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Parkinson's Disease and Parkinsonism

Michael T. Hayes, MD

Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass.

ABSTRACT

Parkinson's disease is a progressive neurodegenerative disease characterized by tremor and bradykinesia and is a common neurologic ailment. Male sex and advancing age are independent risk factors and, as the population ages, is taking an increasing toll on productivity and medical resources. There are a number of other extrapyramidal conditions that can make the diagnosis challenging. Unlike other neurodegenerative diseases, idiopathic Parkinson's disease has effective treatments that mitigate symptoms. Medications can improve day-to-day function and, in cases where medication does not give a sustained benefit or has significant side effects, treatments like deep brain stimulation result in improved quality of life.

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Parkinson disease is a common neurologic disease. It is a progressive, degenerative disease manifested by motor and nonmotor symptoms. First described as a specific syndrome by James Parkinson in 1817 in "An Essay on the Shaking Palsy," the disease is estimated to affect 1 million people in the United States and 4 million people worldwide. The prevalence in industrialized countries is estimated to be 0.3%. It is rarely seen in patients under 40 years of age, but the incidence increases with age. It is estimated that perhaps 3% of the population over 80 years of age are affected.[1] Multiple studies demonstrate that the onset of Parkinson's disease occurs 2 years earlier, on average, in men than women and that twice as many men as women will develop the disease.[2,3] Epidemiologic studies have demonstrated few associations. Living in rural areas and exposure to pesticides (specifically paraquat)[4] are risk factors. Smoking and coffee drinking appear to be protective.[5]

CLINICAL PRESENTATION

Parkinson's disease is manifested by motor and nonmotor symptoms. The classic findings of Parkinson's disease are motor symptoms. These were described in the paper by Hoehn and Yahr[6] in 1967 looking at 183 Parkinson's patients. They include resting tremor, bradykinesia, postural instability, and rigidity. Parkinson's disease frequently presents with tremor, usually unilateral. The tremor is typically seen in one extremity initially (sometimes involving only one finger or the thumb). The tremor is slower (4-6 Hz) than a classic essential tremor (8-10 Hz) and is most prominent when the limb is in a posture of repose (the term "resting tremor" is somewhat misleading, as complete relaxation frequently abolishes the tremor). It is suppressed with movement. While less common, the head, jaw, and tongue may be involved. For some patients, the classic parkinsonian tremor is the only manifestation of the disease. This is referred to as tremor-predominant Parkinson's disease. In our experience, these patients do eventually develop other symptoms of Parkinson's disease, but after a period of time, sometimes a number of years.

Bradykinesia refers to slowing of movement and the simplification of complex motor tasks. Spontaneous movement is decreased. This is manifested in the "masked facies" (also known as hypomimia) of Parkinson's disease. Blink rate decreases and the eyes are more open, giving the appearance of staring. The facial muscles move less, so the face is less emotive. As the condition progresses, the mouth often stays slightly open. Speech becomes softer and monotone, with the words running together. Spontaneous swallowing is reduced and the mechanics of swallowing are affected, resulting in sialorrhea. In Parkinson's disease, sialorrhea is not due to increased saliva production but to an inability to efficiently handle saliva.[7] Hand movements become more restricted. Finger tapping may have normal speed, but the amplitude of movement is decreased. Alternating movement becomes difficult and there is frequent "freezing." This refers to intermittent arrest of motor function. It becomes more difficult to do things such as stir with a spoon or brush one's teeth. Writing becomes

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* Requests for reprints should be addressed to Michael T. Hayes, MD, South Shore Hospital, 55 Fogg Road, Weymouth, MA 02190.
E-mail address: mthayes@bwh.harvard.edu.

