Movement Disorders

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KEYWORDS

• Tremor • Parkinson disease • Restless leg syndrome
• Wilson's disease • Huntington's disease
• Involuntary movements • Drug-induced tremor

PARKINSON DISEASE

How is Parkinson Disease Defined?

Idiopathic Parkinson disease is a progressive disabling neurodegenerative disease that manifests with the following neurologic symptoms: resting tremor, flexed posture, loss of postural reflexes, bradykinesia, and rigidity.

What are the Clinical Features of Parkinson Disease?

The salient clinical features of Parkinson disease consist of resting tremor, bradykinesia or akinesia, cogwheel rigidity, and loss of corrective postural reflexes. Less specific features include dementia; dystonia; psychiatric disorders, such as hallucinations, delusions, and depression; sleep disorders, such as restless legs syndrome, parasomnias, and REM behavior disorders; and autonomic dysfunction. Sensory symptoms are usually less recognized but extremely common symptoms of Parkinson disease. These include olfactory dysfunction and pain secondary to rigidity and dystonias. Resting tremor is present in most patients and usually begins unilaterally; it is almost always prominent in the distal part of the extremity. As disease worsens, the tremor becomes bilateral. Parkinson disease tremor frequency is in the 4- to 6-Hz range and is described as supination-pronation (''pill-rolling'') type. This clinical feature assists clinicians to differentiate it from essential tremor, which usually has a higher frequency and is a flexion-extension form of movement.[1] Bradykinesia, or slowness of movements, is the most characteristic and disabling motor feature in Parkinson disease, causing difficulties in performing daily activities, such as writing and personal hygiene. Other manifestations of bradykinesia are ''mask face,'' reduced arm swing during gait, and loss of spontaneous movements. Rigidity, which occurs in neck, shoulders, wrist, and ankles, leads to the characteristic stooped posture, anteroflexed head, and flexed knees and elbows of patients who have Parkinson disease. Postural instability usually presents later in the course of the disease. The pull test, during which the patient is quickly pulled backward or forward by the shoulders, is used to assess

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Med Clin N Am 93 (2009) 371–388
doi:10.1016/j.mcna.2008.09.002 **medical.theclinics.com**
0025-7125/08/$ – see front matter

retropulsion or propulsion. Taking more than two steps indicates an abnormal postural response. There are several debilitating nonmotor symptoms that can occur in patients who have Parkinson disease. Dementia eventually develops in approximately 35% to 40% of patients who have Parkinson disease. Hallucinations and psychotic behavior resulting from drug treatment are common. Depression and fatigue occur in almost 50% of patients. Autonomic and sleep disturbances are also common features of the disease.

What is the Epidemiology of Parkinson Disease?

The prevalence of Parkinson disease is 1% to 2% in the population 65 years of age or older, and up to 4% in individuals older than 85 years. The usual age of onset is the seventh decade, although up to 10% of those affected are younger than 50 years of age. In the United States, there are currently up to 1 million patients who have diagnosed Parkinson disease.[1] About 40,000 cases of Parkinson disease are diagnosed annually. Lifetime risk for Parkinson disease is 2.0% in males and 1.3% in females. Incidence of Parkinson disease is lower in African Americans than whites.

What is the Cause and Pathogenesis of Parkinson Disease?

The cause of Parkinson disease remains unknown; however, it seems that interactions between genetic background and environmental factors play significant roles in its development. The role of genetic factors in the pathogenesis of Parkinson disease has been discussed for many years. Currently, 13 chromosome loci have been identified and linked to familial forms of Parkinson disease. Mapping of *PARK* genes (**Table 1**) that are associated with development of Parkinson disease supports the role of genetic factors in pathogenesis of Parkinson disease.[2]

One hypothesis on pathogenesis of Parkinson disease links mitochondrial abnormalities and environmental agents to its development. Impaired protein degradation is likely to follow mitochondrial dysfunction and oxidative damage. The folding process of proteins is impaired resulting in an increase of misfolded proteins. The ubiquitin-proteasome system and autophagy-lysosomal pathway are two major degradation systems that are involved in the pathogenesis of nigral neuronal death and the neurodegenerative process in Parkinson disease.

Table 1
Genes responsible for parkinsonism

Type/Gene	Locus	Pattern of Inheritance
PARK 1/α-Synuclein	4q21-23	Autosomal dominant
PARK 2/Parkin	6q25.2-27	Autosomal recessive
PARK5/UCH-L1	4p14	Autosomal dominant
PARK3/unknown	2p13	Autosomal dominant
PARK4/SNCA	4p21-23	Autosomal dominant
PARK6/PINK1	1p35-35	Autosomal recessive
PARK7/ DJ-1	1p36	Autosomal recessive
PARK8/LPRK2	12p11.2-q13.1	Autosomal dominant
PARK9/ATP13A2	1p36	Autosomal recessive
PARK10/unknown	1p32	Sporadic
PARK11/unknown	2q36-37	Autosomal dominant
PARK12/unknown	Xq21-25	Sporadic
PARK13/Omi/HtrA2	2p13	Autosomal dominant?

What Neuropathologic Features does Parkinson Disease have?

Characteristic neuropathologic features of Parkinson disease consist of degeneration and loss of the pigmented neurons of the pars compacta of the substantia nigra and the presence of Lewy bodies. A Lewy body is an eosinophilic intracytoplasmic inclusion that occurs in the locus coeruleus, raphe nucleus, olfactory bulb, and other locations in patients who have Parkinson disease. These intracytoplasmic inclusions consist of dense accumulation of α-synuclein, ubiquitin, and torsinA. These lesions may be responsible for motor and nonmotor symptoms of Parkinson disease.

How do We Diagnose Parkinson Disease?

