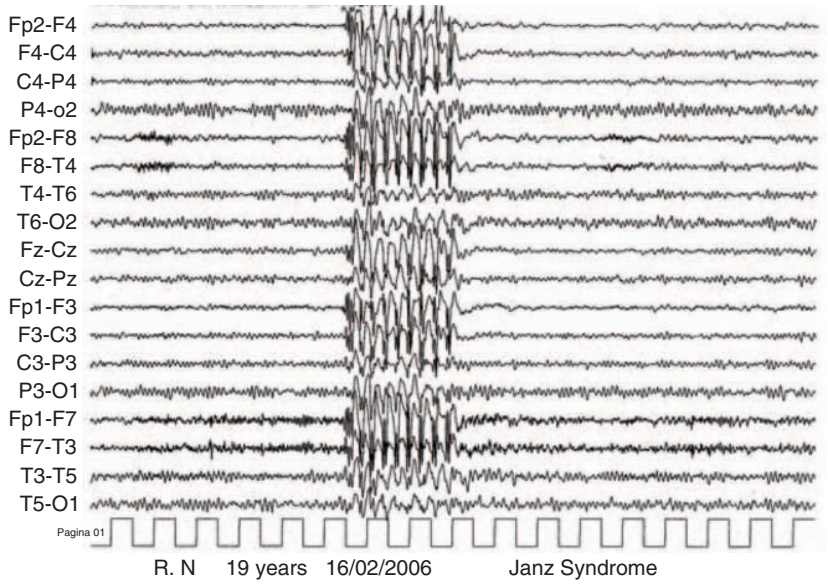

Figure 2 EEG in a 19-year-old patient affected by Janz Sindrome, showing a very regular generalized spike-wave discharges, clearly different from the irregular pattern observed in ULD patient (**Figure 1**).

the association of myoclonic jerks, tonic–clonic seizures, GSWD, and PPRs on the EEG. The progressive worsening of action myoclonus lead to the correct diagnosis of PME.

Other forms of PME, for example, myoclonic epilepsy with ragged red fibers (MERRF), neuronal ceroid lipofuscinosis (NCL), Lafora's disease, dentato-rubral-pallido-luysian atrophy (DRPLA), and sialidoses may be differentiated from ULD, on the basis of the inheritance manner, age of onset, and associated symptoms other than epilepsy and myoclonus (dementia, visual symptoms, dysmorphism). A Palestinian family with ULD phenotype, with a relatively earlier age of onset, with a linkage on chromosome 12, has been described.

Management

Valproate (VPA) is effective both on myoclonus and epileptic seizures. It is usually associated with Clonazepam (CZP), which can be used at high doses, up to 20 mg day^{-1}. High-dose Piracetam (PIR), up to 37 500 mg day^{-1}, has a good antimyoclonic effect, but can provoke chronic diarrhea. Levetiracetam (LEV), a drug chemically related to PIR, has been found useful for both myoclonus and epileptic seizures and should be considered as a first-line option in the treatment of ULD, because it has fewer adverse effects than VPA and is much less expensive than high-dose PIR. Zonisamide (ZNS) has a good antimyoclonic and antiepileptic efficacy. Other drugs used as antimyoclonic agents, including topiramate, baclofen, and chloral hydrate, do not show any satisfactory efficacy in ULD. *N*-Acetylcysteine, an antioxidant, has been reported to slow the course of ULD. Phenytoin, carbamazepine, oxcarbazepine, tiagabine, vigabatrin, gabapentin, and pregabalin should be avoided, since they may aggravate myoclonus.

Prognosis

Although the course of the disease is progressive, the current condition of patients affected by ULD appears less serious than reported in the past. It appears that avoidance of phenytoin and other potentially aggravating drugs, along with an early use of VPA and CZP, has contributed to the improvement of the clinical picture.

In a recent study on the long-term follow-up of ULD patients, has been observed that (1) the intensity of myoclonus is mild at the disease onset and worsens only during the first 5–10 years of illness, to stabilize thereafter (see Video clip, showing a 46-year-old patient affected by ULD with a disease duration of 35 years, who is still able to walk on his own), (2) epilepsy has an active phase in the early 10 years of illness and remits in most patients thereafter; (3) GSWD and PPRs disappear in most patients and BA remains stable. Life expectancy appears to be much longer than in the past, when many individuals died between 8 and 15 years after the onset of disease. Sixty and seventy-year-old patients have been reported.

The phenotype of ULD is very heterogeneous: the severity of myoclonus and epilepsy and the rate of their progression are very different from one patient to another, even within the same family. Phenotypic variability does not correlate with the repeat-size expansion, but no detailed evaluation of phenotype–genotype correlation has been made so far.

See also: Cortical Myoclonus; Cortical Tremor; Cystatin B; Dentatorubropallidoluysian Atrophy; GM1 Type 3 Gangliosidosis; GM2 Gangliosidosis; Juvenile Myoclonic Epilepsy; Lafora Disease; Mitochondrial Encephalopathies; Myoclonic Epilepsy with Ragged Red Fibers (MERRF); Myoclonus; Myoclonus, Animal Models; Myoclonus, Epileptic; Neuronal Ceroid Lipofuscinosis; Tremor.

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V

Variant Creutzfeldt–Jakob Disease

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Glossary

Ataxia – Inability to coordinate voluntary movements, leading to unsteady movements and staggering gait; most often associated with lesions of the cerebellum.

Bovine spongiform encephalopathy (BSE) – A prion disease of cattle; the bovine prions are transmitted to humans through consumption of contaminated meat products, and lead to variant Creutzfeldt–Jacob Disease (vCJD).

Cellular prion protein (PrP^C) – A normal glycoprotein attached to the cell surface through a glycosylphosphatidylinositol (GPI) anchor most abundant in the brain but also in other organs.

Myoclonus – A sudden twitching of muscles or parts of muscles, without rhythm or pattern.

Psychiatric symptoms – Early symptoms frequently seen in vCJD including depression, anxiety, and withdrawal.

Scrapie prion protein (PrP^{Sc}) – An infectious and pathogenic protein also called prion that derives from PrP^C via a structural transition from α-helix into β-sheet. In sharp contrast to PrP^C, PrP^{Sc} is detergent-insoluble, resistant to protease, prone to aggregation, and infectious.

Variant Creutzfeldt–Jakob disease (vCJD) – A variant form of Creutzfeldt–Jakob disease acquired from the consumption of BSE-contaminated meat. It is characterized by young age at onset; early dominant psychiatric symptoms followed by neurologic deficits (cerebellar ataxia, involuntary movements, dystonia, and myoclonus); abundant florid prion plaques; and PK-resistant PrP^{Sc} in the brain.

Definition and History

Variant Creutzfeldt–Jakob disease (vCJD) belongs to a group of highly heterogeneous and fatal transmissible spongiform encephalopathies, or prion diseases, that affect both animals and humans. Animal prion diseases include scrapie in sheep and goats, bovine spongiform encephalopathy (BSE or mad cow disease) in cattle, as well as chronic wasting disease in deer and elk. In humans, prion diseases can be sporadic, inherited, or acquired by infection, depending on their etiology. They mainly manifest four major phenotypes: CJD, Gerstmann–Sträussler–Scheinker disease, kuru, and fatal familial insomnia. As a group, prion diseases are characterized clinically by disorders of cognition and movement; pathologically by spongiform degeneration, neuronal loss, and astrocytosis; and biochemically by deposition of an infectious proteinaceous pathogen called prion or scrapie prion protein (PrP^{Sc}). In addition to these basic characteristics, vCJD also possesses a unique identity: early dominant psychiatric symptoms followed by late neurologic deficits, young age at death, presence in the brain of florid prion plaques, and an abnormal PrP that is resistant to protease digestion and displays distinctive electrophoretic characteristics (**Figure 1**).

vCJD was first discovered by Will and colleagues in the United Kingdom in 1996. Its discovery, together with the immediate demonstration of the causal link between vCJD and BSE, represent milestones in the history of prion disease. Not only did these findings demonstrate, for the first time, that prion disease could be transmitted from animals to humans, but they also greatly accelerated the establishment of surveillance and control of prion diseases. Following the outbreak of BSE, the surveillance of CJD was heightened in the United Kingdom in 1990 in order to monitor any changes in this condition that might be associated with transmission of BSE to humans. Subsequently,

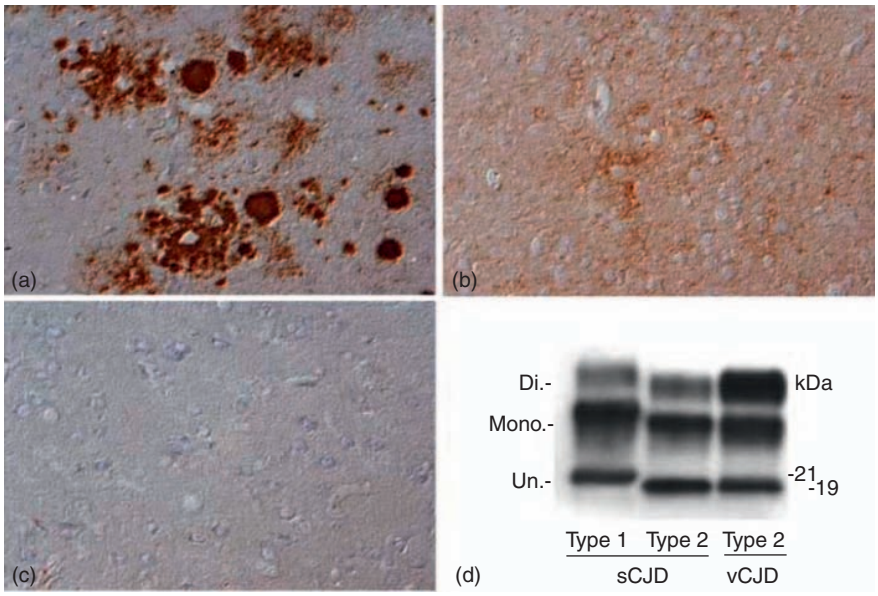

Figure 1 PrP^{Sc} detection by immunohistochemistry and Western Blot analysis. Immunohistochemistry of brains affected by vCJD (a) and sCJD (b), and of a normal brain (c) with anti-PrP antibody 3F4. Amount and pattern of distribution of PrP^{Sc} are different between vCJD, where PrP^{Sc} forms clumps, and sCJD, which shows dot-like formations. No PrP is seen in the normal brain (J. Ironside, National CJD Surveillance Center, Edinburgh, UK, and P. Gambetti, National Prion Disease Pathology Surveillance Center, Cleveland, OH, USA). Probed with 3F4 (d) Homogenates of the frontal cortex from sCJDMM1 (type 1), sCJDMM2 (type 2) and vCJD were treated with proteinase K (PK) prior to Western blotting with 3F4 antibody. The PK-resistant PrP core fragments from sCJD exhibit a dominant middle band corresponding to monoglycosylated PrP and a lower band corresponding to unglycosylated PrP migrating at ~21 kDa (PrP^{Sc} type 1) or at ~19 kDa (PrP^{Sc} type 2). In contrast, the PK-resistant PrP core fragments from all vCJD show a single uniform profile: a dominant upper band corresponding to diglycosylated PrP and a lower band migrating at ~19 kDa. Di.: diglycosylated PrP; Mono.: monoglycosylated PrP; and Un.: unglycosylated PrP.

in 1993, the European Union started a project involving the majority of European countries (extended to all member states in 1998) in which common methodologies and criteria for case definition were adopted. In 1995 and early 1996, through these efforts a number of cases of CJD were identified in the United Kingdom with a unique phenotype distinct from sporadic CJD. By March 1996, ten cases of CJD sharing a very similar phenotype had been collected: the patients were of a young age at death (mean 29 years vs. 66 years in sporadic CJD); and the illness was characterized by long duration (mean 14 months vs. 4.5 months in sporadic CJD) and an unusual and remarkably uniform clinical presentation, distinct from that previously seen in CJD. Subsequent animal inoculation studies confirmed that this novel human prion disease is caused by the same prion strain that causes BSE in cattle.

Pathogenesis

vCJD, along with kuru of New Guinea, and iatrogenic CJD, are the three forms of the disease known to date to be acquired by infection. However, unlike kuru and iatrogenic CJD (caused, respectively, by human-to-human transmission through ritual cannibalism, or medical and surgical procedures), vCJD is caused by transmission from cattle, most likely through an oral route by consumption of prion-contaminated meat products, or possibly through parenteral routes. In addition to the acquired form, the other forms of prion diseases comprise sporadic CJD, the most common form and genetically determined or familial CJD. However, regardless of their distinct etiologies, all prion diseases share a fundamental pathogenetic mechanism: the conversion of the normal or cellular PrP (PrP^{C}) into an isoform, identified as scrapie PrP (PrP^{Sc}). PrP^{Sc} is the only known component of prion that is believed to be pathogenic and infectious but at the same time (and in contrast to viruses and bacteria) is thought to be free of nucleic acids. It is postulated that in acquired prion diseases, including vCJD, prions are acquired by exogenous infection whereas in sporadic and familial CJD prions form spontaneously, either as a result of a random misfolding event or as a result of the presence of PrP destabilizing mutation.

Most of PrP^{C} is full-length, diglycosylated, and attached to the cell surface via a glycosylphosphatidylinisotol (GPI) anchor; but small amounts of PrP^{C} may be N-terminally truncated, monoglycosylated or unglycosylated, anchorless, or cytosolic. PrP^{C} and PrP^{Sc} share their primary structure. The critical difference between these two proteins lies in the conformation, in that PrP^{C} converts into PrP^{Sc} through an α-helix to β-sheet structural transition which results in profound differences in the physicochemical and biological

properties of the two conformers. PrP^{Sc} is rich in β-sheets and is detergent-insoluble, multimeric, resistant to proteinase K (PK) treatment, and infectious. In contrast, PrP^{C} is rich in α-helix, detergent-soluble, monomeric, sensitive to PK, and noninfectious.

Although there is no doubt that the coexistence of PrP^{Sc} and PrP^{C} in the central nervous system (CNS) is a prerequisite for prion diseases, the role of these two PrP conformers in the pathogenesis of prion disease is not completely understood. Two major hypotheses have been proposed to explain how changes in PrP^{C} conformation could cause neurodegeneration: first, functional gain, in which prion pathology is attributable to the acquisition of toxic function; and second, functional loss, in which a PrP^{C} physiologic activity is lost upon conversion to or interaction with PrP^{Sc}.