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cramped and small (micrographia). Eventually, the patient has difficulty rising from a chair. Changes in gait are noted, with a decrease in arm swing, usually asymmetrically. The length of the patient's stride diminishes and arm swing may disappear altogether. The patient can no longer turn on a pivot but turns "en bloc," using multiple small steps to turn. Eventually the patient may develop propulsion or retropulsion. The patient's trunk will "get ahead" of his feet and he will need to take small running steps to regain his balance, which has been termed festination. As the disease progresses this may result in the patient falling.[8] Falling, however, generally occurs later in the disease. If a patient tends to fall early in the course of the disease, one should consider a diagnosis other than Parkinson's disease.

Nonmotor symptoms of Parkinson's disease have become better appreciated over time and can be as debilitating as the motor symptoms. Cognitive decline, depression, anxiety, dysautonomia, and sleep disturbances are all seen with Parkinson's disease. Anosmia (loss of the sense of smell) occurs in as many as 90% of patients with Parkinson's disease[9] and may precede symptoms by many years. Dysautonomia is present in virtually all Parkinson's disease patients and includes constipation (also a very early symptom).[10,11] Other gastrointestinal complaints include bloating, nausea, and abdominal discomfort. A study by Hardoff et al[12] showed slowed gastric emptying times, which were exacerbated by carbidopa levodopa. Orthostatic hypotension is a symptom that presents in some 50% of Parkinson's patients and results in increased debilitation and significantly impacts the higher frequency of falling that is seen later in Parkinson's disease.[13,14] Urinary complaints, including increased frequency and urgency, are common. A study of early, untreated Parkinson's patients showed abnormal urinary function in the storage phase of 84% of the patients studied.[15]

Depression and anxiety are comorbidities with Parkinson's disease, present in approximately 35% of patients.[16] Factors such as female sex, dependency, higher United Parkinson's disease rating scale scores, and lower Mini Mental status scores may predispose patients to depression.[17,18] Some data show different forms of depression related to sex. Women feel more melancholy, and men have more apathy and decreased libido.[19] Anxiety occurs with depression or independently of depression.[20] Apathy is seen with or without depression but is more common in patients with cognitive decline.[21]

Dementia in Parkinson's disease has a prevalence of 30%-40%.[22,23] Cereda et al[24] looked at the onset of Parkinson's disease and found that age, sex, and disease duration were independently associated with Parkinson's disease, with higher rates of dementia found in men between 60 and 80 years of age. Hallucinations and paranoid ideation are also seen in Parkinson's disease, generally in the setting of taking dopaminergic medications. When hallucinations and delusional thinking appear early or without taking medication, a diagnosis of Lewy body disease should be entertained.

CLINICAL SIGNIFICANCE

- Parkinson's disease is the second most common neurodegenerative disorder with only Alzheimer's disease being more prevalent.
- It is defined primarily by its motor symptoms including tremor, bradykinesia and akinesia but may demonstrate a number of non-motor symptoms such as cognitive decline, depression, anxiety, sleep disturbance and dysautonomia.
- Treatment of the motor symptoms is accomplished primarily by dopaminergic medications or, more recently, with deep brain stimulation.

PATHOLOGY

The pathological hallmark of Parkinson's disease is depigmentation of the substantia nigra and locus coeruleus with neuronal loss in the pars compacta of the substantia nigra. Both apoptosis and autophagy are involved in the process.[25] Neuronal loss is also seen in the basal nucleus of Meynert and the dorsal motor nucleus of the vagus nerve. In affected areas, Lewy bodies, which are eosinophilic cytoplasmic inclusion bodies containing alpha synuclein, are noted. The primary cause of Parkinson's disease remains unclear. How Lewy bodies are specifically related to the progression of the disease is not known. Current theories of how neuronal loss occurs in Parkinson's disease include mitochondrial dysfunction, inflammation, abnormalities in protein handling, and oxidative stress (Figure).[26]

PHARMACOLOGIC TREATMENT

The decision of when to treat a patient with Parkinson's disease is made in collaboration with the patient. When symptoms affect the quality of life (the ability to work or socialize), treatment is started. There is no compelling evidence that starting treatment early has any impact on the progression of the disease, and no treatment confers neuroprotection. The decision to treat is based on the impact of symptoms.