Parkinson disease remains a clinical diagnosis. Brain imaging may be only supportive. Possible Parkinson disease requires at least two of the following four features: resting tremor, bradykinesia, rigidity, and asymmetry of onset. Clinical response to levodopa or a dopamine agonist also lends further support to the diagnosis. There should be absence of features that would support a so-called ''Parkinson-plus'' disorder, such as progressive supranuclear palsy, corticobasal ganglionic degeneration, or multisystem atrophy. These features include postural instability in the first 3 years, freezing in the first 3 years, hallucinations not related to levodopa in the first 3 years, dementia preceding motor symptoms, autonomic dysfunction, or supranuclear gaze palsy.[3]

What is the Differential Diagnosis of Parkinson Disease?

Differential diagnosis of Parkinson disease includes essential tremor and other parkinsonism syndromes, such as progressive supranuclear palsy, multiple system atrophy (parkinsonism-type and cerebellar-type), corticobasal ganglionic degeneration, diffuse Lewy body disease, and drug-induced parkinsonism.[1,4]

How is Parkinson Disease Managed?

There is no cure for Parkinson disease and its treatment is mainly symptomatic management of motor and nonmotor features. Available therapeutic approaches include pharmacologic, nonpharmacologic, and surgical procedures. It is important to educate patients about the disease to address safety issues and the role of occupational therapy and regular exercise. Pharmacologic treatment of Parkinson disease includes carbidopa/levodopa, dopamine agonists, amantadine, catechol-O-methyltransferase (COMT) inhibitors, and combination of levodopa and COMT and anticholinergics (**Table 2**). Carbidopa/levodopa remains the most effective agent for treatment of motor symptoms of Parkinson disease. Carbidopa/levodopa decreases rigidity, tremor, and bradykinesia, but has its limitations in controlling motor fluctuations. It may contribute to dyskinesia and neuropsychiatric complications, such as hallucinations. Nausea is the most common side effect, but may be reduced by taking medication following meals. Carbidopa/levodopa is usually administered orally in three or four divided doses. COMT inhibitors in combination with levodopa are used to extend levodopa half-life and decrease the end-of-dose wear-off effect. Dopamine agonists (bromocriptine, pergolide, pramipexole, and ropinirole) are used as monotherapy in early Parkinson disease. Adverse effects of dopamine agonists include nausea and vomiting, orthostatic hypotension, sedation, cardiac arrhythmia, and psychosis. Sleep attacks are an uncommon side effect of dopamine agonists, along with compulsive gambling and sexual activity, about which patients should be warned.

Amantadine possibly acts by direct stimulation of dopamine receptors and inhibiting dopamine reuptake. It has been shown to help with rigidity and akinesia, but it has

Table 2
Anti-Parkinson medications

Medication	Daily Dose (mg)
Anticholinergic agents	
• Trihexyphenidyl	6–10 div tid
• Benztropine	1–2 q hs
• Amantadine	200 div bid
Dopamine agonists	
• Bromocriptine	7.5–60 div tid
• Pramipexole	1.5–4.5 div tid
• Ropinirole	9–24 div tid
• Carbidopa/Levodopa (10/100; 25/250; 25/100)	200/2000 div tid, qid
• Selegiline	10 div bid
• COMT inhibitors	200 with each levodopa dose

Abbreviations: COMT, catechol-O-methyltransferase; div, divided.

minimal effects on tremor. Livedo reticularis, blurred vision, constipation, urinary retention, cognitive deterioration, and hallucinations are adverse effects.

Anticholinergics (benztropine, biperiden, trihexyphenidyl, and procyclidine) are used for reducing tremor in patients who have Parkinson disease, but they have no effect on rigidity or bradykinesia. It is believed that anticholinergics exert their effects by decreasing the amount of acetylcholine that occurs as a result of dopamine deficiency. These agents should be used cautiously in the elderly because of their adverse effects, which include blurred vision, memory impairment, confusion, delirium, urinary retention, and constipation.

What are the Surgical Interventions for Parkinson Disease?

Currently deep brain stimulation is regarded as standard of care for medication-refractory symptoms of Parkinson disease. The subthalamic nucleus and globus pallidus interna are the preferred brain targets of this surgical procedure, which may improve bradykinesia, postural instability, rigidity, and gait dysfunction. Deep brain stimulation (DBS) of the ventral intermediate nucleus of the thalamus is used for treatment of tremor. This treatment does not improve rigidity, bradykinesia, or gait impairment, however. DBS of the internal segment of the globus pallidus suppresses bradykinesia and rigidity and reduces dyskinesia.[5,6]

ESSENTIAL TREMOR

How is Essential Tremor Defined?

Essential tremor is characterized by involuntary shaking most often in the hands or forearms with no other neurologic signs or posturing. The tremor is described as postural (occurring with voluntary maintenance of a position against gravity) or kinetic (occurring during voluntary movement). It may involve the cranial musculature in about 30% of cases with the head being most frequently involved followed by voice.[7] Mild asymmetry is not uncommon. The frequency of essential tremor is 4 to 12 Hz, with older patients exhibiting frequencies in the lower range and younger patients exhibiting frequencies in the higher range.[8] Essential tremor can be disabling for many

patients, with up to 85% of affected individuals reporting significant changes in their livelihood and socializing.[9]

What is the Epidemiology of Essential Tremor?

Essential tremor is one of the most common movement disorders. The prevalence ranges widely between epidemiologic studies with data suggesting estimates from 0.4% to 4.8%.[10] Incidence has been assessed in a retrospective 45-year study showing an age-adjusted incidence of 17.5/100,000/y with the incidence of essential tremor rising sharply after age 49.[11] It can be seen in people of any age but its prevalence tends to increase in those aged 65 and older.[8] Patients who have a positive family history of essential tremor have been observed to have a younger age of onset.

What Genetic Factors are Involved in the Development of Essential Tremor?