A Single Uniform Prion Strain

Based on gel mobility and glycoform ratio, PrP^{Sc} detected in sCJD can be divided into two types: PrP^{Sc} type 1 with an unglycosylated PrP migrating at ~21 kDa and a dominant N-terminal protease cleavage site at residue 82; and PrP^{Sc} type 2 with an unglycosylated PrP migrating at ~19 kDa and a cleavage site at residue 97 on the gel (**Figure 1**). Moreover, all PrP^{Sc} species from sCJD exhibit a dominant monoglycosylated PrP. In contrast, PrP^{Sc} from all vCJD examined so far is invariably of a dominant diglycosylated PrP and a 19-kDa unglycosylated PrP with a primary cleavage site at residue 97 (**Figure 1**). The electrophoretic profile of PrP^{Sc} detected in all vCJD cases is virtually identical to that found in BSE, which indeed implies that prion present in vCJD derives from BSE.

Polymorphism at Residue 129 of PrP

It has been believed that polymorphism at residue 129 of PrP (either methionine (M) or valine (V)) is associated with susceptibility to human prion. Although most sporadic CJD occurs in individuals homozygous for 129 MM, it also affects individuals with genotype 129 MV or 129 VV. Remarkably, all clinically affected vCJD cases studied so far have been 129 MM homozygous. However, the identification, in an anonymous screening study, of two positive appendix tissues from subjects with 129 VV genotype, together with the description of an asymptomatic case of vCJD in an 129 MV patient infected by blood transfusion, highlight the possibility that polymorphisms rather than 129 MM could also be susceptible to variant CJD although they might exhibit atypical phenotypes such as a subclinical form.

Involvement of the Lymphoreticular System

The distinctive pathogenesis of vCJD in comparison with other forms of CJD is also reflected in the involvement of the lymphoreticular system. PrP^{Sc} is readily detectable in lymphoreticular tissues in vCJD including gut-associated lymphoid tissue, tonsil, spleen, appendix, and lymph nodes, whereas it is only detected in the spleen of some sporadic CJD using highly sensitive methods. Prion neuroinvasion bears remarkable similarities to neuroinvasion by viral agents.

Oral or Parenteral Transmission Route

Presumably, all clinically infected vCJD cases are contracted orally, through consumption of contaminated meat products derived from BSE cattle. But exactly how the BSE prion spreads from the gastrointestinal system to the CNS remains an unresolved question. It has been hypothesized that the invading prions undergo two phases to reach the CNS: they accumulate and replicate in the lymphoreticular organs (primary phase) and then disseminate to the CNS through the peripheral nerves. Studies in prion-infected animals revealed that the autonomous nervous system, including both vagal and sympathetic nerve fibers, contributes to the spread of orally administered prions. These results are consistent with a finding that PrP^{Sc} is detected in the sympathetic nervous system (stellate and celiac ganglia) in vCJD but not in sCJD. In addition to the oral route, recent identification of three cases of transfusion-associated vCJD prion infection has raised significant concerns that there may be substantial risks of iatrogenic transmission of vCJD prions. Surprisingly, an asymptomatic transfusion-associated vCJD case exhibited MV polymorphism at residue 129 but no neurologic disorders and no prion-related neuropathologic changes. Moreover, PrP^{Sc} was detectable only in the lymphoreticular tissues but not in the brain. It is unclear whether this preclinical stage resulted from the parenteral route transmission or from the 129 MV heterozygous polymorphism.

Epidemiology and Risk Factors

Variant CJD has been reported in many countries particularly in Europe. As of February 2009, 214 cases of vCJD have been identified worldwide, mostly in the United Kingdom (**Table 1**). The patients in Ireland, Canada, and the United States of America had spent significant periods of time in the United Kingdom, which suggests that these patients contracted the disease through dietary exposure to BSE in the United Kingdom. However, the Italian patient and most French patients had not visited the United Kingdom. How were these patients infected by the BSE prion? Brandel and colleagues recently conducted a study in which they demonstrated that the British and French vCJD cases manifested very similar clinical, histopathologic, and molecular features and concluded that the two sets of vCJD patients shared the same

prion strain. These findings highlight two issues. First, they raise the question of the origin of the infectious prion in the French vCJD: whether it originates from British BSE or from indigenous French BSE; and second, whether vCJD worldwide is caused by one prion strain or whether all vCJD cases carry the same British prion strain. It is critical that these two issues be clarified, so that the diffusion of the BSE epidemics through different continents can be understood and arrested.

Table 1 Number of vCJD reported and countries with the disease

Country	*Number of cases*
Unite Kingdom	169
France	23
Spain	5
Republic of Ireland	4
United States of America	3
The Netherlands	3
Portugal	2
Saudi Arabia	2
Italy	1
Canada	1
Japan	1
Total	214

Data as of February 2009. Quoted from the European and Allied Countries Study Group of CJD (EUROCJD).

Clinical Features, Diagnostic Work-Up and Tests, and Diagnostic Criteria

It is widely believed that the high heterogeneity of sporadic CJD results mainly from the chameleon-like conformation of prions. Indeed, at least five clinical subtypes of sCJD have been identified based on a combination of PrP^{Sc} types and PrP polymorphism at residue 129. Surprisingly, the clinical manifestations of vCJD linked to a single uniform prion strain (PrP^{Sc} type 2 with the homozygous MM) remain relatively heterogeneous (**Table 2**). According to an analysis of clinical features of the first 100 cases by Will and colleagues, 63% of cases present with psychiatric symptoms alone, 15% with isolated neurologic symptoms and 22% with mixed features. Patients with vCJD usually

Table 2 Differences between variant and sporadic CJD

	Variant CJD	*Typical sporadic CJD (MM1)*
Clinical features[a,b]		
Mean age at death	29 years	65 years
Median duration of illness	14 months	4 months
Neurological signs	*Presentation*: affective or psychotic disorder, persistent pain, sensory symptoms, sometimes gait ataxia or dysarthria	*Presentation*: cognitive impairment, ataxia, mental, and visual signs
	Later stage: ataxia, dementia	*Later stage*: myoclonus, ataxia, and pyramidal signs
General diagnostic test[a]		
Thalamic MRI high signal	Pulvinar 90%	Caudate/putamen 60%
EEG	'Typical' 0%	'Typical' 80%
PrP^{Sc} detection in tonsil biopsy	Positive	Negative
Neuropathological features[b,c]		
Cerebral and cerebellar cortex	Multiple florid plaques in H&E sections, numerous small clusters of plaques in PrP stained sections, amorphous pericellular and perivascular PrP accumulation	Widespread fine spongiform degeneration, astrogliosis, neuronal loss; punctate PrP immunoreactivity; 'brush stroke' pattern in cerebellar molecular layer
Caudate nucleus and putamen	Severe spongiform change, perineuronal and axonal PrP accumulation	Fine spongiform degeneration and astrogliosis; punctate PrP immunoreactivity
Posterior thalamic nuclei and midbrain	Marked astrocytosis and neuronal loss	Fine spongiform degeneration and astrogliosis; punctate PrP immunoreactivity; substantia nigra not affected
Brainstem and spinal cord	Reticular and perineuronal PrP accumulation in gray matter	No spongiform degeneration and PrP immunoreactivity
Molecular features of PrP^{Sc}		
129 Polymorphism	MM	MM
Gel mobility (type)	19 kDa (type 2)	21 kDa (type 1)
N-terminal PK cleavage site	Residue 97	Residue 82

[a]Will RG and Ward HJ (2004) Clinical features of variant Creutzfeldt–Jakob disease. *Current Topics in Microbiology and Immunology* 284: 121–132.
[b]Gambetti P, et al. (2003)Sporadic and familial CJD: Classification and characterisation. *British Medical Bulletin* 66: 213–239.
[c]Ironside JW and Head MW (2004) Neuropathology and molecular biology of variant Creutzfeldt–Jakob disease *Current Topics in Microbiology and Immunology* 284: 133–159.
Source EEG, Electroencephalogram.

manifest early psychiatric disorders such as depression, anxiety, and withdrawal. About 6 months later, neurologic disorders emerge, including cognitive impairment, ataxia, and involuntary movements. Chorea, dystonia, and myoclonus are also observable. During the progressive clinical course, dementia and diffuse cortical deficits are predictable. Finally, patients are mute and bed-bound. Death is inevitable after a median of 14 months from the onset of symptoms (range, 6–39 months), largely due to an intercurrent infection such as respiratory infection. It is recommended that the combination of an affective or psychotic disorder with persistent pain, sensory symptoms, gait ataxia, or dysarthria should signal a diagnosis of vCJD, especially in younger patients.

Unlike sCJD, 14–3–3 protein in the cerebrospinal fluid, the electroencephalogram and CT brain scan are less helpful in diagnosing vCJD because these are usually normal. However, an MRI scan may be helpful. For example, specific high signal in the posterior thalamus on T2-weighted images can be detected in over 75% of vCJD cases. Moreover, the sensitivity of an MRI brain scan in vCJD can be improved by fluid-attenuated inversion recovery (FLAIR). The definite diagnosis of vCJD requires neuropathologic examination of brain tissue obtained either at biopsy or autopsy. In 2000, Will and colleagues established the diagnostic criteria, by which accurate antemortem diagnosis can be achieved using a combination of clinical history with special investigations including tonsil biopsy using PrP immunohistochemistry and Western blotting, as well as MRI brain scan.

Differential Diagnosis

For suspect vCJD cases, the main differential diagnosis lies with other human prion diseases, especially sCJD. Sporadic CJD can be readily excluded if detailed clinical data are available and special investigations are included following Will et al. diagnostic criteria. A detailed differential diagnosis between sCJDMM1 (the most common subtype of sCJD) and vCJD, including pathology, is listed in **Table 2**.

Management and Prognosis

Although scrapie in sheep and goats has been recognized for more than 200 years and the first CJD case in humans was identified almost 90 years ago, to date no effective treatment has been found. Many attempts to treat experimental prion diseases in animals have been made over the past 30 years but only a few therapeutic compounds have been tested in patients, and none of them have been found effective in treating human prion diseases.

The following compounds have being studied in clinic. Quinacrine, a widely used antimalarial drug, was found to successfully block formation of PrP^{Sc} in infected mouse neuroblastoma cells. A recent patient-preference trial on all forms of CJD showed acceptable level of tolerance but no effect on the clinical course of CJD. Flupirtine maleate, a centrally acting nonopioid analgesic, has been tested in a randomized double-blind study of subjects with the diagnosis of probable CJD. Treated patients showed significantly slower rate of cognitive deterioration but no significant difference in survival time. Pentosan polysulfate (PPS), a drug for the treatment of interstitial cystitis, has been reported to stabilize and delay the progression of prion disease but there are controversial results in clinical studies. A major problem is that PPS does not cross the blood–brain barrier and it has to be administered intraventricularly. To date, this compound has not been tested in any case-control study. Administration of doxycyclin, a member of the tetracycline group, to sCJD patients under compassionate treatment has been reported to more than double survival rate compared to untreated sCJD subjects. A phase II, multicenter, randomized, double-blind study is ongoing.

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See also: Ataxia; Creutzfeldt–Jacob Disease; Kuru.

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Relevant Websites

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http://www.cdc.gov/ – Centers for Disease Control and Prevention.
http://www.cjd.ed.ac.uk/ – The National Creutzfeldt-Jakob Disease Surveillance Unit (NCJDSU).
http://www.eurocjd.ed.ac.uk/ – The European and Allied Countries Collaborative Study Group of CJD (EUROCJD) plus the Extended European Collaborative Study Group of CJD (NEUROCJD).
http://www.who.int/ – World Health Organization.

W

Weaver Mouse

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Glossary

Basal ganglia – A group of gray matter nuclei inside the brain, subserving movement control, learning, emotions, and cognitive functions.
Cerebellum – A brain structure that subserves balance, movement coordination, and certain cognitive functions. Damage to the cerebellum may lead to ataxia.
Dopamine – An organic molecule used by the brain for the chemical communication (neurotransmission) of neurons.
Hippocampus – A structure in the forebrain that belongs to the limbic system and subserves memory.
Mutation – A change in the genetic material of an organism, induced either spontaneously or experimentally.
Potassium channel – A common type of ion channel found in the membranes of living cells. In neurons, they are crucial for setting the resting potential and for shaping the action potential.

Definition and History

In the era of neurobiological research prior to the advent of targeted knockout and transgenic technology, spontaneous mutations in inbred mouse strains were studied as models of developmental and degenerative neurological conditions. One such mutation is the weaver (*wv*), which occurred in 1961 in a C57BL/6J genetic stock of mice.

Weaver mutants have neuron abnormalities in the cerebellum, mesotelencephalic dopamine (DA) projection system, hippocampus, and pontine nuclei. The cerebellum of the weaver mouse has been investigated in particular regarding neurite extension, neuronal migration, and the remodeling of synaptic circuitry. The loss of DA cells in the weaver mouse midbrain produces a pathophysiological phenocopy of Parkinsonism, useful in tackling issues of the survival and growth of intrastriatal grafts in the chronically denervated striatum.

Cerebellar Pathology

The cerebellum of homozygous weaver mutants is atrophic. Postmitotic granule cell precursors in the external germinal layer fail to migrate inward to the internal granular layer and die massively at the interface of the former and the molecular layer during the first 2 weeks postnatally. Heterozygous weaver mice (*wv*/+) show reduced rates of granule cell migration and an intermediate degree of granule cell loss; in adult animals, arrested granule cells are found at the interface of the molecular and Purkinje cell layer.

Purkinje cells are reduced in number as early as postnatal day 5. Overall reduction in Purkinje cells is 28% in homozygotes and 14% in heterozygotes. The apical dendrites of Purkinje cells in the weaver cerebellum are oriented randomly and display a 'weeping willow' shape of arborization. One observes unattached Purkinje dendritic spines with postsynaptic specialization densities but devoid of a presynaptic input from the parallel fibers; the circuitry remodeling involves formation of heterologous synapses on free spines by axon terminals of mossy fiber rosettes and by climbing fiber varicosities, and formation of attachment plate-like junctions by free postsynaptic sites of apposing Purkinje dendritic spines.

Mesotelencephalic Dopamine System Deficits

The cerebrum of adult weaver homozygotes has 52% lower DA levels than normal. At birth, young weaver neurons undergo degeneration beneath the subependymal plate. The substantia nigra of weaver mice has 40%

fewer DA cells than the wild-type on postnatal day 20 and 70% fewer DA cells at 3 months of age; DA neuron loss is also seen in the ventral tegmental area and retrorubral nucleus. A further wave of DA neuron degeneration is effected during the second year of life, bringing the total DA cell loss to 85% in the substantia nigra by 24 months. In regression fits, DA neuron fallout combines two independent components, an initial exponential decay, superceded by a linear regression, with a threshold at about 100 days. The half-life ($T_{1/2}$) of neurons degenerating during the first (exponential) phase is 58 days; the probability per unit time that a neuron will die is a constant (λ), estimated at 0.012 per day. During the second (linear) phase of degeneration, the probability of a neuron dying becomes a function of time and declines with advancing age, that is, the longer a cell survives, the less likely it is to degenerate.