Levodopa was the first effective medication for Parkinson's disease and is still the most potent. Virtually all patients will use levodopa at some point during their disease. It is the immediate precursor to dopamine, which can cross the blood–brain barrier. It allows the depleted number of dopaminergic neurons to produce more dopamine and alleviate symptoms. It is usually paired with carbidopa, which blocks metabolism of levodopa in the periphery, increasing central nervous system bioavailability and lessening peripheral side effects, particularly nausea. Other side effects include hallucinations, delusions, somnolence, dystonia, and, prominently, dyskinesias. Dyskinesia (involuntary writhing movements) often limits the dose that can be used and is a prime reason why other medications or surgical interventions are considered.

Dopamine agonists (pramipexole, ropinirole, and rotigotine) stimulate dopaminergic receptors in the central nervous system, which alleviate symptoms of Parkinson. While they improve symptoms, they are predictably less potent than levodopa. They are frequently used because they are less likely to

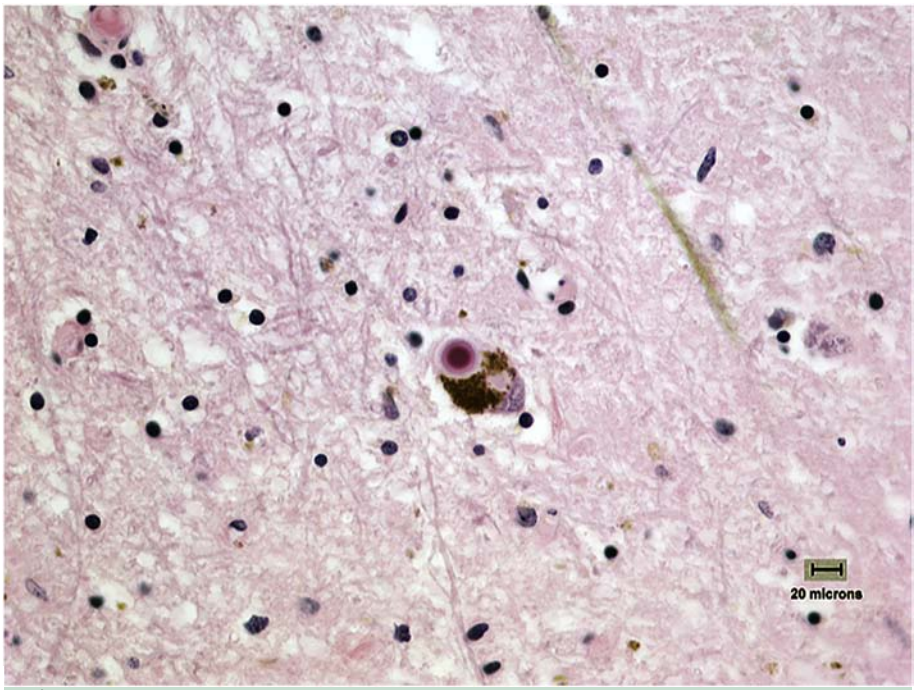

Figure Lewy body, kindly provided by Dr. Mel Feany, Harvard Medical School.

cause dyskinesias and they tend to have a longer half-life. The decreased risk of dyskinesias may be because they are less potent stimulators of the D2 receptors. The decreased specificity, in the way that they stimulate dopaminergic receptors, may be the cause of their increased risk of hallucinations, hypotension, somnolence (sometimes with sleep attacks), leg edema, and the risk of compulsive behaviors such as compulsive sexual behavior, buying, or gambling. The risk of hypotension and hallucinations are higher in elderly patients, and it is prudent to try to use carbidopa/levodopa in the elderly, if possible, to avoid complications.