Essential tremor is frequently described as familial, with a positive family history in 17% to 100% of patients. It is usually inherited as an autosomal dominant trait but may have variable penetrance.[12] A few susceptibility loci have been found. The first was found in a study of 75 members of 16 Icelandic families. A link was identified in the FET1 (also known as ETM1) gene located on chromosome 3q13.[12] Another gene, designated ETM2, mapped to chromosome 2p22–25 in a large American family of Czech descent who had many members affected by ET.[13] In the same family, an ancestral haplotype on chromosome 2p24.1 was also found.

What is the Pathophysiology of Essential Tremor?

The cause of essential tremor remains unknown. Suggestions that essential tremor originates from an abnormal oscillation within thalamocortical and cerebello-olivary loops can be supported by reports that have noted that essential tremor is reduced in lesions of the cerebellum and thalamus. Positron emission tomography (PET) studies of patients who have essential tremor have demonstrated an increase in cerebellar blood flow during the tremor and at rest, which can be observed to decrease with the consumption of alcohol.[14,15] Other areas of increased blood flow revealed by functional MRI imaging include the dentate nucleus, red nucleus and contralaterally in the thalamus, globus pallidus, and primary sensorimotor cortex. A reduced *N*-acetyl-L-aspartate to creatine ratio in the cerebellar cortex, which is consistent with neuronal loss, has been shown on magnetic resonance spectroscopy.[16]

What is the Differential Diagnosis of Essential Tremor?

The differential diagnosis includes Parkinson disease tremor, dystonic tremor, cerebellar tremor, rubral tremor, psychogenic tremor, and asterixis. Tremor may be observed alone or in the context of other neurologic diseases, such as idiopathic Parkinson disease, Parkinson-plus syndromes, multiple sclerosis, Wilson disease, Huntington chorea, and cerebellar degenerative diseases. Drugs, toxins, and systemic illnesses may also precipitate tremor.

How can the Diagnosis for Essential Tremor be Made?

Essential tremor is a clinical diagnosis and the proposed diagnostic guidelines consist of the following core criteria:

- Bilateral action (postural or kinetic) tremor of the hands and forearms (but not rest tremor)
- Isolated head tremor with no signs of dystonia
- Absence of other neurologic signs with the exception of the cogwheel phenomenon

Secondary criteria consist of long duration (>3 years), positive family history, and beneficial effect of alcohol.[17]

What is the Treatment of Essential Tremor?

Reassuring the patient that he or she does not have a progressive neurologic disease, such as Parkinson disease, is an important first step. No medication is necessary if the tremor does not cause functional impairment or embarrassment to the patient. If medical treatment is required, the two medications that are considered first-line therapies in suppressing tremor are propranolol and primidone. Propranolol is a nonselective beta-adrenergic antagonist that has been shown to be more effective than drugs with selective B1-adrenergic activity.[18] An average dose of 120 mg/d of propranolol has been shown to significantly reduce tremor in these patients. One study showed that long-acting propranolol was as effective as conventional propranolol, and compliance with the long-acting formulation is significantly better.[19] Propranolol is usually well tolerated; however, relative contraindications include asthma, congestive heart failure, insulin-dependent diabetes mellitus, and atrioventricular block. Primidone is an anticonvulsant medication that is metabolized to phenylethylmalonamide and phenobarbitone. It is usually started at 25 mg/d or less to avoid acute adverse effects, including somnolence, flulike symptoms, vertigo, nausea, and ataxia. The primidone dosage may be increased by 25-mg or 50-mg increments until efficacy or a dose of 250 mg/d is achieved. It has been shown that low-dose therapy (<250 mg/d) is just as effective as high-dose therapy (750 mg/d).[20]

Second-line medications, which include alprazolam, gabapentin, topiramate, nimodipine, clozapine, clonidine, and theophylline, may be tried if propranolol and primidone fail to improve tremor. Botulinum toxin A seems to suppress tremor amplitude when injected into intrinsic hand muscles but no significant recovery of function is noted because it is associated with a dose-dependent, reversible weakness.[20] The injections may have more clinical impact when used to treat voice tremor and possibly head tremor; adverse reactions, such as breathiness, hoarseness, and swallowing difficulties, may occur after treatment of voice tremor.[19]

Thalamotomy and thalamic DBS are surgical procedures that have been shown to effectively reduce limb tremor; however, both carry risk for certain complications, such as hemorrhage, infection, or dysarthria.[20] There is currently insufficient evidence to support use of these procedures to reduce head or voice tremor.

RESTLESS LEGS SYNDROME

What is Restless Legs Syndrome?

Restless legs syndrome is characterized by an irresistible urge to move, usually the legs, to stop an uncomfortable or strange sensation. The movement relieves the sensation temporarily. The symptoms are most often worse at night than during the day. It can be idiopathic, which usually starts at a younger age, and can progressively get worse over the years, or it can be secondary, usually starting more suddenly and associated with a medical condition or drugs.

What is the Epidemiology of Restless Legs Syndrome?

Restless legs syndrome is often an under-diagnosed condition that exists in about 10% of the adult population. It can be mild in most cases, but it seriously affects the quality of life in 2.5% of the population. Patients seeking treatment represent only a small portion of those affected. The ratio of women to men is 2:1.[21]

How is Restless Legs Syndrome Diagnosed?

The National Institute of Health established the following criteria to aid in the diagnosis of restless legs syndrome: (1) an urge to move the limbs with or without sensations, (2) improvement with activity, (3) worsening at rest, and (4) worsening in the evening or night.

Supportive clinical features[22] of restless legs syndrome include: (1) history of restless legs syndrome–like symptoms in other family members, (2) relief with dopamine agonist therapy, (3) periodic limb movements in sleep and during wakefulness, and (4) ferritin level less than 50 μg/L.

What is the Cause and Pathophysiology of Restless Legs Syndrome?