Heterozygous weaver mice have normal midbrain DA neuron numbers at 3 months of age. However, DA dendrites projecting from the substantia nigra pars compacta into the pars reticulata appear defective in length and density, varicosity diameter, intervaricose segment length, and afferent synaptic connectivity.

Additional Phenotypic Characteristics

In hippocampal area CA3 of adult homozygous weaver mice, one observes pyramidal cell ectopia as well as alterations of hippocampal mossy fiber trajectories, most likely reflecting disturbances in neuronal migration. The weaver mutation also affects neuronal survival in pontine nuclei that project to the cerebellar cortex via pontocerebellar mossy fibers; while neuronal numbers appear normal in the first week of life, they become reduced to one-third of the wild-type values by postnatal day 18.

The phenotype of weaver mutants further includes reduced levels of serum thyroid hormone (hypothyroidism) in association with delays in somatic development and a decreased expression of striatal transforming growth factor alpha (TGFα), possibly stemming from a regulatory defect at the level of the hypothalamic–hypophyseal axis.

Behavioral Signs

Homozygous weaver mutants (*wv*/*wv*) display locomotor, spatial orientation, and memory deficits, including gait instability, poor limb coordination, resting and intention tremor, navigational deficits, reduced activity in the open-field, delayed spontaneous alternation, and a hind-paw clasping reflex when held by the tail. Moreover, weaver mice express learning deficits similar to those found in other DA-deficient organisms.

Heterozygous weaver mice (*wv*/+) do not have locomotor abnormalities, but they intermittently manifest generalized tonic–clonic convulsions that are usually lethal. Such an effect might conceivably pertain to the DA dendrite deficit of the substantia nigra pars reticulata, as that midbrain structure implicated in the pathophysiology of experimental seizures.

It appears that chronic pharmacologic treatment of homozygous weaver mutants with fluoxetine (a serotonin reuptake inhibitor) may alleviate some of the motor defects and prevent neuron loss in the cerebellum and pontine nuclei. Intrastriatal grafting of fetal mesencephalic tissue – containing primordial DA cells – partially counteracts the structural and functional neurological deficits of weaver homozygotes.

Molecular Genetic Defect

The *wv* allele has been mapped to the distal end of mouse chromosome 16 (at a distance of 68.75 cM from the centromere), within a phylogenetically conserved region highly homologous to telomeric human chromosome 21 (gene map locus 21q22.1). The *wv* mutation, which is considered to be incomplete dominant or semidominant, was identified as a missense mutation with a G→A substitution in nucleotide 953 of the G-protein-activated inwardly-rectifying K^+ channel gene *Kcnj6* or *Girk2* (subfamily J, member 6) and an ensuing Gly→Ser replacement at residue 156 of the encoded protein (alternatively called $K_{ir}3.2$).

The amino acid residue substitution in the pore-forming H5 region of $K_{ir}3.2$ disturbs the homomeric channel properties, producing a lethal depolarized state in weaver neurons. In hippocampal slices from weaver mice in particular, the mutation in the pore region of the K^+ channel subunit results in a functional phenotype that resembles $K_{ir}3.2$-deficient mutants, since in disinhibited slices the $GABA_B$ receptor agonist R-baclofen fails to induce K^+ currents or any other conductance change.

See also: 6-OH Dopamine Rat Model; Ataxia; Basal Ganglia; Basal Ganglia, Functional Organization; Dopamine; Juvenile Parkinsonism; Movement Disorders: Overview; Multiple System Atrophy; Multiple System Atrophy: Animal Models; Parkinsonism: Genetics; Parkinson's Disease: Animal Models; Parkinson's Disease: Genetics; Substantia Nigra; Transplantation.

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Western Blot

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Glossary

Chemiluminescence – The emission of light through a chemical reaction.
Homogenization – The process by which a complex sample is dispersed into a uniform mixture of components.
Immunoreactivity – The binding of an antibody to a specific target antigen in vitro, as detected by an antibody-specific labeling reaction.
Proteomics – The study of the expression and structural and functional properties of the entire protein complement in an organism, tissue, or cell.
Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) – The process by which proteins extracted from a complex cell or tissue sample are denatured in anionic SDS and separated by molecular weight in a polyacrylamide gel subjected to an electric current.

Introduction

The western blot (or immunoblot) analytical procedure enables the identification and quantitation of individual proteins from a complex mixture (e.g., cell or tissue extract). In general, the technique involves separating proteins under denaturing conditions by gel electrophoresis, transferring or 'blotting' the proteins electrophoretically from the gel to a solid support membrane, probing the membrane with an antibody specific for a target protein, and then visualizing the bound antibody using labeled secondary immunological reagents. Hence, the western blot technique is an essential assay for proteomic analysis of tissues in health and disease or cultured cells under varying conditions. The following are more specific technical considerations for performing western blot analysis.

Preparation of Samples

Protein samples from cultured cells can be extracted either by direct dissolution in a denaturing buffer or by homogenization in a buffer containing protease inhibitors. Sample denaturing buffers contain the powerful anionic detergent sodium dodecyl sulfate (SDS), which linearizes the proteins, and a reducing agent such as 2-mercaptoethanol to break disulfide bonds. Cells and tissue (e.g., frozen postmortem brain samples) collected in homogenization buffers are mechanically disrupted using methods such as sonication and tissue grinding. This process permits fractionation protocols to remove debris, pellet nuclei, and separate functional compartments (e.g., membrane and cytosolic) prior to denaturation. Sample extracts

must be analyzed for protein concentration using one of the several commercially available methods in order to ensure that the total protein amount in each sample under analysis is equivalent.

Electrophoresis of Proteins

Denatured proteins in individual samples are separated by SDS-polyacrylamide gel electrophoresis (SDS-PAGE, **Figure 1**). Polyacrylamide gels are formed from the polymerization of two compounds, acrylamide and the cross-linking agent *N*,*N*-methylenebisacrylamide, in a buffered solution containing 1% SDS. The polymerized gels are essentially three-dimensional networks of long hydrocarbons cross-linked by methylene groups, thus, creating a sieve of pores through which the proteins migrate within an electric field. The sieving properties of this separating gel are determined by the pore size; higher percentages of acrylamide (e.g., 12%) create smaller pore sizes which favor resolution of lower molecular weight proteins, whereas lower percentages of acrylamide (e.g., 8%) provide a better resolving environment for higher molecular weight proteins. The migration speed during SDS-PAGE is based on protein molecular weight since the amount of anionic SDS bound by each denatured protein in a sample is proportional to its size (i.e., larger proteins will move more slowly toward the anode than smaller proteins). After the separating gel is polymerized in a vertical gel casting stand, a second, stacking gel (5% acrylamide) containing sample loading wells is polymerized on top of the separating gel.

SDS-PAGE is typically carried out in a discontinuous buffer system wherein the ionic strength of the buffer used to cast the gel (Tris–HCl) is different from the running buffer (Tris–glycine) which conducts the electric field. Thus, the SDS–protein complexes sieve through the relatively large pores of the stacking gel in a zone of lower conductivity and steeper voltage gradient that concentrates the proteins on the surface of the separating gel, and greatly increases their resolution during separation. Molecular weight standard proteins are loaded concurrent with the sample proteins in a separate lane to track the progress of different size proteins during SDS-PAGE, and to gauge the relative molecular weight of the target proteins. However, it should be mentioned that posttranslational modifications such as glycosylation or phosphorylation will impede the migration of proteins in the gel. If a target protein migrates more slowly than expected based on its primary sequence, then the presence of these modifications can be verified by preincubating the samples with commercially available glycosylase or phosphatase.

Transfer of Proteins to Solid Supports

Once SDS-PAGE is complete, the proteins in the gel can be visualized directly by staining with coomassie blue or silver stain. Alternatively, the proteins can be transferred electrophoretically from the gel onto a sheet (or membrane) composed of nitrocellulose or polyvinylidene difluoride (PVDF). The proteins transferred to the membrane retain the same pattern of separation they had in the gel and will now be accessible to antibody detection (**Figure 1**). Transfer can be done in wet or semi-dry conditions. In wet transfer, the gel and membrane are sandwiched tightly together between filter paper

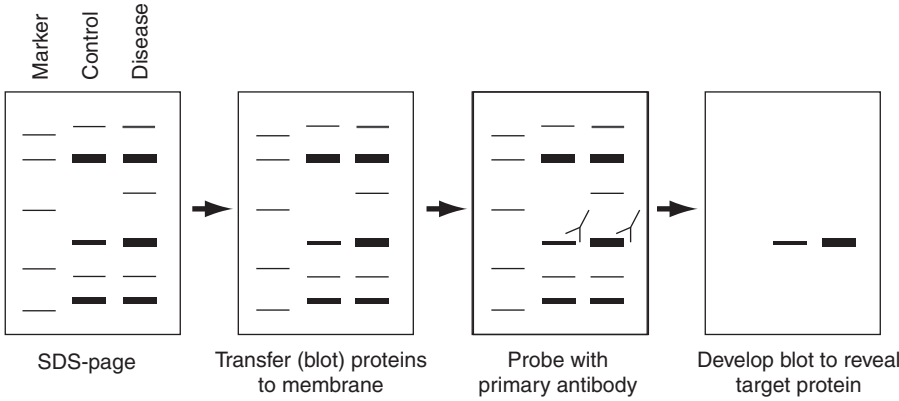

Figure 1 Schematic of western blotting process. In this example, denatured proteins from control and disease tissue are separated by SDS-PAGE. The approximate molecular weight of the proteins in the gel is determined by the protein standards (marker) that run in the left lane. The proteins are transferred electophoretically (or 'blotted') to a PVDF membrane, and probed with a specific primary antibody. The primary antibody is followed with a labeled secondary antibody (not shown), and the label is developed to reveal the target protein. Here, the target protein is revealed to be more abundant in the disease tissue relative to control.

(membrane side toward the anode), and submerged in a transfer cell to which an electrical field is applied. A standard transfer buffer is composed of Tris–glycine without SDS (which can impede blotting of smaller proteins). 20% methanol is added to the buffer for nitrocellulose membranes; PVDF membranes can be prewetted with methanol, and then used with standard transfer buffer. The success of the protein transfer can be assessed by staining the membranes with Ponceau S, which is compatible with immunological methods of detection.

Binding of the Primary Antibody to the Target Protein

Significant background may be introduced through the nonspecific binding of proteins in the immunological reagents. To reduce this background and increase sensitivity, the membranes should first be 'blocked' in a solution containing irrelevant proteins such as 1–5% nonfat dry milk or bovine serum albumin. A nonionic detergent (e.g., 0.01% Tween 20) can also be included to reduce nonspecific binding without disrupting specific binding of antibody to target. Once effectively blocked, the membranes can then be incubated with the primary antibody (**Figure 1**). Virtually, all western blotting techniques involve a two-step incubation process wherein incubation with an unlabeled primary antibody specific for the target protein is followed by a species-specific labeled secondary antibody directed against the primary immunoglobulin (e.g., goat antirabbit IgG for rabbit primary antiserum). The antibodies are typically diluted in the blocking buffer at empirically determined concentrations. In addition, proteins A and G, which bind immunoglobulin heavy chains, can also be used as secondary reagents. These secondary reagents can be radiolabeled (e.g., with ^{125}I) or, more commonly, conjugated to biotin, fluorescein, or to an enzyme such as horseradish peroxidase (HRP). A major advantage of the two-step procedure is that a single secondary reagent can be used to detect a wide variety of primary antibodies. Moreover, more than one molecule of secondary reagent can usually bind one primary antibody molecule, thus achieving signal amplification.

Visualization of the Bound Primary Antibody

Visualization of immunoreactive bands on the membrane requires development of the conjugated label on the secondary reagent (**Figure 1**). For instance, HRP labeled secondary antibodies are visualized using chemiluminescence by incubating the membrane with commercially available solutions containing the HRP substrate luminol. The membrane is then exposed to X-ray film or a digital imager.

Quantitative Assessment of the Target Protein

The optical density of immunoreactive bands is considered a proxy to target protein concentration in the sample. Several programs, including the publicly accessible NIH Image programs (http://rsb.info.nih.gov/nih-image/) and digital image analysis software, are available which allow bands of interest to be selected and quantified based on the signal intensity. However, a few caveats should be considered to ensure that measurements are quantitative. First, the specificity of the antibody should be rigorously characterized to mitigate concerns over cross-reactivity with nontarget proteins. For instance, structurally similar proteins can migrate to the same position on the gel (**Figure 2(a)**); hence, control experiments should be performed to show that the primary antibody does not erroneously bind nonspecific proteins and alter the quantitative data. In addition, the membranes should be probed with the secondary reagent alone to ensure the immunoreactive band is specific for the primary antibody. Second, although the advent of digital imaging has broadened the linear dynamic range of signal detection compared to traditional X-ray film, a standard curve showing antigen signal intensity in a range of samples with varying total protein should be generated to ensure that immunoreactive signals in the sample amount loaded will fall along a linear range of detection (**Figure 2(b)**). Finally, the membranes should also be probed with a primary antibody to a 'housekeeping' protein (e.g., β-tubulin or glyceraldehyde-3-phosphate dehydrogenase) that is not expected to change under the experimental conditions examined (**Figure 2(c)**). Immunoreactivity of this housekeeping protein serves as an internal control for even sample loading. Hence, the immunoreactivity of the target antigen is normalized to the immunoreactivity of the housekeeping protein in each sample for quantitative analysis. Care should be taken in selecting the loading control, and the ideal antigen may need to be determined empirically. For example, western blotting and densitometry of housekeeping protein levels can be performed in samples from different experimental or diagnostic groups, and equivalent total protein loading for each sample can be assessed by staining of the same gels or membranes.

Beyond Western Blotting

Western blots are commonly incorporated with other techniques to allow for more detailed proteomic studies.