Catechol-O-methyl transferase inhibitors (entacapone) and monoamine oxidase aldehyde dehydrogenase B (MAO-B) inhibitors (rasagiline and selegiline) inhibit enzymes involved in the breakdown of levodopa and dopamine. They prolong the effect of carbidopa/levodopa. They may also increase the side effects of levodopa, specifically, hallucinations, dyskinesia, and nausea. In the case of the MAO-B inhibitors, there is a risk of interaction with multiple drugs, including antidepressants in terms of causing serotonin syndrome.

Anticholinergic medications (trihexyphenidyl and benztropine) are not effective in treating bradykinesia, but may be effective in decreasing rigidity, dystonia, and tremor. In patients (generally younger) whose early disease manifestations are rigidity and tremor, these medications, even as the sole agent, may be effective. Side effects limit dosing and include dry mouth, dry eyes, urinary retention, memory issues, and hallucinations. These agents should be used with caution in the elderly.

Antipsychotics are sometimes necessary to treat the symptoms of hallucination and paranoid delusions occurring in Parkinson's patients. Traditional agents, like haloperidol and the like, increase parkinsonian symptoms. The most well-tolerated agents include quetiapine, clozapine, and pimavanserin.

Depression is a frequent comorbid symptom in Parkinson's disease. Treatment with tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitors, or serotonin reuptake inhibitors have all been used.[27,28] Cognitive behavioral therapy has been reported to be helpful,[29] but no large-scale trials have been done (Table).

FUNCTIONAL NEUROSURGICAL TREATMENT

Before levodopa became the primary treatment for Parkinson's disease (in the early 1960s), some patients received lesions to the thalamus pioneered by Cooper and others.[30,31] Surgical treatment of Parkinson's disease was largely abandoned until the limitations of dopaminergic therapy became apparent. These included motor fluctuations, dyskinesias, hallucinations, and intractable tremor.

There was a resurgence of stereotactic ablative surgery to the thalamus, subthalamic nucleus, and globus pallidus interna. This procedure was largely replaced by the implantation of stimulating electrodes into those nuclei.[32,33] Deep brain stimulation (DBS) has become a staple of treatment in patients with complications of medical treatment that include precipitous and unpredictable motor fluctuations and disabling dyskinesia or the presence of intractable tremor. The treatment effect looks similar to the ablative procedures, but exactly how the stimulation produces the effect is not known. DBS frequently allows a decrease in the dosage of medication and gives the smoother response throughout the day in terms of motor symptoms. DBS does not impact the progression of cognitive decline or axial instability, which is to be expected, as dopaminergic medications tend not to improve these symptoms either.[34,35]

Table Medications Commonly Used to Treat Parkinson Disease

Medication	Supplied	Dosage	Comment
Dopaminergic Medication			
Carbidopa/ levodopa	Multiple immediate release and controlled release formulations	Start at 25/100 TID, titrating dose and dosing interval to symptomatic relief.	Most potent medication but with short half-life. Dyskinesias more common.
Pramipexole	Immediate and extended release formulations	Start at 0.125 mg TID increasing weekly based on clinical response to total daily target dose of up to 1.5 to 4.5 mg.	Less fluctuation of efficacy but less potent than carbidopa/levodopa. May develop compulsive behaviors. Fatigue and marked drowsiness are noted frequently.
Ropinirole	Immediate and extended release formulations	Start 0.25 mg TID with gradual increases based on clinical response to daily total dose of up to 24 mg.	
Rotigatine	Transdermal patch	2-mg patch daily, increase weekly based on clinical response, up to 8 mg/day.	
COMT and MAO-B inhibitors			
Entacapone	200 mg. Also supplied in combination drug with carbidopa/levodopa	Take with each dose of carbidopa levodopa.	COMT inhibitor
Rasagiline	0.5 mg and 1 mg	Take 0.5 to 1 mg daily.	MAO-B inhibitor. Contraindicated with multiple drugs because of potential serotonin syndrome.
Selegiline	1.25 mg and 5 mg	Take 5 mg daily, if tolerated, increase to 5 mg BID.	
Anticholinergics			
Benztropine	0.5 mg, 1 mg, 2 mg	Starting with 0.5 mg BID. Increase rating based on clinical response up to 2 mg TID.	Use with caution in elderly. Dry mouth and urinary retention are side effects.
Trihexyphenidyl	2 mg, 5 mg	Start at 2 mg QD. Increase based on clinical response up to 2 mg TID.	
Treatment of hallucinations and delusions			
Quetiapine	25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg	Start at 25 mg QHS and increase based on clinical response. Doses earlier in the day may be necessary.	Rarely need to go above 400 mg/day total dose.
Clozapine	25 mg, 50 mg, 100 mg, 200 mg	Start at 12.5 mg QD and increase based on clinical response up to 300-450 mg total daily dose.	Close following of absolute neutrophil count is mandatory.
Pimavanserin	10 mg, 34 mg	34 mg QD	