The exact cause of restless legs syndrome remains unknown; however, many conditions associated with dopamine production and metabolism have been linked to restless legs syndrome along with genetic factors. Genetic factors play a role in the development of restless legs syndrome; about 60% of cases have been reported as familial with an autosomal dominant pattern with variable penetrance.[23] Restless legs syndrome may be associated with peripheral neuropathy. Several factors support the involvement of dopamine metabolism in the pathogenesis of restless legs syndrome. Medications that increase dopamine activity are effective in relieving symptoms of primary and secondary restless legs syndrome, but dopamine antagonists can exacerbate symptoms. Aggravation of symptoms at night is also indirect confirmation of dopamine metabolism involvement. The level of dopamine activity is influenced by the circadian rhythm with an increase in the level of activity in the morning and decrease of the level at night.[24] Iron is another factor that is involved in pathogenesis of restless legs syndrome because iron is a necessary element in dopamine production pathway. In patients who have restless legs syndrome low iron levels have been identified in the substantia nigra.[25,26] In addition, restless legs syndrome can be associated with low serum iron levels; during diagnostic work-up, serum iron and ferritin levels should be assessed.

Folate deficiency has also been associated with restless legs syndrome. Folate is also involved in the dopamine pathway in the central nervous system as a cofactor of tyrosine hydroxylase production, which is a catalyst in the production of levodopa, which is subsequently decarboxylated into dopamine.[25]

What are the Clinical Manifestations of Restless Legs Syndrome?

The primary and most recognizable feature of restless legs syndrome is the need to move the legs. Sometimes patients describe the need to move other parts of the body also. Patients describe the sensation in their legs as itching, burning, creeping, tingling, and even pain. Sometimes they are unable to describe the sensation, but describe feeling the need to move the legs. Any relaxing activity during the day or night may precipitate the symptoms but they are usually worse at night. Patients who take naps during the day also report symptoms, which may indicate a circadian rhythm involvement. The urge to move is relieved partially or totally by movement; however, this relief is only temporary and the sensation or urge to move can return as soon as the movement subsides. Often, there is a disturbance of sleep secondary to the symptoms. The neurologic examination is usually normal in idiopathic cases; however, patients may have signs of peripheral neuropathy or other signs that may point to a secondary cause of restless legs syndrome.

What is the Differential Diagnosis of Restless Legs Syndrome?

The differential diagnosis of restless legs syndrome includes peripheral neuropathy, positional discomfort, neuroleptic- or other medication–induced akathisia, dyskinesia, peripheral vascular disease, and moving toes. Peripheral neuropathy can be confirmed or ruled out by electrophysiologic studies and its clinical manifestations generally do not improve with movements. Positional discomfort is relieved by specific movements and changing a position of one body part. In neuroleptic-induced akathisia, the patient improves with dopamine blockers and symptoms do not worsen at night. Painful legs with moving toes is a rare disorder with almost continuous movements of the toes as opposed to the whole body stretching and walking, which is seen in restless legs syndrome.[22]

How is Restless Legs Syndrome Treated?

The primary treatment of restless legs syndrome is dopaminergic drugs, such as levodopa, non-ergot dopamine agonists (ropinirole, pramipexole), and ergot derivatives (bromocriptine, pergolide, cabergoline). Non-ergot preparations are preferred to ergot secondary to a more favorable side effect profile. The main potential problem with dopaminergic drugs in the treatment of restless legs syndrome is augmentation, which is a switch of symptoms to an earlier time of day and increase in severity and frequency. Augmentation may be overcome by adding an earlier dose of drug to the regimen, but if symptoms progress to an earlier time, the drug should be tapered off and an alternative medication, such as carbidopa/levodopa or gabapentin, or a benzodiazepine, such as clonazepam, should be considered. Severe intolerable symptoms may require a chronic opioid treatment approach with an agent such as methadone. Iron therapy is promising but cannot be used as monotherapy because it takes a moderate amount of time to raise the serum ferritin level.[26]

HUNTINGTON DISEASE

What is the Definition of Huntington Disease?

Huntington disease is an autosomal dominant, progressive neurodegenerative disorder typically affecting middle-aged adults. It is characterized by a distinct phenotype that includes chorea and dystonia, incoordination, cognitive decline, and various psychiatric and behavioral disorders that generally evolve into dementia.[27]

What is the Epidemiology?

Worldwide prevalence of Huntington disease shows a stable but striking regional variation. The prevalence of Huntington disease has many variations ranging from 0.5/100,000 in Finland to 10/100,000 in parts of the United Kingdom. In Japan, the prevalence of the disease is 0.5/100,000 and the rate is much lower in most of Asia.[27] African populations show a similarly reduced prevalence. In the United States, 5 to 7 whites per 100,000 are affected with Huntington disease. Asymptomatic individuals account for two to four times as many cases as symptomatic individuals. The higher incidence of Huntington disease in the white population compared with African or Asian people relates to the higher frequency of huntingtin alleles with 28 to 35 CAG repeats in whites.[27] The Australian Aboriginal population has shown similar prevalence to that of European origin. Because of the lack of European genetic influence, cases of Huntington disease are not documented in native North or South Americans. The Lake Maracaibo region in Venezuela and the Tasmanian region are two of several regions of the world where the high prevalence of Huntington disease has been shown to have originated from a single gene carrier migrating to that region.

What is the Genetic Basis of Huntington Disease?