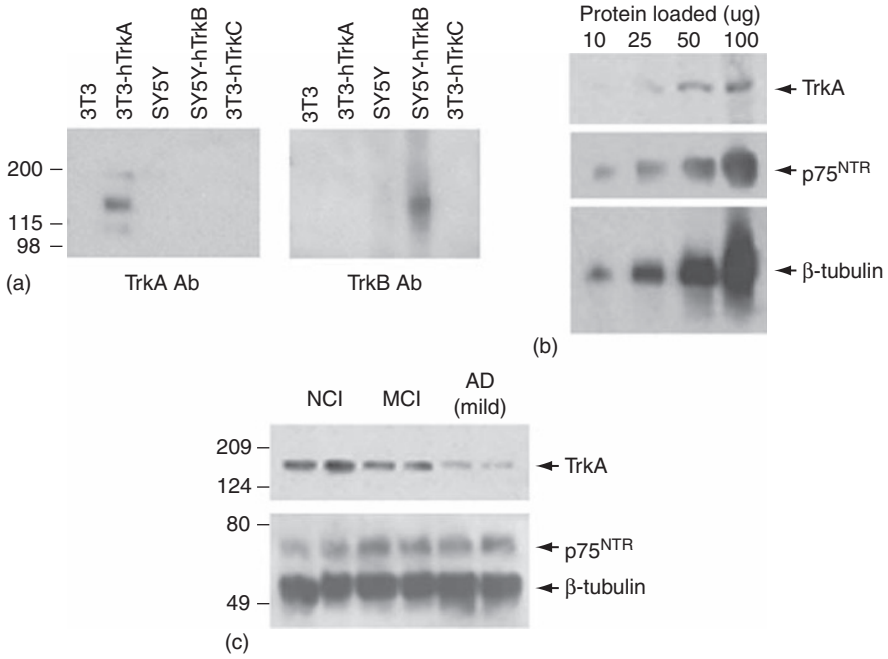

Figure 2 Representative western blotting data and quality control considerations for quantitative analysis. (a) Western blot showing that a primary antibody is specific for its target. Denatured protein samples (25 μg) of naïve NIH-3T3 mouse fibroblast cells, NIH-3T3 cells transfected with human trkA (3T3-hTrkA) or trkC (3T3-hTrkC) receptor tyrosine kinase cDNA, naïve SH-SY5Y human neuroblastoma cells (SY5Y), and SH-SY5Y cells transfected with human trkB cDNA (SY5Y-hTrkB) were separated by SDS-PAGE, blotted to a PVDF membrane, and probed with rabbit TrkA antiserum or rabbit TrkB antiserum. The TrkA antiserum detected hTrkA, but not the structurally similar hTrkB or hTrkC proteins. The anti-TrkB antiserum confirmed the presence of hTrkB in the SY5Y-hTrkB sample. (b) Western blot shows increasing antigen immunoreactivity for TrkA, the $p75^{NTR}$ neurotrophin receptor, and β-tubulin with incremental amounts of denatured protein sample (10–100 μg) extracted from the temporal cortex of an aged, cognitively intact individual. Densitometry (not shown) demonstrated that immunoreactive signals from 50 μg loaded protein fell within a linear range of detection. (c) Western blot shows TrkA, $p75^{NTR}$, and β-tubulin immunoreactivity in denatured protein samples (50 μg) from the temporal cortex of people who died with no cognitive impairment (NCI), mild cognitive impairment (MCI), and mild Alzheimer's disease (AD). Densitometry (not shown) was performed by normalizing TrkA or $p75^{NTR}$ immunoreactive signals to β-tubulin signals on the same blots. TrkA levels were reduced ~50% in the temporal cortex of mild AD subjects, whereas $p75^{NTR}$ levels were not changed across the diagnostic groups. Adapted from Counts SE, et al. (2004) Reduction of cortical TrkA but not p75(NTR) protein in early-stage Alzheimer's disease. *Annals of Neurology* 56: 520–531, with permission from John Wiley & Sons Inc.

For instance, to analyze protein–protein interactions, target protein complexes can be isolated by immunoprecipitation or chromatography followed by western blotting to probe for potential binding partners. Likewise, western blotting can be used to verify proteins of interest in exploratory proteomic techniques such as two-dimensional gel electrophoresis. Thus, the western blot procedure is an essential tool for protein analysis of complex systems, and the identification of potential mechanisms underlying aberrant tissue function or disease.

See also: Confocal Microscopy; Gene Microarrays; RNA Interference; Stereology.

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Westphal Variant

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Glossary

Athetosis – A worm-like, twisting or writhing movement of the limbs or trunk.
Bradykinesia – Slowness of movement. Often accompanied by hypokinesia or paucity of movement.
Chorea – 'Dance-like' involuntary movements that can affect the limbs, trunk, diaphragm, tongue, facial muscles, and any other muscles that are ordinarily under voluntary control.
Dopaminergic agent – A drug that increases dopamine content, function, or action in the brain. Includes levodopa, which is converted into dopamine in the brain, dopamine agonists, such as pramipexole and ropinirole, monoamine oxidase inhibitors such as selegiline and rasagiline, which prevent the breakdown of dopamine released into the presynaptic space, and amantadine, the exact mechanism of action of which is not fully understood.
Dystonia – An increase in muscle tone accompanied by stiff or awkward posturing of the affected body part, typically in an extreme end of the range of motion.
Hyperkinesia – Excessive amounts of movement. Depending on the part of the limb affected, hyperkinetic movements may appear fidgety (for instance, in the fingers of trunk), athetotic, choreiform, of ballistis (for instance, involuntary movements of the shoulder girdle may result in ballistic, flinging movements of the entire arm).
Opisthotonus – Hyperextension and rigidity of the back and neck.

Definition and History

'Westphal variant' is an eponym of moderate historical interest, but of unclear definition and uncertain clinical or biological relevance. The term was coined in recognition of the lengthy description by Professor Westphal in 1883 of an 18-year old with progressive posture and gait changes, his term for which was translated into English as 'pseudosclerosis,' to emphasize its distinction from other progressive sclerosing conditions (such as multiple sclerosis). It was recognized only later that Westphal's patient in fact had Huntington's disease, and the term 'Westphal variant' came to be used to describe people with Huntington's disease whose initial clinical presentation was heavily laden with rigidity and hypokinesia. Additional reports accrued over the next 80 years of dystonic, hypokinetic Huntington's disease patients, whose presentation contrasted strikingly with the typical choreiform, hyperkinetic movements that defined this disease (which at that time was known as Huntington's chorea). These case reports were summarized in great detail in a lengthy and influential work by Professor Georges Bruyn in 1968.

Bruyn used the term 'Westphal variant' to describe a broad range of Huntington's disease-related features. In addition to a 'primary' Westphal presentation, he recognized that adults with Huntington's disease often 'develop the Westphal variant in the ultimate stage' of their disease. He made a number of other observations about the Westphal variant:

1. it may present with rigidity alone or in combination with dystonic chorea.
2. rigidity may later give way to chorea.
3. there can be a dissociation between the akinesia or bradykinesia, and the rigidity. He was quite emphatic but confusing on this point, perhaps meaning that akinesia can be seen in patients who do not have the Westphal variant, but that it is the combination of akinesia with rigidity that is critical to the definition of the Westphal variant.
4. a fine (postural) tremor often accompanies the other symptoms.
5. an abnormal 'putaminal' posture is common (adduction of the arm with flexion of the elbow, wrist, and fingers, and hyperextension of the lower extremities, similar to a 'decorticate' posture).
6. other clinical features that often accompanied akinesia and rigidity in the Westphal variant included dystonia, athetosis, torticollis, opisthotonus, pyramidal involvement, abnormal vertical pursuit eye movements, and inability to perform facial commands such as frowning, raising eyebrows, protruding the tongue, and whistling. Dementia and dysarthria were universal, and patients often developed complete immobility, mutism, cachexia, and decubitus ulcers.

This represents, historically, the broadest use of the term 'Westphal variant.' The term is usually used in a more restricted fashion today.

Epidemiology

The majority of people presenting with this variant are children or young adults. Noting this, Kremer went so far as to say that 'a patient with a Westphal variant and a disease onset after age 50 should be considered exceptional, warranting publication.' The published incidence of this variant among adults with Huntington's disease is 6–12%.

Bruyn made the interesting observation, based on his thorough review, that the vast majority of Westphal variant cases reported in the literature were female. This thought, otherwise forgotten – and still unexplained – was echoed three decades later by Louis and his colleagues at Columbia University, who found that 13 of their 15 dystonic Huntington's disease patients were female.

Confusion About the Definition

The concept of the Westphal variant has been confounded by the distinct tendency for patients with juvenile-onset Huntington's disease to present with rigidity and akinesia rather than chorea. Bruyn would use the term 'Westphal variant' to describe anyone, child or adult, presenting with (or later developing) rigidity, hypokinesia/akinesia, and lack of chorea, as the predominant motor phenotype. Some later writers use the term specifically to refer to (rigid) juvenile-onset Huntington's disease, while others use the term to refer only to adults presenting with rigidity and hypokinesia. Still some use the term essentially as a synonym for rigid-akinetic Huntington's disease whenever it occurs in any patient.

Two other issues complicate today's interpretation of the clinical literature on the Westphal variant. Firstly, twenty-first century readers of the twentieth century literature maintain some skepticism about the accuracy of the diagnosis of reported cases prior to the advent of genetic testing. And secondly, the use of neuroleptic and other dopamine-depleting and dopamine-blocking agents, popularized in the later half of the twentieth century, could easily render a choreic Huntington's disease patient rigid and bradykinetic, creating a 'secondary Westphal variant.'

It remains unclear today whether the term Westphal variant should be used to describe the entire syndrome complex (including nonmotor features) in patients presenting with early rigidity-akinesia or just the motor syndrome, whether it should refer solely to children, solely to adults, or both, and whether it should refer to a patient's initial (untreated) presentation it can also encompass the later development of rigidity and akinesia in late-stage patients or patients whose rigidity and akinesia are entirely or partially caused by medications.

Pathological Correlates

Lending some biological credence to the concept of a rigid form of Huntington's disease are two pathological studies hinting at a neuropathological correlate to the clinical syndrome. While in hyperkinetic Huntington's disease, striatal neuronal loss is most prominent in the projections to the globus pallidus externa, two groups have shown an association between rigidity as a primary clinical feature and prominent loss of striatal projections to the substantia nigra and globus pallidus interna. It should be a testable hypothesis, in the modern brain imaging era, that early and prominent loss of pallidal (interna) projections is more common in children and young adults (and perhaps in females) and that the timing and severity of this loss is what determines whether a person clinically presents with (or develops) the Westphal variant.

Clinical Relevance

In the end, it is debatable whether the term 'Westphal variant' is a useful one. The concept of a rigid-akinetic form of Huntington's disease is certainly important in the diagnosis, treatment, and understanding of the disease. Clinicians unattuned to the possibility of Huntington's disease in a patient lacking chorea who has evident rigidity, dystonia, or bradykinesia can fail to make the correct diagnosis, with consequences for both the patient and the family. Although there is no rationale for the use of dopaminergic agents in patients with chorea, there are case reports documenting the benefits of dopaminergic agents such as levodopa and amantadine in Huntington's disease patients with rigidity, dystonia, and hypokinesia. And indeed, a better understanding of influences of age, gender, and disease duration on the development of this clinical phenomenon might help us to understand the genetic, environmental, biological, developmental, and neuropathological underpinnings of Huntington's disease.

Unfortunately, the eponym 'Westphal variant' has no firm definition, is used in a contradictory fashion by different experts in the field, and as an eponym, conveys no information directly to the listeners or readers. It may be preferable to abandon the use of this term and instead refer to the 'rigid-akinetic presentation' of Huntington's disease, which, in summary, (1) is common as an initial presentation in juvenile Huntington's disease, (2) occurs in 6–12% of adults with Huntington's disease, but almost exclusively in young adults, (3) appears to be more common in females, (4) may correlate with loss of neuronal projections to the globus pallidus interna, and (5) commonly develops as the disease progresses in patients of all ages.

See also: Athetosis; Bradykinesia; Chorea; Choreiform Disorders; Dystonia; Dystonia, Secondary; Rigidity.

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Whipple's Disease

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Glossary

Bruxism – Grinding of the teeth or clenching of the jaw which may be involuntary (may be considered a form of focal dystonia).

Cell-mediated immunity – Recognition of antigen by T cells and secretion by T cells of lymphokines that enhance the ability of macrophages to remove the antigen. Independent of antibody production.

Humoral immunity – Antibody production by B cells for the purpose of neutralizing foreign antigen.

Myorhythmia A hyperkinetic involuntary movement disorder characterized by a tremor of irregular frequency (from 1 to 4 Hz).

Myoclonus – Quick lighting-like involuntary twitch or spasm of a muscle or group of muscles. The pattern of the movements is usually not rhythmic.

Periodic acid-Schiff (PAS) – A histological staining technique used to identify carbohydrates in tissues.

Polymerase chain reaction (PCR) – A technique used in molecular genetics to analyze short segments of DNA or RNA by amplifying it in a test tube so it can be studied in greater detail.

Definition and History

Whipple's disease is a rare disease that predominantly affects the gastrointestinal (GI) tract, the mesentery, the heart, the joints, and the central nervous system (CNS), but can affect almost any tissue of the body. The illness is caused from infection by the bacillus *Tropheryma whipplei.* Dr. George H. Whipple first described a disease he called lipodystrophia intestinalis in 1907. His patient had infiltration of the intestinal mucosa and lymph nodes with foamy cells as well as inflammatory changes in the aorta, the pleura, and the pericardium. Curiously, it was later discovered that Whipple's patient was not the first documented case of the disease. A.D. Morgan, when reorganizing GI sections at Westminster Hospital in London, discovered a specimen of intestine that was incorrectly labeled as stomach. When he applied the periodic acid-Schiff (PAS) stain to it, it was strongly positive. This specimen was from a patient evaluated in 1895, making it the first documented case of Whipple's disease, though it was not correctly diagnosed at the time. In 1948, Black-Shaffer et al. in the *American Journal of Pathology* described the histopathological criteria for the diagnosis of lipodystrophy intestinalis and recommended it be named 'Whipple's disease.'

CNS symptoms of Whipple's disease were only thought to be present in patients who had not been

appropriately treated. It was Knox et al. in 1976 who first described late CNS complications ('dementia, myoclonus, ataxia, and supranuclear ophthalmoplegia') in patients who were treated and had shown initial response to antibacterial therapies.

The organism initially described by Whipple was thought to perhaps be a spirochete, because he was able to demonstrate rod-shaped organisms that 'closely resembled the tubercle bacillus.' It was not until the early 1960s that the bacillus was demonstrated using electron microscopy and was confirmed to be of bacterial origin. The bacterium was found by most to be Gram positive and Acid-Fast Bacillus (AFB) negative. Its bacterial genome was sequenced in 1991 and was classified into the Actinomycetes class at that time. The name *Tropheryma whipelii* was given, but this was changed in 2001 to the current form to accurately represent the true spelling of Dr. Whipple's name.