BID = twice a day; COMT = catechol-O-methyl transferase; MAO-B = monoamine oxidase-B; QD = once a day; TID = three times a day.

DIFFERENTIAL DIAGNOSIS

Lewy Body Disease

Lewy body disease is akin to classic Parkinson's disease, clinically and pathologically. Pathologically, in addition to Lewy bodies being found in the striatum, there is widespread involvement of Lewy bodies in cortical neurons, with a relative paucity of the neurofibrillary tangles and amyloid plaques associated with Alzheimer disease.[36,37] The diagnosis is clinical and consists of the appearance of parkinsonian symptoms, dementia, hallucinations and delusions, frequently fluctuating with periods of lucidity. If motor signs precede the onset of cognitive decline and hallucinations, patients are often diagnosed with Parkinson's disease, but the cognitive symptoms generally follow the onset of motor symptoms fairly closely. In some patients, cognitive symptoms precede the motor symptoms. These patients may initially be diagnosed with Alzheimer disease. Patients with motor symptoms may initially respond to dopaminergic medication, although worsening hallucinations may be noted. Eventually, dementia and axial instability became the most limiting symptoms. As with Parkinson's disease, rapid eye movement (REM) sleep disorder is common. Patients with Lewy body dementia are exquisitely sensitive to most neuroleptics,[38] although quetiapine and clozapine may be tolerated.

Drug-Induced Parkinsonism

Parkinsonism as a side effect of certain medications is an underdiagnosed entity. It is due to postsynaptic blockade of dopamine receptors (especially D2 receptors).[39] It occurs primarily with first-generation neuroleptics, many second-generation neuroleptics, and may be seen with gastrointestinal prokinetics like metoclopramide and domperidone.[40] Although dopamine receptor blockade occurs within hours of taking the medication, the parkinsonian effect may not be seen for days to weeks. Half to three-quarters are evident in 1 month, and 90% of cases occur within 3 months of starting the medication.[39] Symptoms include masked face, tremor, rigidity, and bradykinesia. Symptoms tend to be symmetric

(unlike idiopathic Parkinson's disease), but it may be difficult to differentiate between drug-induced parkinsonism and Parkinson's disease. A dopamine transporter scan, while limited as a tool for diagnosing idiopathic Parkinson's disease, as it is positive in other degenerative Parkinsonian disorders,[41,42] may be useful in diagnosing drug-induced Parkinsonism, as it is normal in those cases.[43] Treatment is reduction or discontinuation of the offending agents. Agents less likely to cause drug-induced parkinsonism (and best tolerated in idiopathic Parkinson's disease) include clozapine[44] and quetiapine.[45]

Progressive Supranuclear Palsy (PSP)