In 1983, two years after the US-Venezuela Huntington Disease Collaborative Research Project began, a genetic marker was recognized on the short arm of chromosome 4.[28] It was not until 10 years later that the mutant Huntington disease gene was finally identified. Pathogenesis of Huntington disease involves the mutation of the huntingtin protein. Huntingtin protein (htt) is a 3144-amino acid antiapoptotic protein of unknown function that is expressed in all human and mammalian cells. The highest concentrations can be found in the brain and testes.[27] The *IT-15* gene, which is a 210-kb gene located near the tip of the short arm of chromosome 4 (4p16.3), encodes for the huntingtin protein. Patients with Huntington disease have an expanded and unstable trinucleotide CAG (cytosine-adenine-guanine) repeat in the *IT-15* gene within exon 1.[29] Huntington disease is therefore considered one of the trinucleotide repeat disorders. The huntingtin protein becomes toxic when the CAG repeat, which codes for a polyglutamine stretch at the amino terminus, becomes expanded.[30] This expanded polyglutamine segment is considered the mutant form of the huntingtin protein and leads to cellular dysfunction and neuronal death. The American College of Medical Genetics and the American Society of Human Genetics suggested that laboratories use the following standards when reporting results of patients tested for Huntington disease: fewer than 27 CAG repeats, normal individual; 27 to 35 repeats, normal but repeats may expand in future generations; 36 to 39 repeats, abnormal but may show variable or reduced penetrance; 40 or more repeats, abnormal.[31]

The number of CAG repeats has significant implications for age at onset, disease severity, and stability of the gene between generations. There is a robust inverse correlation between the number of polyglutamine repeats and the age at disease onset so that longer repeat lengths are associated with earlier onset of Huntington disease.[32] This correlation accounts for about 60% of the variation in age of onset. The number of CAG repeats is not an absolute prediction of disease onset. The causes of such a wide variation are not clear; however, rare genetic modifiers, such as GluR6 and ApoE, may contribute, along with environmental factors. The CAG repeat length accounts for about 50% of the disease variance. The effect of trinucleotide length on the rate of progression of Huntington disease is not well defined.

What are the Neuropathologic Features of Huntington Disease?

The most prominent neuropathologic features of Huntington disease consist of neuronal loss and gliosis in the cortex and striatum, particularly the caudate nucleus.[33] Initially, neuronal injury occurs in the caudate tail, in the medial paraventricular caudate, and in the dorsal part of the putamen. As the neurodegenerative process progresses, further neuronal loss and an increase in astrocytes can be observed in widespread cortical and subcortical regions. Pathologic observation of affected striatum shows loss of GABAergic spiny projection neurons with preservation of the aspiny interneurons and large aspiny acetylcholinesterase-positive neurons. There is a decrease of important neurotransmitters and neuropeptides, such as γ-aminobutyric acid (GABA), calbindin, enkephalin, and substance P, as a result of selective loss of the medium spiny neurons.

How is Huntington Disease Diagnosed?

A confirmed family history of Huntington disease combined with clinical manifestations in a patient is sufficient for a diagnosis of the disease. Neuroimaging (MRI and CT) typically reveals severe atrophy of the caudate nucleus in patients who have moderate disability but may also be relatively normal in patients in the early stages of

Huntington disease. This atrophy can be detected in a presymptomatic state by the finding of head of caudate hypometabolism by PET scan. In some cases, caudate nucleus atrophy may be detected anatomically before the onset of symptoms. There is an inverse correlation between the area of the head of the caudate nucleus and the duration of the disease. The degree of cortical atrophy may be more conspicuous than caudate atrophy in elderly patients who have Huntington disease. A patient who has a questionable clinical syndrome of Huntington disease can undergo DNA testing to confirm the diagnosis. The patient's cognitive decline can be evaluated and monitored by neuropsychologic examination.

What is the Differential Diagnosis of Huntington Disease?

Clinical manifestations of Huntington disease, such as chorea, dystonia, and dementia, can present with other diseases. The most likely disorder to be confused with Huntington disease is choreoacanthocytosis, which causes dementia, involuntary movements, and caudate atrophy. Patients who have choreoacanthocytosis display abnormal red blood cell morphology, neuropathy, seizures, myopathy, elevated creatine phosphokinase, self-mutilation, and an unusual eating dystonia. These manifestations are not seen in patients who have Huntington disease. Chorea can have numerous causes and can manifest in disorders such as Sydenham chorea, chorea gravidarum hyperthyroidism, systemic lupus erythematosus, polycythemia vera, neurosyphilis, external pallidal atrophy, dentatorubropallidal atrophy, Wilson disease, Pick disease, Creutzfeldt-Jakob disease, neuronal ceroid lipofuscinosis, multiple system atrophy, glutaric aciduria, Lesch-Nyhan disease, benign familial chorea, and drug-induced chorea. Many drugs, such as estrogens, carbamazepine, phenytoin, anticholinergics, amphetamines, and drugs that cause tardive dyskinesia, can have chorea as an adverse effect.

How is Huntington Disease Treated?

Huntington disease has no definitive cure and presently our therapeutic options are limited. Medical, social work, and physical therapy teams should provide a coordinated effort to develop treatment strategies for patients who have Huntington disease. Therapy of Huntington disease is tailored to the individual. Common symptoms of Huntington disease include depression, mania, delusions, paranoia, and chorea. Selective serotonin reuptake inhibitors are effective in treating depression symptoms, along with other aspects related to depression, such as rumination, perseveration, and obsessive-compulsive disorder. Suicide remains a major concern. For patients who have Huntington disease with symptoms of bipolar disorder, mood stabilizers, such as valproate, carbamazepine, lamotrigine, or lithium, may be effective. Side effects of valproate and carbamazepine include blood dyscrasias and hepatic abnormalities, which require periodic monitoring of complete blood count and liver function test. For those who have delusions and paranoia symptoms neuroleptics are effective; they are also effective in treating chorea. Low doses of neuroleptics are well tolerated but high doses of neuroleptics may impair a patient's motor and cognitive functions. For those patients who have psychosis, the atypical antipsychotics, such as risperidone, clozapine, olanzapine, and quetiapine, provide sufficient control of psychotic symptoms with a lower risk for extrapyramidal adverse effects and tardive dyskinesia. Nutrition is another concern regarding management in patients who have Huntington disease because their caloric requirements may be increased. As the disease progresses, patients may become bedridden, mute, and rigid, with dysphagia and aspiration eventually occurring. The individual patient's plan in palliative care must be addressed in managing the latter stage of the disease.