Pathogenesis/Pathophysiology

The pathogenesis of *Tropheryma whipplei* is as yet still very poorly understood. The DNA of the bacillus has been found in sewage plant waste and in human feces, so it is speculated that the organism could be transmitted through a fecal–oral route similar to that of *Giardia lamblia*. The DNA of *T. whipplei* has been found in the saliva and the feces of a small percentage of healthy subjects. It has also been speculated, therefore, that people who do get Whipple's disease are genetically predisposed to it. *T. whipplei* tends to invade the small intestine from the lamina propria layer rather than from the lumen. When it is found intracellularly it does not seem to cause any direct cell injury, nor does it cause an intense immune response. Rather, it causes an influx of macrophages, and to a much lesser degree, neutrophils and eosinophils. It seems that the bacillus induces a cell-mediated immune response rather than a humoral immune response. The majority opinion is that T cells are diminished in their ability to activate macrophages in affected patients. The macrophages still maintain their ability to phagocytosize, but their ability to completely degrade all bacterial antigens is impaired. Of note, granulomas can also be found in Whipple's disease patients. They have been reported in one-tenth of patients, which has caused some of them to be misdiagnosed as having sarcoidosis.

Epidemiology/Risk Factors

The typical patient who has contracted Whipple's disease is male (87% of patients), Caucasian (over 95%), and is 40–60-year old (60%). Overall, though, it is a very rare disease as >1000 cases have been reported so far. Patients who have been farmers or who are in farm-related trades account for <1/3 of reported cases. There have also been cases of multiple first-degree relatives acquiring the disease as well as multiple people from the same village or town who had the disease. From these latter points, it may be deduced that the disease may be acquired from the environment, that either the disease is transmissible from human to human (though direct transmission is highly unlikely), or that there is genetic predisposition to fall sick from it. Accordingly, about 26% of cases of the disease have been found to be HLA-B27 positive further suggesting a genetic tendency for Whipple's.

Clinical Features and Diagnostic Criteria

The classic clinical features of Whipple's disease are weight loss, diarrhea, and arthralgias though about 15% of cases can present with other symptoms. Other manifestations may also include culture negative endocarditis (rare) or Whipple's with isolated infection of somewhere along the neuroaxis. The Whipple bacillus can infect almost any organ or tissue of the body. The organs that seem to be least affected are the kidneys, the thyroid, and the testes.

Neurologically, the most common symptoms encountered are cognitive changes, ophthalmoplegia, and myoclonus. The cognitive changes usually present as an encephalopathy that can advance to a progressive dementia. Ophthalmoplegia with this disease is of the external type; vertical supranuclear gaze palsy may occur. Myoclonus tends to affect the head, trunk, and upper extremities, though it can occur anywhere. It has been proposed that these three symptoms be a diagnostic triad for CNS Whipple's disease. Other neurologic symptoms may include seizures, nystagmus, hypothalamic signs (insomnia, hypersomnia, polydipsia), cerebellar ataxia, cranial nerve dysfunction, and hemiparesis. Movement disorders associated with this disease include myoclonus (cerebral, brainstem, and spinal localizations), palatal tremor, parkinsonism, other types of tremor, dystonia (in the form of bruxism), and oculomasticatory myorhythmia. Oculomasticatory myorhythmia and the associated oculofacialskeletal myorhythmia are seen in about 15% of cases and are considered pathognomonic signs of CNS Whipple's disease. Whipple's disease not only can present with any of these isolated symptoms, but also these symptoms can be seen with more classic Whipple's symptoms (see above). The last form of neurologic symptomotology is relapse from classic disease after successful treatment. This form may occur many years after successful treatment, and it usually involves a progressive dementia that is quite refractory to medical treatment. Other symptoms of CNS relapse may include ataxia, hypothalamic signs, ophthalmoplegia, seizures, and hemiparesis, and psychosis.

E.D. Louis et al. have proposed diagnostic criteria for CNS Whipple's disease in their 1996 paper (see **Table 1**) based on a literature review of 84 cases.

Table 1 Guidelines for diagnostic screening, biopsy, and treatment of CNS Whipple's disease (WD)

Definite CNS WD
Must have any one of the following three criteria:
1. Oculomasticatory myorhythmia or oculofacialskeletal myorhythmia
2. Positive tissue biopsy
3. Positive polymerase chain reaction (PCR) analysis
If histological or PCR analysis is not performed on CNS tissue, then the patient must also demonstrate neurological signs. If histological or PCR analysis is performed on CNS tissue, then the patient need not demonstrate neurological signs (i.e., asymptomatic CNS infection)
Possible CNS WD
Must have any one of four systemic symptoms, not of another known etiology:
1. Fever of unknown etiology
2. Gastrointestinal symptoms (steatorrhea, chronic diarrhea, abdominal distension, or pain)
3. Chronic migratory arthralgias or polyarthralgias
4. Unexplained lymphadenopathy, night sweats, or malaise
Also must have any one of four neurological signs, not of another known etiology:
1. Supranuclear vertical gaze palsy
2. Rhythmic myoclonus
3. Dementia with psychiatric symptoms
4. Hypothalamic manifestations

Source: Louis ED, Lynch T, Kaufmann P, Fahn S, and Odel J (1996) Diagnostic guidelines in central nervous system Whipple's disease. *Annals of Neurology* 40(4): 561–568.

Differential Diagnosis

Because it can affect almost every organ system, Whipple's disease is a mimicker of many diseases. In the classic presentation, it can be confused with any disease that causes malabsorption. As other symptoms become apparent, the disease has historically been misdiagnosed as other multisystem diseases such as sarcoidosis, collagen vascular diseases, syphilis, and lymphoma. Because of the wide variety of presentations of CNS Whipple's, the diagnosis should be entertained in suspected cases of any progressive dementia (e.g., Alzheimer's disease and Creutzfeld–Jacob disease), HIV infection, Lyme disease, CNS lymphoma, neurosarcoidosis, Lupus cerbebritis, and vitamin B12 associated neurologic disease.

Diagnostic Work-up/Tests

After the diagnosis of Whipple's disease has been considered based on clinical criteria (see **Table 1**), there are a number of blood, radiological, and pathological studies that can be done to help confirm the diagnosis. In lab studies, some expected findings would be leukocytosis, steatorrhea, anemia, and elevation of acute-phase reactants. For CNS disease, MRI has been shown to be superior to CT for detecting smaller lesions. Expected MRI lesions may show T1 hypointensity and T2 hyperintensity. The lesions typically do not have any mass effect and may enhance after administration of gadolinium. The most common sites of involvement on MRI imaging are the medial temporal lobes, the hypothalamus, and the pons. Atrophy may also be present.

Widely considered one of the most sensitive techniques, biopsy of the small bowel via endoscopic techniques can be done to reveal PAS positive macrophages. Electron microscopy can also be done in conjunction to reveal the characteristic tri-laminar appearance of the organism's cell wall or sickle-shaped inclusions inside of macrophages (remnants of the cell walls). PAS staining can also be done on other tissues, but it can be less specific of a test.

A more recently utilized procedure of testing is polymerase chain reaction (PCR) techniques. If a patient is suspected of having more localized symptoms of Whipple's disease, a PCR assay can be done on most tissues. Multiple reviews suggest that a diagnosis of certain Whipple's disease can be made if a tissue is both PAS and PCR positive while positivity of either one or the other implies a possible diagnosis.

Management

Management of this disease involves introduction of antibiotics as soon as the diagnosis is suspected or confirmed. Because of the high rate of CNS involvement, the antibiotic should have the ability to penetrate the CNS by crossing the blood–brain barrier. Some such medications are trimethoprim-sulfamethoxazole (TMP/SMX) and ceftriaxone. Some other medications that have been used include penicillin, chloramphenicol, tetracyclines, doxycycline, ampicillin, some fluoroquinolones, and streptomycin. There does not seem to be a universal consensus for treatment, and no clinical trials exist for treatment because of the rarity of the disease. Some recommended antibiotic courses include IV penicillin G and streptomycin for 10–14 days followed by TMP/SMX by mouth for 1 year; doxycycline and hyroxychloroquine for 1 year with possible addition of SMX if CNS symptoms are present; and Penicillin G for 2 weeks followed by TMP/SMX by mouth for 1 year. Previously treatment courses were prescribed for as little as 3–6 months, but now that there is more experience in the outcomes of relapses, treatment for a year or more is the norm. When treating CNS disease or CNS relapse, monitoring of CSF PCR may help to dictate how long the treatment should last. Some recommend at least 2 years of additional treatment following CNS relapse.

Corticosteroids should not be used for treatment of this disease unless it is for symptomatic treatment of the acute phase of the illness. One study has cited that use of intravenous immunoglobulin (IVIg) in conjunction with antibiotic therapy in a patient who was diagnosed after

3 years of disease progression. The IVIg was started after the patient failed to show clinical response after being treated with antibiotics for 2 weeks. The patient subsequently showed some improvement. Use of interferon γ has also been used specifically for the CNS relapse form of the disease.

Prognosis

Untreated Whipple's disease invariably leads to death. With proper treatment, though, the disease can be brought into remission. Treatment with antibacterial agents treats any and all of the symptoms listed above. The exception is that if the disease is left untreated for some time, CNS symptoms such as dementia arise and may be more refractory to treatment. The earlier the patient is treated in the course of the disease, the higher the likelihood of treatment success.

See also: Oculomasticatory Myorhythmia.

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Wilson, Samuel Alexander Kinnier

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Glossary

Clinical method of neurology – The rational process by which a neurologist makes a diagnosis, which is the sequence from symptoms to syndrome to disease. In the diagnostic process, laboratory data are subordinated to the clinical aspects of the disease.
Extrapyramidal motor system – Motor structures in the basal ganglia: caudate nucleus; lenticular nucleus with its two subdivisions, the putamen and globus pallidus; thalamus; subthalamic nucleus; substantia nigra.
Extrapyramidal syndromes – Clinical syndromes characterized by reduction of movement (akinesis, rigidity, or dystonia) or excess of movement (hyperkinesis, ataxia, or athetosis) due to disease of the extrapyramidal motor system.
Movement disorders – A group of diseases and syndromes affecting the ability to produce and control movement. Disorders causing abnormal movements and postures due to disease of the extrapyramidal motor systems include, among many others: Wilson's disease, Parkinson's disease, Huntington's disease, inherited ataxias, and Tourette syndrome.
Orphan diseases – Rare diseases, prevalence less than 150 per 1 000 000. Wilson's disease has been the first orphan disease for which an orphan drug, penicillamine, has been developed.

Biographical Data

Samuel Alexander Kinnier Wilson (1878–1937) studied medicine in Edinburgh. He obtained his Bachelor of Medicine degree in 1902 and started to work in 1904 in the National Hospital, Queen's Square, London, where he became a registrar in neurology and trained to become a pathologist. While working at the National Hospital, Wilson became interested in a patient whose mysterious disorder prompted him to perform a thorough clinical and pathological study. His thesis (University of Edinburgh, 1911) was

entitled '*Progressive Lenticular Degeneration; A Familial Nervous Disease Associated with Cirrhosis of the Liver.*' Wilson was appointed as the professor of neurology at King's College Hospital – the first chair of this discipline in England. He died of cancer in 1937, at the age of 59.

Thesis (1911)

In his thesis, Wilson described four patients whom he had observed personally and eight similar cases he had found in the literature. Wilson performed the autopsy and neuropathological studies on three of his patients. Wilson's paper introduced the term 'extrapyramidal' into neurology and focused attention upon the importance of the basal ganglia. Wilson gave an exceptionally thorough and well-written description of the clinical characteristics of progressive lenticular degeneration, and much of what he reported is still valid today (**Figure 1**). To illustrate this, a summary of one of the case histories is given.

Patient ST

A 26-year old woman was under observation in the National Hospital, London. She was the youngest of nine children. The family history was uneventful. Except for dysmenorrhea, the patient had been in perfect health up to the age of 21, when she suffered a self-limiting attack of jaundice with duration of ~5 weeks (**Figure 2**). Since then, she has complained of edema in her legs. At the age of 25, she experienced that her right hand trembled when she attempted to write, and that her speech had become slurred. In the course of the next year, her condition worsened noticeably. The tremor spread to the left arm. A stiffness of the musculature was noted and abnormal posturing of the head, trunk, and limbs developed. Her mouth was often open; her face wore a constant smile, and saliva occasionally escaped from her mouth. Her relatives said that her emotional condition had changed; she had become restless, was easily provoked to laughter, and had become unnaturally cheerful. Her mental acuity and memory had apparently been left unchanged.

It was obvious to Wilson that the nervous disease of this patient did not correspond to any familiar type. Although the disease bore some resemblances to disseminated sclerosis and paralysis agitans, it was quite distinct from either. Wilson was struck by the fact that the clinical condition of this patient was quite similar to that of another patient with a mysterious neurological disease, in whom, autopsy revealed unexpected cirrhosis of the liver. The patient died suddenly after an acute attack of hematemesis at the age of 29 years.

Wilson himself performed the autopsy, 25 h after death. The liver had a striking appearance. It was cirrhotic and its surface was covered with irregular rounded nodules. Histological examination of the brain showed that bilateral and symmetrical destruction of the lenticular nucleus had occurred (**Figure 3**).

Wilson concluded his thesis with the hypothesis that the abnormalities in the brain might be caused by a toxin generated within the cirrhotic liver.

Figure 1 Samuel Alexander Kinnier Wilson (1878–1937), the British neurologist who described, in 1911, an extrapyramidal movement disorder associated with progressive lenticular degeneration and cirrhosis of the liver (hepato-lenticular degeneration, 'Wilson's disease'). Reproduced from Hoogenraad TU (2001) Kinnier Wilson SA (1878–1937) *Journal of Neurology* 248: 71–72, with permission from Jim Kinnier Wilson.

The First Extrapyramidal Motor Syndrome: Rigidity, Distorted Posture, and Tremor

In 1911, Wilson introduced the term extrapyramidal motor syndrome, which he delineated on clinical grounds. In the movement disorder, he described that the most striking abnormality in the nervous system was cavitation

Figure 2 Pictures from Wilson's PhD thesis. Patient S.T. (left) before the onset of symptoms; (right) at the age of 28 years, 4 years after the onset of neurological symptoms, she had a spastic smile and severe generalized dystonia. Reproduced from Wilson (1912), with permission from Oxford University Press.