Progressive supranuclear palsy,[46,47] unlike the alpha-synucleinopathy that is Parkinson's disease, is a tauopathy. It may initially be diagnosed as Parkinson's disease, as early symptoms include difficulty rising from a chair, tenuous gait, and changes in speech similar to Parkinson's disease. With progression, it diverges clinically from Parkinson's disease. Classically, the condition begins with progressive unsteadiness of gait and multiple falls. At some point, the patient develops difficulty with voluntary vertical eye movement. It is difficult to look down and the patient has difficulty going downstairs. Later there is difficulty with voluntary eye movements in all directions, with saccadic breakdown. In extreme cases there are no voluntary eye movements, although if the patient fixates on an object and the head is slowly turned, full eye movement can be obtained. This demonstrates that the abnormalities of eye movements are indeed “supranuclear.” Speech becomes soft and monotone and mildly dysarthric. The patient may develop axial dystonia, with the neck muscles becoming spastic. They may develop pseudobulbar affect. Dysphasia is sometimes seen. In our experience there may be a transient response to carbidopa/levodopa, but overall, dopaminergic medications have no effect on symptoms. Anticholinergic medications may help with the dystonia, although botulinum toxin injections in focal dystonia are more effective. The patient may develop difficulty with decreased sleep with decreased REM sleep. Dementia is less common in progressive supranuclear palsy. Treatment is supportive. The patient eventually becomes less mobile. A feeding tube is sometimes employed in patients with severe dysphasia.

The syndrome of pure akinesia with gait freezing has been demonstrated to be a variant of progressive supranuclear palsy.[48] In this condition, patients develop a marked inability to initiate gait with their feet “frozen” to the floor. Other symptoms of progressive supranuclear palsy may not be present or may occur very late in the course.

Pathologically there is atrophy of the dorsal midbrain, with neuronal loss and gliosis in the superior colliculus, subthalamic nucleus, red nucleus, periaquaductal gray, pallidum, dentate, and pretectal nuclei. Neurofibrillary degeneration and neurofibrillary tangles are noted, as is Tau deposition.[49]

Multiple System Atrophy

Multiple system atrophy is a degenerative neurologic disease. As the name implies, multiple systems are affected. These include the extrapyramidal system, the cerebellum, and the autonomic nervous system. Subtypes of multiple system atrophy are determined clinically by their predominant symptoms. If extrapyramidal symptoms are more prominent, it is characterized as MSA-P (parkinsonian subtype). The parkinsonian symptoms are frequently preceded by urinary urgency, sexual dysfunction, orthostatic hypotension, and sometimes, inspiratory stridor. REM sleep disorder is common.[50] In the parkinsonian form, rigidity and akinesia are early symptoms, but the classic parkinsonian tremor is not seen. Orthostatic hypotension eventually becomes symptomatic in virtually all patients, and some cerebellar signs are generally noted. Dystonia is a prominent feature in a number of patients.[51] Imaging will often show atrophy of the pons and cerebellum. Atrophy of the pontocerebellar fibers resulted in the "hot cross bun" sign seen on magnetic resonance imaging, but this occurs so late in the disease that the diagnosis has been clinically obvious for some time.

Pathology shows proteinaceous oligodendroglial cytoplasmic inclusions containing misfolded alpha-synuclein. Along with these inclusions, olivopontocerebellar atrophy and striatonigral degeneration are prominent findings. There may also be involvement of the hypothalamus, dorsal nucleus of the vagus nerve, and noradrenergic and serotonergic brainstem nuclei.[51,52]

Corticobasal Degeneration

This condition is similar to Parkinson's disease in that it has an asymmetric onset and asymmetric tremor and rigidity. It appears in mid to late life, as does Parkinson's disease. With progression, the patient frequently develops apraxia of the affected limb, not typical of Parkinson's disease. Myoclonus may be prominent in the affected limb. Dementia, sometimes profound, may develop.[53,54] There is no response of the motor symptoms to dopaminergic drugs.

Gross pathology shows atrophy in the superior frontal gyrus, parasagittal gyri, and the superior parietal lobule. Unlike progressive supranuclear palsy, the brainstem is not obviously atrophic.[55] The affected cortex shows astrocytic plaques containing tau proteins. Neuronal loss and gliosis is also seen in the globus pallidum, thalamus, and substantia nigra.

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