DRUG-INDUCED MOVEMENT DISORDERS

What is the Definition of Drug-Induced Movement Disorders?

Drug-induced movement disorders (DIMDs) involve a group of disorders that include acute dystonia, akathisia, neuroleptic malignant syndrome, tardive dyskinesia, neuroleptic-induced parkinsonism, asterixis, chorea, and serotonin syndrome. Acute DIMDs, such as akathisia and acute dystonic reaction, can manifest within minutes of drug ingestion. Akathisia is a feeling of inner restlessness and a constant urge to move. Neuroleptic malignant syndrome is a rare complication in patients treated with neuroleptics and can be life threatening. Symptoms of NMS include autonomic dysfunction, altered mental status, hyperthermia, and muscle rigidity.[34] Patients who have been on neuroleptic treatment for 3 months or longer are susceptible to acquiring tardive dyskinesia, which is defined as involuntary repetitive movements. Asterixis is a motor disturbance marked by arrhythmic, intermittent lapses of an assumed posture attributable to interruptions of sustained muscle contraction, resulting in a ''flapping'' of the outstretched pronated hands. Serotonin syndrome presents as a life-threatening adverse drug reaction that can manifest within minutes of exposure to the offending medication. Clinical findings of serotonin syndrome include tachycardia, myoclonus, rigidity, tremor, ataxia, hyperreflexia, hyperthermia, confusion, and coma.[35]

What are the Epidemiology and Risk Factors?

Because various medications can induce movement disorders the incidence of DIMDs is difficult to quantify. Dopamine receptor blockers, however, account for most cases of DIMDs. The risk for development of DIMDs with atypical antipsychotics is much less than with conventional drugs. DIMDs also occur more frequently with parenteral drugs than with oral drugs.[36]

What is the Pathogenesis?

The exact pathogenesis of DIMDs remains unknown. There are two diverging hypotheses to explain the pathogenesis of DIMD causing acute dystonias regarding either a hypodopaminergic or a hyperdopaminergic state associated with dopaminergic receptor blockade in the caudate, putamen, or globus pallidus. The delay between receptor blockade and the onset of symptoms of acute dystonia suggests involvement of other mechanisms, such as secondary dopamine-receptor hypersensitivity. Hypotheses about the underlying cause of akathisia include dopamine blockade in the mesocortical dopamine pathway and involvement of central serotonergic and adrenergic neurotransmitter systems. In serotonin syndrome, no single receptor seems to be completely responsible; however, agonism of 5HT2A and 5HT1A receptors located in the brainstem seems to contribute substantially.

How are Drug-Induced Movement Disorders Diagnosed?

DIMDs do not usually require further testing for diagnosis. They are differentiated from non–drug-induced dystonic reactions, such as torticollis, by their acute onset, presence of precipitating factors, and cessation when the precipitating factor is removed. Focal seizures and hypocalcemia are included in the differential diagnosis of DIMDs; if the diagnosis is unclear in any way, an EEG and calcium level can be obtained to help aid in the diagnosis.

How are Drug-Induced Movement Disorders Treated?

Most treatments are aimed at reducing or stopping the offending agent. Dystonia is treated by this method, which may briefly worsen the dystonia initially. If discontinuing

the offending agent is not possible, switching to a less potent drug is the next step. Intramuscular or intravenous benztropine, diphenhydramine, or diazepam may be used to treat acute dystonia.

Akathisia usually has a favorable prognosis. Reducing the dose of the insulting drug is the first step in treatment; however, if this is not possible then switching to a less potent antipsychotic treatment is the next step. If symptoms still persist, evidence-based treatment is strongest for beta-blockers, such as propranolol, although benzodiazepines may also be beneficial. Other choices for management include anticholinergics (especially if parkinsonian features are present) and amantadine.

Neuroleptic malignant syndrome treatment involves not only withdrawing the insulting drug but also supportive measures, such as fluid and electrolyte correction, lowering the temperature of the patient, and management of cardiopulmonary and renal complications. Dantrolene, bromocriptine, lisuride, benzodiazepines, and *N*-methyl-D-aspartate receptor blockers (ie, amantadine and memantine) have been used in the treatment of neuroleptic malignant syndrome.

Treatment of tardive dyskinesia involves stopping the offending drug, or at least lowering the dose. If withdrawing the antipsychotic drug is not possible, switching to an antipsychotic with a low propensity to cause the disorder (quetiapine or clozapine) would be the next step. Other medications that have shown to be effective include propranolol, clonidine, GABA agonists (valproate and clonazepam), anticholinergics (trihexyphenidyl), and vitamin E. The dopamine-depleting agent, tetrabenazine, is the only licensed treatment of tardive dyskinesia in the United Kingdom (not yet available in the United States), but can produce symptoms of depression.

Serotonin syndrome is serious and severe cases should be monitored in an ICU. Removal of the causative agent is the initial treatment. In most cases, symptoms resolve within 24 hours of cessation of the causative agent. Symptoms of agitation can be managed by benzodiazepines. Other drug treatments that have been used include propranolol, diphenhydramine, chlorpromazine, diazepam, methysergide, and cyproheptadine.

WILSON DISEASE

What is Wilson Disease?

Wilson disease, also known as progressive hepatolenticular degeneration,[37] is an autosomal recessive systemic disorder of copper metabolism. It is characterized by impaired incorporation of copper into ceruloplasmin and its reduced biliary excretion, which leads to decreased serum concentration of ceruloplasmin and excessive deposition of copper initially in the liver and later into the brain and other organs. The defective gene is located on the long arm of chromosome 13q14.3, which codes for a P-type adenosine triphosphatase protein (ATP7B).[38] ATP7B binds copper and transports it across cellular membranes for exocytosis from hepatocytes.