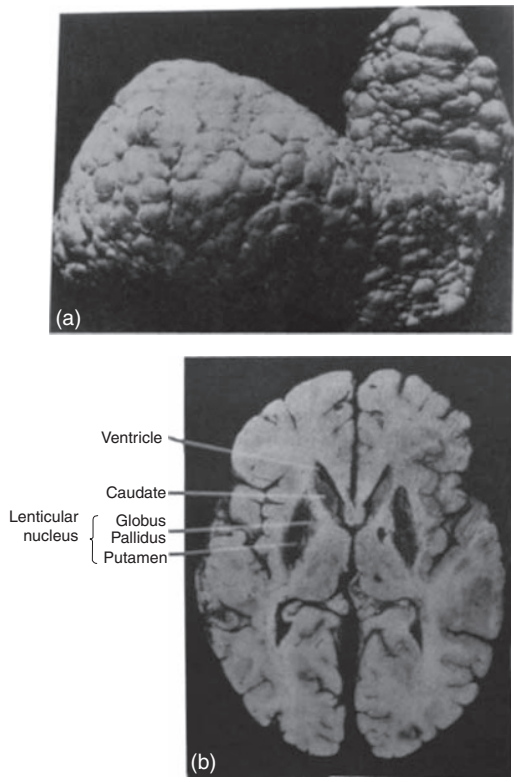

Figure 3 Patient S.T. (a) Cirrhotic liver; (b) bilateral and symmetrical cavitation of the lenticular nucleus. Reproduced from Wilson (1912), with permission from Oxford University Press.

of the putamen of the nucleus lentiformis. Wilson attributed the characteristic symptoms of rigidity, distorted posture, and tremor to the lenticular lesion and in this way, these three symptoms formed the first extrapyramidal motor syndrome. We now know that in Wilson's disease, the neurodegenerative changes are widespread and not at all localized to the nucleus lentiformis. Nevertheless, the striking demonstration by Wilson of lenticular cavitation in patients with rigidity, distorted posture, and tremor is a milestone in the history of movement disorders.

Wilson's Disease and the 'Clinical Method of Neurology'

In the preface of their textbook '*Principles of Neurology*,' Adams and Victor remarked that although neurology is regarded by many as one of the most difficult and exacting specialities of medicine, many of the difficulties could be overcome by adhering to the basic principles of '*The Clinical Method of Neurology*.' Subsequently, they refer to the rational mental process by which a neurologist makes an accurate diagnosis, by following the diagnostic sequence from symptoms to syndrome to disease. In this mental process, laboratory data are subordinated to the clinical aspects of the disease. Wilson has been a protagonist of this clinical method of neurology. As clinician, Wilson took little interest in laboratory work and most of his numerous papers concerned clinical neurology.

A major purpose of the clinical method of neurology is to accomplish an accurate diagnosis and to determine the proper treatment of the patient. By creating the concept of the extrapyramidal system and the extrapyramidal syndrome, Wilson made a major contribution to the syndrome diagnosis, an important step in the clinical method of neurology.

A major aim of the clinical neurologist is not to overlook a disease for which there is an effective treatment. For copper toxicosis in Wilson's disease, effective and safe treatment is available since the introduction of antidotal zinc therapy. Therefore, in accordance with the principles of neurology and in order not to overlook the treatable hereditary copper toxicosis, Wilson's disease should be included in the differential diagnosis of all patients with unexplained movement disorders, especially in syndromes dominated by dystonia, parkinsonism, or ataxia.

See also: Wilson's Disease.

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Wilson's Disease

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Glossary

Antidote – A substance which can counteract a form of poisoning; zinc is an antidote for copper poisoning.
Chelating agent – Metal binding agent used to remove metals from the body.
Clinical method of neurology – The evidence based approach to neurologic medicine.
Deductive method – The method of offering general causal explanations for a phenomenon and then testing them deductively against their predictions. The method aims at identifying errors.
Evidence-based medicine – The conscientious use of current best evidence in making decisions about the care of individual patients.
Free copper – The small portion of plasma copper that is not bound to ceruloplasmin.
Inductive method – Induction-based experiments seek verification of the theory.This method does not detect errors and may lead to entrapment in fallacies.
Penicillamine fallacy – The tragic, induction-based misconception that treatment of copper toxicosis can best be started with the chelating agent penicillamine.
Seductive method – The method of choosing a therapy simply on the basis of recommendations of authorities, experts, pharmaceutical representatives, or advertisements.
Zinc therapy – The use of zinc supplements to treat copper poisoning. It is based on the current best evidence available. Zinc therapy offers maximum benefits with minimal risks.

Definition and History

Wilson's disease is a rare autosomal recessive hereditary disease caused by a defect in the cellular copper transport that leads to failure of copper excretion into the bile and to a failure of incorporation of copper into the ceruloplasmin. Poisoning by unbound 'free' copper results and manifests itself with neurological symptoms and liver disease.

The approach to the patient with neurological Wilson's disease should be in accordance with the clinical method of neurology, that is, with the basic principles of clinical medicine.

Milestones in the history of Wilson's disease (**Figure 1**; **Table 1**): In 1911, Wilson gave a conscientious description of the clinical characteristics of hepatolenticular degeneration. It was the first study in which a link was made between a movement disorder and degenerative lesions in the basal ganglia. In 1912, Alzheimer described abnormal glia cells and normal ganglion cells in the grey matter of a patient with hepatolenticular degeneration (**Figure 2**). In 1912, Fleischer described that the brown–greenish corneal ring, first described by Kayser, is a highly specific characteristic of hepatolenticular degeneration (**Figure 3**). In 1948, Cumings discovered that the urinary copper excretion is increased in patients with Wilson's disease, and suggested that copper accumulation could be the cause of Wilson's disease. In 1956, the biochemist Walshe published in *The Lancet* an article on a new oral therapy after he had discovered that treatment of Wilson's disease patients with penicillamine stimulated excretion of copper via the urine. It became a methodological milestone: a shift in approach from the clinical method of neurology to an inductive biochemical method. In 1961, the neurologist Gerrit Schouwink (**Figure 4**) published, in Dutch, his doctoral thesis on the influence of zinc supplementation in Wilson's disease. He described that the copper balance became negative when zinc sulfate was administered.

In 1978, we published, a letter to the editor of *The Lancet* entitled: 'Oral zinc in Wilson's disease.' This letter to *The Lancet* would generate widespread interest in the possibilities of zinc therapy. In 1996, publication of monograph: Wilson's disease, in the *Series Major Problems in Neurology*. Development of hypothesis that Wilson's disease can be seen as juvenile free copper toxicosis (**Figure 5**). In 2008, disclosure of hypothesis that age-related (type-II) free copper toxicosis may play a role in the pathogenesis of age-related cortical neurodegenerative Alzheimer's disease (**Figure 5**).

Pathogenesis/Pathophysiology

Wilson's disease is an autosomal recessive disorder. The responsible gene on chromosome 13 encodes a transmembrane protein ATPase (ATP7B), which functions as a copper-dependent P-type ATPase. The protein has a synthetic role for incorporation of copper into ceruloplasmin, and an excretory role for excretion of copper into the bile. In Wilson's disease, defective ATP7B function results

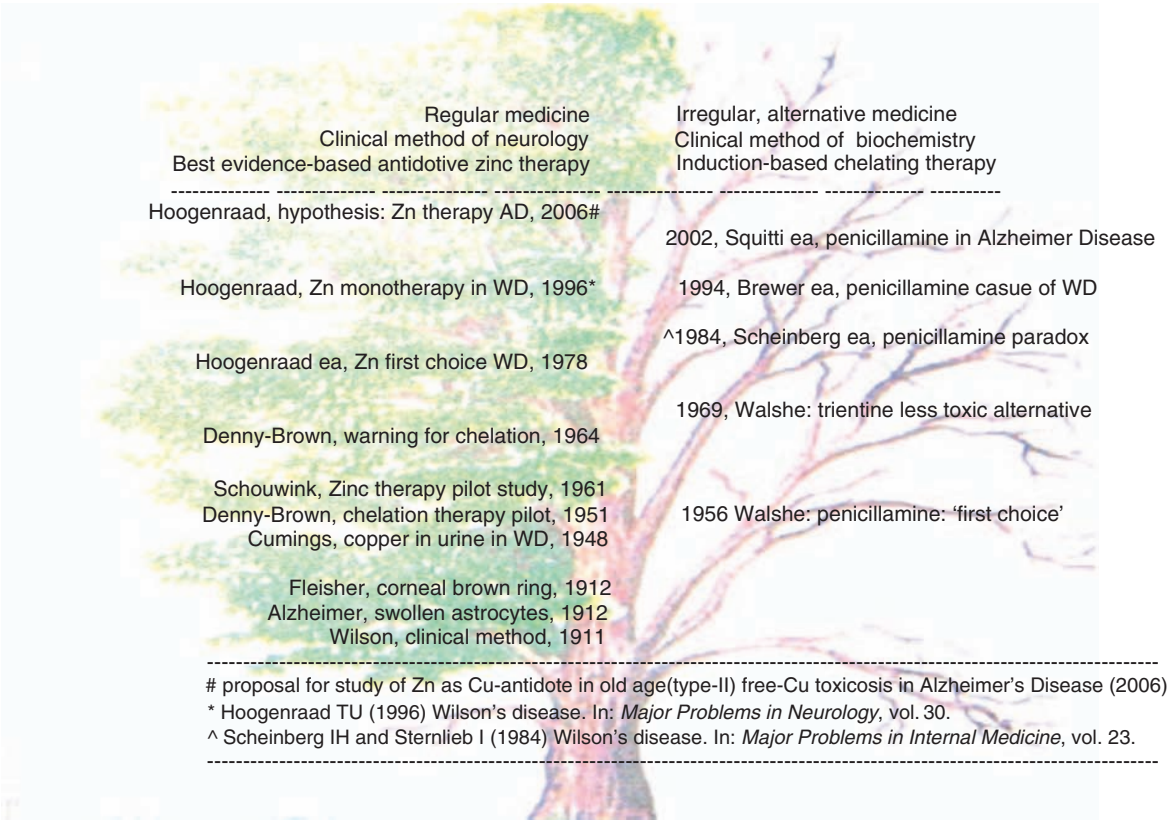

Figure 1 Symbolic tree of historic milestones of WD. Left: healthy, but rare, branches of regular medicine. Right: unhealthy, withered, but popular, ways of irregular, alternative treatments with chelating agents.

Table 1 Milestones in the history of Wilson's disease

1. Description of clinical characteristics of a juvenile movement disorder (Wilson, 1911)
2. Discovery of copper poisoning (Cumings, 1948)
3. Discovery of decoppering treatment: two oppositional strategies
   - Penicillamine therapy; chelation strategy (Walshe, 1956)
   - Zinc sulfate therapy; antidotal strategy (Schouwink, 1961)
4. Methodological shifts
   - 1956: from the clinical method of neurology to the inductive biochemical method
   - 1996: paradigm shift from copper accumulation to free copper poisoning

in increased serum level of free copper. This leads to free copper poisoning which causes the hepatic and neurological features of Wilson's disease.

The primary pathogenetic mechanism is the inherited defect in cellular copper transport that leads to failure of copper excretion into the bile and to a failure of incorporation of copper into ceruloplasmin. Increased levels of nonceruloplasmin bound copper induce metallothionein, a metal binding and detoxificating protein. Hepatic copper levels rise as increasing amounts of 'free' copper are bound to metallothionein in the hepatocytes. Increase of free plasma copper, and not copper accumulation, is the central feature of Wilson's disease. Poisoning by free copper manifests itself with neurological symptoms and liver disease.

Epidemiology/Risk Factors

The prevalence of Wilson's disease is about 1 in 30 000 with a carrier frequency of about 1 in 90.

Clinical Features and Diagnostic Criteria

Clinical symptoms of Wilson's disease usually develop between 3 and 40 years of age, but may begin even at an advanced age. Approximately 40% of patients present with hepatic disease, and another 40% present with nervous system disease.

Neurologic Wilson's Disease

There are three movement disorder syndromes in Wilson's disease: (1) dystonic, (2) ataxic, and (3) parkinsonian syndrome. These syndromes seldom occur in isolation.

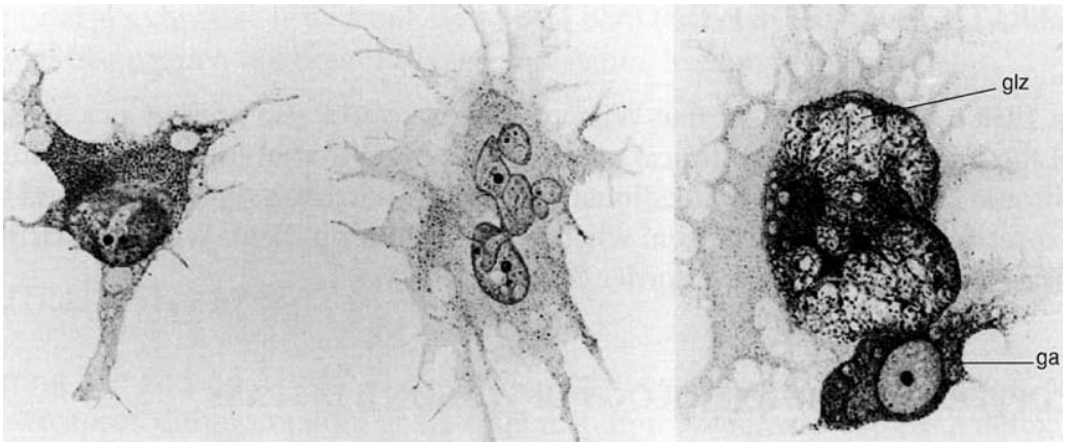

Figure 2 Pictures from Alzheimer's study on the neuropathology of pseudosclerotic hepatolenticular degeneration. *Left* – Alzheimer type-I cell: astrocyte with swollen nucleus and many granules. *Middle* – Alzheimer type-II cell: abnormal astrocyte with vesicular nucleus. *Right* – normal ganglion cell (ga) next to abnormal swollen glia cell (glz).

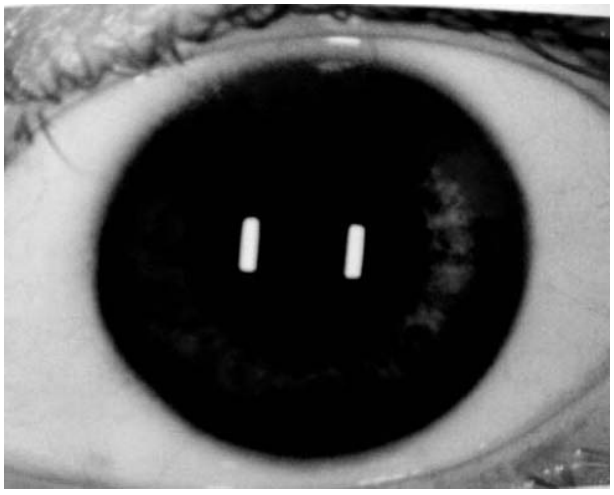

Figure 3 Circumferential brown-golden Kayser–Fleischer ring in the cornea of a 25-year old woman with Wilson's disease. The presence of the Kayser–Fleischer ring indicates that free copper has been released into the circulation. The deposits of copper in the ring are protein-bound and harmless.

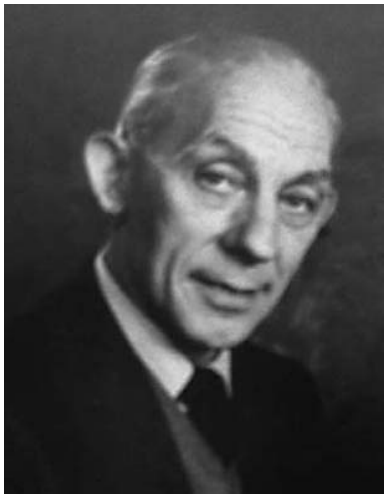

Figure 4 Gerrit Schouwink (1926–1999).
The Dutch neurologist Gerrit Schouwink who postulated in 1961 the hypothesis of zinc therapy in Wilson's disease.

Dystonia and choreoathetosis

Dystonia may be focal or generalized. Focal dystonia can appear in almost any part of the body. In severe cases generalized dystonia develops. Limbs become stiffer and over extension of the legs can lead to a clumsy gait. The fixed smile (risus sardonicus) seen in Wilson's disease represents a lower facial dystonia. Involuntary tic-like movements, like those seen in Tourette's syndrome, may be the first signs of Wilson's disease. Choreoathetosis is frequently seen in Wilson's disease. It is a major clinical problem.

Ataxic tremor

Various types of ataxic tremor may occur in one patient, especially postural and action tremor. Denny-Brown used the term flapping tremor when describing the postural tremor of the outstretched arms of Wilson's disease patients. The term wing-beating tremor is sometimes used for the proximal postural tremor enhanced by lifting the arms, flexing at the elbow, and holding the hands in pronation at chest level. The classical form of cerebellar tremor when the limb is in motion is also common. This type of tremor is present during voluntary movements such as drinking or writing.

Parkinsonian syndrome

Rigidity with lead-pipe stiffness, bradykinesia with slowness of movements, parkinsonian gait, and micrographia resemble the signs of the hypokinetic-rigid syndrome of Parkinson's disease. A typical rest tremor is frequently seen in the parkinsonian type of Wilson's disease.

Figure 5 Bronze sculpture symbolizing the hypothetic Wilsonian/Alzheimerian free copper toxicosis connection. The fish riding musselman (T.U.H) guides, with help of the small (Wilsonian) pilot fish on his fishing rod, the big (Alzheimerian) fish away from the dangerous, irregular, penicillamine pathway towards the regular, best evidence based, zinc route. The sculpture was modelled by T.U.H in 2006 and presented at conference on Alzheimer Disease at the Department of Neurology, Fatebenefratelli Hospital Rome as an illustration to the paper entitled: Free-copper disease: a new way of looking at Alzheimer's disease (June 19, 2006).

Another common symptom of Wilson's disease is dysarthria, related to involvement of the extrapyramidal system, the cerebellar nuclei, and the upper motor neurons. A mixed dysarthria with ataxic, hypokinetic, and dysphonic features is typical. Some patients may have anarthria with complete loss of speech.

Psychiatric symptoms are very common in Wilson's disease, and include irritability, depression, cognitive impairment, hallucinations, and delusions.

Hepatic Wilson's Disease

Liver disease may present as tiredness, increased bleeding tendency, or confusion (due to hepatic encephalopathy), and portal hypertension. The latter condition leads to esophageal varices, splenomegaly, and ascites. Chronic active hepatitis has caused cirrhosis in the liver of most patients by the time they develop symptoms. A small proportion, that is, ~5% of all patients is diagnosed only when they develop fulminant acute liver failure, often in the context of hemolytic anemia.

The Kayser–Fleischer ring is a golden brown or greenish pigmentation at the margin of the cornea near the limbus. It can often be detected with the naked eye, but slit-lamp examination may be required.

Early diagnosis is the keystone of the successful management of the patients with Wilson's disease. Most patients are children, adolescents, or young adults. Patients presenting with neurological manifestations often report symptoms suggestive of hepatic disease.

Table 2 Two laboratory tests needed to calculate free plasma copper for monitoring Wilson's disease

1. Total plasma copper (normal value: ± 1.00 mg l^{-1} or 16 μmol l^{-1})
2. Ceruloplasmin (normal value: >200 mg l^{-1})
Ceruloplasmin contains 0.3% copper.
Normal value of free copper: <0.10 mg l^{-1}
Example: (untreated Wilson's disease with free copper poisoning)
1. Total plasma copper: 0.60 mg l^{-1}. (decreased)
2. Ceruloplasmin: 100 mg l^{-1} (=0.30 mg l^{-1} copper bound to ceruloplasmin)
Calculated free copper = 0.60 mg l^{-1} minus 0.30 mg l^{-1} = 0.30 mg l^{-1} (increased)

Determination of free copper level is important for monitoring the effect of treatment (**Table 2**).

Differential Diagnosis

Wilson's disease should be included in the differential diagnosis of patients with unexplained syndromes dominated by dystonia, Parkinsonism, or ataxia. The diagnosis is easy to establish in individuals with neurological symptoms, Kayser–Fleischer rings, and low ceruloplasmin concentration.

Diagnostic Tests

There are several diagnostic laboratory tests:

1. Ceruloplasmin concentration decreased (<200 mg l^{-1});
2. Slit-lamp examination for Kayser–Fleischer rings;
3. Free plasma copper level (>0.10 mg l^{-1} or 1.6 μmol l^{-1});
4. Urine copper (>0.10 mg l^{-1} or 1.6 μmol l^{-1});
5. Liver copper concentration (>250 μg g^{-1} dry tissue);
6. Absence of incorporation of radio copper into ceruloplasmin;
7. DNA analysis.

Management

The approach to the treatment of a patient with neurologic Wilson's disease should be directed on the basis of its evidence.

The treatment of Wilson's disease has undergone a marked change over the years.

Old Treatment Aim: Stimulation Urine Copper Excretion

Initially, the focus of treatment was ridding the body of copper by increasing its excretion through the urine using chelation therapy.

Penicillamine

The aim of penicillamine chelation is to increase the copper excretion and remove copper from deposits in the tissues. Chelation promotes 'cupriuresis', the excretion of copper from the body via the urine. Walshe advised to start treatment with 1.5–2.0 g day^{-1}, but when used, the dose is more likely to be 125 mg day^{-1}. Penicillamine chelation is associated with Iatrogenic worsening of neurologic manifestations in a minority of patients during the first weeks of therapy. Even in those who tolerated the adverse effects, clinical improvement is slow, the first signs of improvement occurring after ~6 months. The side effects of penicillamine may be serious, and include systemic lupus erythematosus, nephrotic syndrome, myasthenia gravis, and elastosis perforans serpiginosa.

Penicillamine therapy is monitored by urinary copper levels. Scheinberg and Sternlieb advised to maintain urinary free copper at the normal value of 0.10 mg l^{-1}.

Penicillamine Fallacy

Evidence-based medicine disputes its efficacy and safety, and indeed much of the theory behind chelation therapy. The fatal flaw of the chelation strategy is that it is based on the method of induction. By abdicating, in 1956, to the copper chelation strategy, the approach to the patient with Wilson's disease changed from the scientific clinical method of neurology to an unscientific, inductive, alternative method of clinical biochemistry. In 1964, Denny-Brown warned against copper chelation using penicillamine and in 1969, Walshe introduced the concept of using trientene, a copper chelating agent believed to be less toxic than penicillamine. In 1994, Brewer warned against iatrogenic copper poisoning, the induction of copper poisoning by chelating agents.

New Treatment Aim: Normal Free Copper Level

Zinc therapy aims at the normalization of increased levels of free plasma copper, providing effective therapy with few side effects and low costs. The mechanism of action is based on the antagonism between copper and zinc. Zinc antagonizes the absorption of copper in the gut and promotes the excretion of copper via the stools. Zinc supplements stimulate the synthesis of the copper binding protein metallothionein in the mucosal cells in the gut and in the hepatocytes. Zinc supplements tend to normalize the plasma free copper level and the urine copper level.

Zinc Sulphate

Three daily doses of 200 mg zinc sulfate provide 135 mg of elemental zinc, and the dose is given in the form of tablets, capsules, or liquid before meals. The recommended dose is lower for children and adolescents. For children of age 6 and younger, 110 mg zinc sulfate is given twice daily (50 mg elemental zinc daily). Between age 7 and 16 years, 110 mg zinc sulfate is given three times daily (75 mg elemental zinc daily). The first effects of treatment can be expected within the first weeks or months of treatment. In general, the results are excellent or good. Zinc sulfate is an effective, well-tolerated, and inexpensive therapy for Wilson's disease. It is an excellent choice for both neurologic and hepatic Wilson's disease. Normalization of plasma free copper concentrations is a good intermediate goal of decoppering treatment. During effective therapy, urinary excretion of copper will also normalize to values below 0.10 mg Cu per liter.

Changing from Penicillamine to Zinc

Czlonkowska et al. compared treatment with penicillamine to treatment with zinc in 67 newly diagnosed Wilson's disease patients. The two treatments were equally efficacious, but penicillamine was less well tolerated. About 44% of penicillamine-treated *versus* 12% of zinc-treated patients discontinued treatment due to side effects. In 2002, Squitti et al. published on a clinical trial of penicillamine for free copper poisoning in Alzheimer's disease. The trial was discontinued due to severe, even fatal toxicity (**Figure 5**). Evidence-based medicine now suggests that copper chelation is hazardous, and favors a strategy aimed at normalization of free plasma and urine copper. The risks of treatment should be as low as possible.

Physicians treating penicillamine-treated Wilson's disease patients should inform them that penicillamine may be effective in the majority of patients, but that zinc therapy is the prefered mode of treatment of copper poisoning in Wilson's disease and that penicillamine should be withdrawn and that zinc therapy should be started.

Prognosis

Over the last 50 years, most patients with Wilson's disease have been treated with chelating agents. In these years, the prognosis has changed from a uniformly fatal disease to a treatable disease. However, the success of chelation treatment of copper toxicosis is counterbalanced by serious adverse effects. Up to now, only a few patients have profited from the therapeutic improvements realized by zinc sulfate monotherapy. The prognosis of treatment will profit intensively if the patients treated with penicillamine are changed over to zinc sulfate.

Acknowledgments

This article is dedicated to the clinical neurologist Gerrit Schouwink, and to Cassandra, patron of modellers. This work on rational treatment of copper poisoning could not

have been fruitfully accomplished without the very special stimulating help of Prof. J.van Gijn, former series editor of the series: Major problems in Neurology and former Head of the Department of Neurology of the UMC Utrecht.

See also: Kayser–Fleischer; Wilson, Samuel Alexander Kinnier.

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www.ncl.ac.uk/clsm/misc/cassandra.jpg – Cassandra, patron of the modellers.
www.wilsonsdisease.org/ – Wilson's Disease Association International.

Writer's Cramp

B Illowsky Karp, National Institutes of Health, Bethesda, MD, USA

Glossary

Writer's cramp – A form of focal hand dystonia activated by writing.
Musician's cramp – A form of focal dystonia activated by and specific to playing a musical instrument.
Repetitive stress injury – Damage to an area of the body, such as the hand, due to overuse. The predominant symptom of repetitive stress injury (RSI) is pain.
Complex regional pain syndrome (CRPS) – A syndrome consisting of pain, autonomic dysfunction, and skin changes in a traumatized body area.

Introduction

Focal hand dystonia (FHD) refers to dystonia, usually idiopathic and of adult onset, that affects the hand, fingers, and arm. FHD can interfere with the ability to perform activities of daily living, hobbies, and occupations. FHD is often named according to the affected activity, such as 'writer's cramp (WC),' or 'musician's cramp.' WC is the most common form of FHD.

Clinical Features

The onset of WC is usually insidious. Most patients recall a feeling of fatigue or aching when using the affected hand and arm with the need to take frequent breaks or rests. Eventually, there is involuntary posturing of the hand, cramping of muscles, and loss of motor control, leading to difficulty in controlling a pen and writing. The loss of fine motor control is particularly disabling to those with other types of FHD, such as musicians who rely on fast, fine, and accurate hand and finger movements.

Dystonic posturing in WC can involve flexors, extensors, or both of individual or multiple fingers, the wrist, and the

more proximal arm, as well as pronators, supinators, abductors, and adductors. Muscle tightness and cramping are uncomfortable, but rarely cause severe pain. Reflexes and sensation are normal, although careful testing may uncover subtle sensory integration deficits. Some patients have a decreased arm swing or a slightly increased resting tone in the affected arm but no other parkinsonism signs. Postural tremor accompanies WC in a little less than half of the patients. Primary writing tremor, in which tremor rather than dystonic posturing is elicited during writing, may be a variant of WC. Up to 50% of those with WC have 'mirror dystonia' in which the affected hand assumes a dystonic posture while writing with the nonaffected, nondominant hand.

FHD tends to develop in those who perform small, repetitive hand and finger movements. The particular pattern of flexion and extension can be characteristic of the type of activity usually performed. For example, writing requires flexion of the wrist and fingers and thus flexor muscles are more commonly involved in WC than extensors. Pianists and violinists with musician's cramp both tend to have dystonic flexion of the fourth and fifth fingers. However, in pianists, the right hand, which faces more technical demands in playing than the left hand, is more commonly affected. In violinists, the technical burden is on the left hand, which is thus more likely to become dystonic than the right bowing hand.

An interesting aspect of WC, present in about half of patients, is 'task specificity.' In such cases, the dystonia is only elicited by writing. Other actions, including those performed using the same hand and similar muscles or movements, are spared so that patients are able to type, draw, and put on makeup normally. Task specificity is also a feature of other forms of FHD. Some musicians with FHD can play other, even similar, instruments without difficulty. While task specificity is common and characteristic of FHD, in many patients, dystonia is elicited by almost any use of the hand or even imagined use of the hand. When severe, patients have dystonic posturing at rest. WC rarely generalizes, but can spread to more proximal muscles or to involve the other hand.

Differential Diagnosis

The differential diagnosis of WC includes repetitive stress injury (RSI) and mononeuropathy of the median or ulnar nerve. Similar to WC, RSI commonly affects a hand used in a repetitive fashion. Unlike dystonia, the most prominent symptom of RSI is pain, which may initially be present only during the use of the hand but can progress to produce pain even at rest. RSI is due to injury and inflammation and responds to rest and antiinflammatory medication.

Median and ulnar neuropathies can often be identified by sensory loss or weakness in the appropriate distribution, which are not present in WC. Although uncommon, some patients with ulnar neuropathy have involuntary flexion of the fourth and fifth fingers in the absence of other sensorimotor disturbances. In those cases, identification of ulnar nerve entrapment may require near nerve recording. In some cases, ulnar nerve release leads to resolution of dystonic posturing.

About 10–30% of patients with complex regional pain syndrome (CRPS), especially type 2 CRPS, have dystonia. The dystonia may appear before other CRPS symptoms and often differs from idiopathic FHD by the presence of fixed postures, pain, and persistence during sleep.