What are the Neurologic Manifestations Caused by Wilson Disease?

About half of all patients who have Wilson disease have a neurologic or psychiatric problem. Postural and intention tremors are the most common neurologic manifestation of Wilson disease. Other common symptoms include ataxia, titubation, dysarthria, chorea, akinetic-rigid syndrome, postural and gait abnormalities, and generalized dystonia. Cognitive and psychiatric problems can include inappropriate and uncontrolled grinning, drooling, cognitive impairment with below-average memory function, depression, anxiety, psychosis, and organic mood disorders.[39]

What is the Epidemiology of Wilson Disease?

The best estimate for the prevalence of Wilson disease is about 1 in 30,000 to 1 in 40,000 live births in most populations. The carrier frequency of the abnormal ATP7B gene is about 1 in 100.

How do you Diagnose Wilson Disease?

Wilson disease can be suspected when a patient presents with liver or neurologic manifestations. Mild to moderate elevations in alanine transaminase (ALT), aspartate transaminase (AST), and bilirubin can be seen, with AST usually greater than ALT. Uric acid may be decreased from associated renal tubular acidosis. The most common specific screening test for Wilson disease is a measurement of serum ceruloplasmin level. Serum ceruloplasmin is usually low (<20 mg/dL); however, in 10% of patients, serum ceruloplasmin level may be close to normal. Elevated 24-hour urine copper concentration is also characteristic with more then 40 μg (600 nmol) considered abnormal. Kayser-Fleischer rings may be seen with a slit-lamp ocular examination. Abnormal hyperintense signals in the bilateral lentiform and caudate nuclei, thalamus, brainstem, and white matter are characteristic MRI findings in the brain.[40–42] The liver biopsy with quantification of hepatic copper is the most specific test to provide a definitive diagnosis of Wilson disease. Genetic testing is possible but not very useful because of a high variety of disease-specific mutations.

What is the Differential Diagnosis?

Wilson disease must be differentiated from other genetic extrapyramidal disorders, including Huntington disease, juvenile parkinsonism, dopa-responsive dystonia, neurodegeneration with brain iron accumulation, idiopathic torsion dystonia, chorea-acanthocytosis, and benign familial chorea. The combination of neurologic or psychiatric features with the presence of a Kayser-Fleischer ring or hepatic disease is a diagnostic clue. Early schizophrenia, drug abuse, or a personality disorder can obscure the diagnosis, especially if the initial manifestations are psychiatric.

How is Wilson Disease Treated?

Once diagnosed, Wilson disease requires aggressive treatment, which prevents severe neurologic and psychiatric manifestations and can even reverse them to some extent.[40] Avoidance of foods rich in copper, especially liver and shellfish, is recommended. The mainstay of treatment is focused on the inhibition of copper absorption or an increase of copper elimination. Currently available pharmacologic agents include penicillamine, zinc acetate, trientine, and ammonium tetrathiomolybdate. Zinc acetate blocks copper absorption. The typical dose is 50 mg three times a day. Side effects include abdominal discomfort. Penicillamine and trientine have a similar mechanism of action. Both chelate and allow for urinary excretion of copper. The standard doses are penicillamine 250 to 500 mg four times a day and trientine 600 mg three times a day. They have similar side effects, including acute hypersensitivity, bone marrow suppression, Goodpasture syndrome, and chronic effects on collagen and the immune system. Trientine is known for its lower frequency of side effects as compared with penicillamine. Ammonium tetrathiomolybdate promotes copper/protein complex formation to prevent copper absorption and to promote detoxification of circulating copper but it can cause copper deficiency anemia. It is slowly titrated from 20 mg three times a day up to 60 mg with the option of possibly adding an additional three doses of 20 to 60 mg. Albumin dialysis is provided along with chelating therapy. Liver transplantation is indicated for fulminant liver failure in patients who fail to respond to medication. It has been shown to result in reduction of neurologic and psychiatric symptoms.[43]

TOURETTE SYNDROME

What is Tourette Syndrome?

Tourette syndrome is a hyperkinetic disorder characterized by combination of multiple motor and vocal tics that typically starts in childhood. It is frequently associated with psychiatric comorbidities, such as obsessive-compulsive disorder, impulse control disorder, and attention deficit hyperactivity disorder.

What is the Epidemiology of Tourette Syndrome?

The disease can be seen in all ethnic and racial groups with a strong predisposition for males over females by a ratio of 4:1. The peak incidence falls into early preadolescence with further resolution of symptoms in adult life in 50% of the cases.[11] There are mixed prevalence rates recorded in various studies that make an accurate prevalence rate difficult to establish. Some studies estimate the prevalence of Tourette syndrome as 0.1% to 1% of the general population.[44] One observational study recorded a prevalence of tics in 18.7% of 13- to 14-year-old students and Tourette syndrome in 1.85% of the same population.[45]

What is the Cause and Pathophysiology of Tourette Syndrome?

Multiple mechanisms have been proposed as the cause of Tourette syndrome; however, the exact cause is still unknown. Genetic, autoimmune, and environmental factors seem to be involved. There is a complex mechanism of inheritance that can be different in different families. Several different theories connect Tourette syndrome with the centromeric region of chromosome 5[46] and an autosomal dominant mechanism of inheritance with incomplete penetrance, but none of them has been solidly proved. There is strong evidence that the first-degree relatives of a proband have an increased risk for Tourette syndrome or multiple chronic tics. Several large families have been described with multiple family members having a spectrum of involvement in tic expression from mild transient tics, to chronic tic syndrome, to actual Tourette syndrome. Genetics do not explain the entire clinical picture, however, and environmental (including intrauterine) factors and autoimmune mechanisms[47] have been postulated to influence the clinical expression of the disorder. Antineuronal or antinuclear antibodies obtained from some patients who have Tourette syndrome have been shown to increase oral stereotypies in rats that have been infused with the sera.[48]

The imbalance of dopamine and serotonin metabolism has been studied as a potential pathophysiologic mechanism of the disease. By PET studies, a significant increase in dopamine release has been shown in the ventral striatum with predisposition to the left. Additional PET studies show that glucose reuptake and regional cerebral blood flow are decreased in the same area. Serotonin transporter binding protein is increased in the midbrain and striatum.[49] An impaired limbic-motor interaction has been implicated from PET studies of regional cerebral metabolic rates showing positive functional coupling between motor and lateral orbitofrontal circuits, which is a reversal of the normal interrelationship.[50] The volume of the left lenticular nucleus is reduced, which has been demonstrated by volumetric MRI studies.[51]

How can the Diagnosis of Tourette Syndrome be Made?

The DSM-IV[52] criteria for the diagnosis of Tourette syndrome include the following:

History or finding of multiple motor tics
History or finding of one or more vocal tics
Onset before 18 years of age

Duration of more than 1 year
Tics cause marked distress or significant impairment in daily functioning

Tics are involuntary or semivoluntary sudden, rapid, stereotyped motor movements or sounds. They can easily be confused with chorea or other hyperkinetic disorders. Tics can be divided into simple tics (abrupt, purposeless, and isolated movements) or complex tics (coordinated, sequenced movements resembling normal motor acts or gestures that are inappropriately intense and timed). Simple motor tics include shoulder shrugs, eye blinking, and head jerks. In 80% of cases, tics initially started in the face and neck area. Complex motor tics include touching, throwing, hitting, and jumping. Other examples of complex motor tics are grabbing or exposing one's genitalia (copropraxia), imitating gestures (echopraxia), or imitating sounds (echolalia). Phonic tics can involve vocal cords or can be generated by mouth, throat, and nose, and present as clearing the throat, coughing, and nose blowing. Simple phonic tics are inarticulate noises, whereas complex phonic tics include words, word fragments, or musical elements. Up to 20% of patients express coprolalia, which is the obsessive use of obscene language. Tics can be stopped voluntary for a while but usually produce an uncomfortable feeling, which eventually must be relieved by executing the tic behavior.

What is the Treatment of Tourette Syndrome?

Because of the complexity of the disease, a multidisciplinary approach with a team consisting of a neurologist, psychiatrist, psychologist, and other appropriate specialists is required. The goal is to access the maximum control with the smallest number of side effects possible. The general principles are to start medication in the lowest possible dose and slowly titrate until the lowest effective dose is obtained or intolerable adverse effects become a problem.

For tics, the standard treatment may be typical and atypical neuroleptics, if clearly believed to be clinically indicated. The older drugs include fluphenazine, pimozide, haloperidol, thiothixene, trifluoperazine, and molindone. Their use is restricted by severe and in 50% of patients permanent side effects of drug-induced movement disorders, from acute dystonic reactions to tardive syndromes. Fluphenazine is effective and least sedating. Pimozide is effective but it can cause prolongation of the Q-T interval and requires frequent EKG follow up. Haloperidol, the first and oldest of this group of medications, has the greatest number frequent side effects, including sedation, depression, weight gain, and school phobia. Newer neuroleptics, such as risperidone, olanzapine, quetiapine, and ziprasidone, tend to have fewer side effects than the typical antipsychotics and can be just as effective at reducing tics. Clonidine, an alpha blocker, (0.05–0.5 mg/d) also has tic-suppressant effects and can be used in children who have associated attention deficit hyperactivity disorder for whom antipsychotics are contraindicated. Presynaptic catecholamine depletors, such as reserpine and tetrabenazine, have been shown to suppress tics. The side effects of reserpine (0.1–1 mg three times daily) include postural hypotension, parkinsonism, and depression. Tetrabenazine is not currently available in the United States.

The treatment of concomitant obsessive-compulsive disorder includes the use of antidepressants, tryptophan, monoamine oxidase inhibitors, mianserin (a selective serotonin antagonist), and benzodiazepines. In mild to moderate cases, selective serotonin reuptake inhibitors have replaced older antidepressants. They are recommended in treatment of Tourette syndrome associated with obsessive-compulsive disorder and other behavioral changes. These include fluoxetine (20–60 mg/d), sertraline (50–200 mg/d), paroxetine (20–60 mg/d), and fluvoxamine ($\geq$50 mg/d). They may

improve obsessive-compulsive disorder symptoms without affecting tic severity. The effectiveness of these drugs is dose dependent, so doses higher than standard antidepressant doses are often required. Clomipramine (initiated at 25 mg/d) is equally effective but its side effects (anticholinergic, cardiotoxic, and seizure-potentiating) make it less commonly used. Clonazepam (0.5–5 mg/d) may be used as once-daily medication because it may relax the patient and ameliorate concomitant emotional and behavioral abnormalities.

Botulinum toxin can be used in the area of tics. It is especially effective when tics involve strong, forced movements of the neck that can cause physical trauma. Botulinum therapy can stop the involuntary movements and premonitory sensory component associated with the tics. The effects can last 3 to 4 months and repetitive injections are required. Botulinum injections are usually free from serious complications, but caution should be used when injecting into the neck area because of potential dysphasia.

Behavioral techniques and support groups have been used for treatment of tics. Vagus nerve stimulation and deep nerve stimulation have been tried as surgical procedures. Thalamic area, globus pallidus interna and externa, and the anterior limb of the internal capsule/nucleus accumbens have been tried as targets.[53]

Education of the patients and their families is important. Parents need to understand their child's limited ability to suppress the tics, which become most prominent when the child feels nervous or under stress. Parents should inform the child's teachers of the diagnosis and of any medications for this disorder. In severe cases home education can be recommended as temporary measure.

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