Epidemiology

WC most often begins in the fourth decade, somewhat earlier than blepharospasm or cervical dystonia. Epidemiologic studies report a prevalence of 7–69 per million population for writer's cramp and 0.2–0.5% for musician's cramp. Although most other focal dystonias are more common in women, FHD, especially musician's cramp, affects men more commonly than women. There appears to be a genetic component to FHD. Up to 20% of those with WC and 9% of those with musician's cramp have a family member with some form of dystonia. However, the genes and mutations identified to date in association with generalized and a few other focal dystonias are not common in those with FHD.

Pathophysiology

The diagnosis of WC is made clinically, based on the characteristics of the movement disorder and the absence of other neurological signs. There are no imaging or laboratory tests that are useful in making the diagnosis, although they may help to exclude an underlying cause of a secondary dystonia. The diagnosis of WC may be supported by EMG demonstration of a difficulty in initiating movement, prolonged and uncoordinated cocontraction of agonist/antagonist muscle pairs, and activation of muscles not typically used for a particular task.

While not specific to dystonia, physiologic studies have revealed a loss of inhibition at multiple cortical and subcortical levels involved in motor control and in sensorimotor integration. There is a loss of reciprocal inhibition at spinal and cortical levels. Transcranial magnetic stimulation studies have identified deficient intracortical and 'surround' inhibition, which serves to prevent movement of nearby muscles not needed during the performance of a particular task.

Increasing attention is being focused on identifying and understanding sensory abnormalities in dystonia and the role the sensory system may play in the pathophysiology of this movement disorder. Defects in temporal and spatial sensory discrimination as well as distortion of cortical sensory maps have been identified in patients with WC, both in the dystonic and in the nondystonic hand.

Many people who develop WC report writing excessively. However, the role of overuse in the development of such focal dystonia is uncertain. Similarly, while musicians and others with occupations who rely on overpracticed, repetitive movements seem prone to FHD, most of those in such occupations do not develop dystonia. In addition, FHD and WC often arise in those with no more than average use of their hands. It has been proposed, therefore, that the development of FHD requires both a genetic predisposition and a trigger, such as overuse.

Treatment

Most people who develop symptoms of FHD first try adapting or altering the way they perform the acts that elicit the dystonia. For example, those with WC often try different pens or pen grips; musicians try to refinger passages, change hand position, or modify their instruments. When these measures are unsuccessful, some musicians practice longer or harder, while others try to rest and practice less. Neither approach is usually helpful. Those with WC often limit writing as much as possible and many resort to writing with the nondominant hand. Unfortunately, about 25% of those who successfully switch go on to develop dystonia in the nondominant hand.

Many nonpharmacological approaches have been applied to the treatment of FHD, including physical therapy, occupational therapy, chiropractic treatment, and acupuncture, but none has been shown to be particularly effective. In some patients, splinting to restrain the use of the dystonic limb for various periods of time can improve dystonia briefly after the splint is removed. However, in other patients, especially those with CRPS, dystonia can first appear following splinting or immobilization. Sensory retraining therapy focuses on trying to improve motor function by remediating the deficient sensory discrimination associated with dystonia. Sensory retraining procedures studied to date include having sighted patients learn to read Braille with the affected hand or stimulating dystonic fingers individually with or without additional motor training. Such approaches have led to improvement in WC in small clinical trials. However, it is not yet known whether long-term benefit can be achieved or whether maintenance of any benefit attained will require sustained practice or therapy.

Brain stimulation techniques such as repetitive transcranial stimulation of motor cortex or transcranial direct current stimulation are presently being explored for possible therapeutic application to WC. Stereotactic neurosurgery, including pallidotomy, thalamotomy, and deep brain stimulation, has rarely been performed in patients with WC but appears to be effective in carefully selected patients.

Oral medications used for generalized dystonia or other focal dystonias include anticholinergics, benzodiazepines, muscle relaxants, dopamine agonists, dopamine antagonists, and dopamine depletors. These medications can be tried in those with FHD. However, they are rarely more than minimally successful and often have unacceptable side effects.

The current first line treatment for WC is chemodenervation with botulinum toxin. For botulinum toxin treatment to be successful, the selection of muscles to be injected and the dose of toxin must be carefully tailored to the individual. Proper selection of muscles relies on patient report and physician observation of muscle tightness and dystonic postures. Patients should be watched at rest and with actions that elicit the dystonia. The delineation of involved muscles can be complicated by the presence of compensatory movements. For WC, it may be necessary to inject small muscles, such as hand intrinsics or individual fascicles of finger flexor or extensor muscles. Every effort should be made to adjust the dose and concentration of the toxin in a way that limits toxin spread to adjacent unaffected muscles. A series of injection sessions is usually required to determine the best combination of muscles and doses for an individual patient.

The most limiting side effect of botulinum toxin when used for WC is weakness of injected or nearby muscles, which may be unavoidable. Weakness is usually most intense during the first few weeks after injection and then diminishes. Once dose and muscle selection have been optimized, about 60% of patients have at least 25% improvement in WC with botulinum toxin. Benefit lasts ~3 months, and with repeat injection, can be sustained for years without loss of benefit or tolerance to the dose.

See also: Botulinum Toxin; Complex Regional Pain Syndrome; Dystonia; Dystonia, Task-specific.

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Y

Yale Global Tic Severity Scale (YGTSS)

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Glossary

Global severity score – This score is derived by summing the total motor tic score, total phonic tic score, and overall impairment rating (range = 0–100).

Overall impairment rating – Score rated on a 50-point scale anchored by 0 (no impairment) and 50 (severe impairment) to assess impairment experienced in interpersonal, academic, and occupational realms.

The Yale Global Tic Severity Scale (YGTSS) – A semistructured rating that is administered by a trained clinician to assess the presence, severity, and interference associated with motor and phonic tics.

Total Tic Severity Score – This score is derived by adding the total motor tic (range 0–25) and total phonic tic (range 0–25) scores and is often the score (0–50) used in treatment studies to rate tic severity.

The Yale Global Tic Severity Scale (YGTSS) was developed by Leckman and colleagues (1989) to assess the presence, severity, and interference associated with motor and phonic tics. Prior to its development, a range of methods for assessing tic severity was used, most notably the Tourette Syndrome Severity Scale (TSSS), the Tourette Syndrome Global Scale (TSGS), and structured protocols for assessing tic frequency. While informative, concerns about their use as a primary outcome measure existed such as differing ranges and item weights on the TSSS, an incomplete assessment of both tic severity and functional impairment, the practicality and efficiency of several of the methods, and finally, limited psychometric support of certain approaches (e.g., tic counts).

Given the multiple drawbacks inherent in such existing measures, Leckman and colleagues set out to create an improved scale to measure tic severity. Currently considered as the gold standard of tic assessment for adult and pediatric populations, the YGTSS incorporates a semistructured instrument that is administered by a trained clinician to assess symptomology over the previous week. The presence of motor and phonic tics is rated based on child and parent(s) reports as well as behavioral observations made by the clinician. Thereafter, the severity of motor and phonic tics is rated across five separate dimensions each: number, frequency, intensity, complexity, and interference. An item assessing the distress and impairment experienced in interpersonal, academic, and occupational realms is also rated at the end of the interview.

Overall, five index scores are obtained from the YGTSS: Total Motor Tic Score, Total Phonic Tic Score, Total Tic Score, Overall Impairment Rating, and Global Severity Score. The Total Motor Tic Score is derived by adding the five items pertaining to motor tics (range = 0–25); the Total Phonic Tic Score is derived by adding the five items pertaining to phonic tics (range = 0–25); the Total Tic Severity Score is derived by adding the Total Motor Tic and Total Phonic Tic Scores and is often the score used in treatment studies; and the Overall Impairment Rating is done on a 50-point scale anchored between 0 (no impairment) and 50 (severe impairment). A Global Severity Score is derived by summing the Total Motor Tic Score, Total Phonic Tic Score, and Overall Impairment Rating (range = 0–100). This measure is less often used in treatment studies due to the influence on the impairment rating by comorbid conditions.

Psychometric Properties

Overall, psychometric studies on the YGTSS are quite positive. In the original psychometric study by Leckman et al., involving 105 adults and children with a tic disorder, reliability, and validity of the YGTSS were examined. Generally strong interrater agreement was found in a subsample of participants (intraclass correlation coefficients (ICC) for index scores ranging from 0.62 to 0.85): a finding that was further supported by Walkup et al. The YGTSS ratings

showed a strong convergent validity vis-a-vis robust correlations with corresponding TSGS scores (*r*s ranging from 0.86 to 0.90), strong correlations with clinician impairment-ratings (*r*s ranging from 0.65 to 0.82), and moderate to strong relations with the TSSS (*r*s ranging from 0.54 to 0.76). Support for discriminant validity was demonstrated by weak to moderate relations with clinician impairment-ratings of other forms of psychopathology.

Recently, Storch et al. investigated the reliability and validity of the YGTSS in a study of 28 children and adolescents (between 6 and 17 years of age) with TS. Internal consistency was high with Cronbach's α of 0.92 at the first and second administrations (separated by 6 weeks) for the Total Motor Tic Score, $\alpha = 0.93$ and $\alpha = 0.93$ for the Total Phonic Tic Score, and $\alpha = 0.93$ and $\alpha = 0.94$ for the Total Tic Score. The Total Motor Tic Score was moderately correlated with the Total Phonic Tic Score and YGTSS Overall Impairment Rating, signifying that these measures are distinct, but the associated aspects of TS. The Total Phonic Tic Score and YGTSS Overall Impairment Rating were strongly correlated for both assessments, suggesting that phonic tics may result in a greater impairment than motor tics. Stability over a period of 48 days ranged from good to excellent for the Total Motor Tic Score (ICC = 0.77), Total Phonic Tic Score (ICC = 0.90), Total Tic Score (ICC = 0.88), Overall Impairment Rating (ICC = 0.88), and the Global Severity Score (ICC = 0.89). Convergent validity was supported with strong correlations among the YGTSS scores and parent-reports of tics. Divergent validity was supported, as the YGTSS showed weak correlations with measures of obsessive-compulsive, aggression, inattention/hyperactivity, depressive, and anxious symptoms.

Storch et al. conducted a factor analytic study of the YGTSS in 76 youth with TS to confirm the optimal factor structure of the measure. Overall, the factor structure found by Leckman et al. was supported with the resultant factors showing good reliability and validity with measures of diverging and converging constructs. For example, parent-rated tics were moderately correlated with the YGTSS Motor Tic Scale ($r = 0.47$) and strongly correlated with the YGTSS Phonic Tic Scale ($r = 0.72$). Similarly, in terms of divergent validity, the YGTSS Phonic Tic Scale was directly, albeit weakly, correlated with ADHD symptoms and overall psychopathology.

Several translations of the YGTSS and studies of their psychometric properties have been published, including versions in Spanish and Polish. Garcia-Lopez et al. investigated the psychometric properties of the Spanish version of the YGTSS. Principal component factor analysis confirmed that the scale consists of two factors: Motor Tic factor and Phonic Tic factor. The internal consistency was high across factors, with Cronbach's α of 0.997 and 0.996, respectively. Interrater reliability was high for Motor Tic, Phonic Tic, and Overall Impairment ratings (ICC $\geq$ 0.95). Finally, scores showed good treatment sensitivity over 15 days of pharmacological intervention. Stefanoff and Wolanczvk examined the psychometric properties of a Polish version of the YGTSS. Factor analysis again supported the two-factor model with Motor Tic and Phonic Tic factors. Internal consistency for the Global Severity Score was adequate ($\alpha = 0.73$).

In addition to these studies, which have directly examined the psychometric properties of the YGTSS, there have been a number of studies that support its treatment sensitivity to psychiatric medications. Similarly, treatment sensitivity has been shown in trials of habit reversal training. Across trials, score reductions on the YGTSS correspond well with change ratings on the Clinical Global Improvement scale.

Conclusions

Clearly, the YGTSS has many positive qualities that result in its widespread use, including an intuitive scoring structure, comprehensiveness of item content, and strong psychometric properties. However, at times, the YGTSS Severity Score may provide a misrepresentation of symptom severity when a person has primarily motor or phonic tics. For example, if a person presents with only phonic tics, the maximum YGTSS rating could be 25. Yet, the associated impairment and symptom severity may be greater than a person receiving respective scores of 12 and 13 on the Motor and Phonic Tic scales, despite the fact that both the Total Tic Scores are equal. This rating disparity may hold particular import, given that many clinical trials utilize a cutoff score as a part of the inclusion criteria or to assess treatment response. In the instance where the presentation involves primarily one form of tics, either primarily motor or phonic tics, the person may be excluded from clinical trials with clinically impairing symptoms. Many experts believe that the separation between phonic and motor tics is artificial and the scale may benefit from an integrated scoring rather than the two subscales.

In addition, there are several areas that warrant further empirical attention. First, it is unclear whether there is differential item treatment sensitivity,that is, do certain items respond more or less rapidly to particular interventions? Second, should certain items receive higher weighting such as intensity or interference? Each item on the scale is cumulative so that an individual with a very loud and frequent simple phonic tic may score 13 for severity (1 = number, 0 = complexity, 4 = frequency, 4 = intensity, 4 = interference), whereas someone with complex motor tics that are infrequent or less intense may also score 13, but the impact is different (3 = number, 4 = complexity, 2 = frequency, 2 = intensity, 2 = interference). The Impairment score reflects overall coping and functioning that may be worsened by coexisting depression, OCD,

or ADHD. Finally, the YGTSS can be lengthy to complete and requires a trained clinician. Thus, there may be benefit to developing a parent-rated measure that parallels the YGTSS in item content for a more rapid assessment of symptoms.

See also: Tics; Tics, Complex; Tics, Simple; Tourette Syndrome.

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Subject Index

Notes

Abbreviations:

AAAD - Aromatic amino acid decarboxylase

COMT - Catechol-*O*-methyl transferase

CT - Computed tomography

DBS - Deep brain stimulation

EEG - Electroencephalography

EMG - Electromyography

MRI - Magnetic resonance imaging

PD - Parkinson's disease

PET - Positron emission tomography

SPECT - Single-photon emission computed tomography

TMS - Transcranial magnetic stimulation

Cross-reference terms in italics are general cross-references, or refer to subentry terms within the main entry (the main entry is not repeated to save space). Readers are also advised to refer to the end of each article for additional cross-references - not all of these cross-references have been included in the index cross-references.

The index is arranged in set-out style with a maximum of three levels of heading. Major discussion of a subject is indicated by bold page numbers. Page numbers suffixed by T and F refer to Tables and Figures respectively. *vs* indicates a comparison or differential diagnosis.

This index is in letter-by-letter order, whereby hyphens and spaces within index headings are ignored in the alphabetization. Prefixes and terms in parentheses are excluded from the initial alphabetization.

Where index subentries and sub-subentries pertaining to a subject have the same page number, they have been listed to indicate the comprehensiveness of the text.

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