Parkinson Disease: Research Update and Clinical Management

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Abstract: More than 1 million people in the United States have Parkinson disease (PD), more than are diagnosed as having multiple sclerosis, amyotrophic lateral sclerosis, muscular dystrophy, and myasthenia gravis combined. PD affects approximately 1 in 100 Americans older than 60 years. It burdens patients, their care partners, and the overall healthcare system. This article reviews the epidemiology, clinical features, putative environmental risk and protective factors, neuropathological aspects, heterogeneity, medical management, and recent studies regarding genetics and PD. The article suggests that based on new research, the prevalence of PD varies in different regions of the United States. Some progress has been made in identifying the risk and protective factors of PD, and a newly emphasized area of study in PD is genetics. Patient care recommendations, based on American Academy of Neurology practice guidelines, are outlined to show the state of contemporary medical management of PD and related disorders.

Key Words: Parkinson disease, practice recommendations, research update

Parkinson disease (PD) is a neurodegenerative disorder with unknown cause(s). It affects primarily older adults, although there is an early-onset (often defined as younger than 40 years old). Rarely, PD presents as early as age 18. PD is a complex disorder involving not only motor impairment but also deficits in behavior, cognition, and daily function.

Epidemiology

Reported PD prevalence and incidence rates vary widely because of the use of different criteria for defining PD, differences in case-finding methodologies (eg, records based, door-to-door screenings), and, in incidence studies, variation in follow-up periods to identify PD conversion and exclude other diseases. A review of PD epidemiology finds a prevalence rate of approximately 1% in people 60 years old and older.1 Prevalence rates increase with advancing age and until recently, the highest reported prevalence was approximately 4%.2,3

A population-based study of US Medicare beneficiaries found a mean prevalence of PD of 1.6% among individuals aged 65 years and older and an annual incidence of approximately 446 cases per 100,000 population.2 The prevalence of PD in blacks and Asian Americans was approximately 50% lower than it was in whites. The study found nonrandom distributions of PD across counties within states ranging from 1.175% to 13.8%. There were substantially higher rates in the Midwest/Great Lakes region and along the northeastern US seaboard. This higher prevalence has been attributed to industrial and agricultural exposures that are presumably higher in these geographic regions.2

Key Points

- The clinical presentation of Parkinson disease (PD) represents an intersection of four major areas: motor symptoms, cognitive changes, behavioral/neuropsychiatric changes, and symptoms related to autonomic nervous system failures.
- Studies show that environmental factors may increase or decrease the probability of developing PD, and recent work emphasizes genetic contributions to the disease.
- Contemporary medical management is heavily reliant on pharmacologic interventions, although surgical treatments (eg, deep brain stimulation) also play a role. Exercise interventions for PD are being implemented more widely.
Clinical Features

The clinical presentation of PD represents an intersection of four major areas: motor symptoms, cognitive changes, behavioral/neuropsychiatric changes, and symptoms related to autonomic nervous system failures. Unrelated comorbidities such as arthritis or diabetes can further complicate the differential diagnosis.

Motor Symptoms

The cardinal motor symptoms suggesting the possibility of PD are resting tremor, bradykinesia (slowness to initiate movements), rigidity, shuffling gait, and postural instability. Positive response to levodopa therapy is strongly suggestive of PD. PD is characterized by an insidious onset in which patients often attribute its early clinical manifestations to normal aging. The disease is inexorably progressive, but there is great variability in the rates of motor progression.

A qualitative review of the literature found that greater baseline impairment, early cognitive problems, older age, and lack of tremor at onset are associated with more rapid rates of change. An 8-year prospective study of people with idiopathic PD found average annual rates of motor change ranging from 3.1% to 3.6% across four different measures. Age at onset was the strongest independent predictor of motor decline. Those with late-onset PD had a 3.8% annual rate of decline, whereas the rate for those with early-onset was 2.4%.

Cognitive Symptoms

Subtle neuropsychological changes that are difficult to assess in a typical primary care encounter are often evident early in the course of PD. The executive functions—ability in “set-switching,” problem-solving strategies, concept formation, attention capacities, decision making and effective use of working memory—are the first and most severely affected cognitive domains. Clinically, executive function deficits can be expressed as difficulties with everyday activities such as organizing medications, paying bills, and losing productivity. Impairment in visuospatial function also is an early cognitive outcome of PD, although often it is detected only with specific neuropsychological testing such as a complex figure copy or facial recognition test. Memory deficits are seen mainly as the illness progresses. Clinically, these deficits manifest as retrieval deficits rather than disturbances in immediate recall, suggesting that unlike Alzheimer disease (AD), encoding processes are not disrupted.

In clinical encounters, most practitioners will not assess function in the detail that a neuropsychologist would; however, the American Academy of Neurology (AAN) practice parameters suggest that the Mini-Mental State Examination is a reasonably good screen for global cognitive function in PD. A score of <24 is generally considered to indicate cognitive impairment. Crum and colleagues published age- and education-adjusted norms that should be used for cognitive screening with the Mini-Mental State Examination. The clock-drawing test has been recommended for assessment of visuospatial and executive functions.

The prevalence of all dementias increases with age and duration of illness. Between 30% and 50% of people with PD eventually develop dementia. The differential diagnosis of dementia in PD is complicated because AD, dementia with Lewy bodies (DLB), and PD dementia (PDD) share key features. If a person presents with dementia, then he or she may have AD, DLB, or PDD. If the person already has received a PD diagnosis, then chances are high that he or she has PDD only.

Behavioral/Neuropsychiatric Changes

Neuropsychiatric symptoms are common in the later stages of PD. A cross-sectional study of 1351 people with PD who did not have dementia found that the most commonly observed neuropsychiatric symptoms were depression (70%), anxiety (69%), apathy (48%), and irritability (47%) and that 87% of subjects had at least one neuropsychiatric symptom.

An attempt has been made to study the interrelations among neuropsychiatric signs, in other words, to develop neuropsychiatric profiles. In a study of 129 individuals who had been clinically diagnosed as having probable, possible, or definite PD, five neuropsychiatric clusters were identified: psychosis and agitation; mild depression; high levels of depression, anxiety and apathy; sleep disturbances; and high scores across all of these neuropsychiatric domains. When compared to the others, clusters 1 and 5 included relatively more demented than nondemented people.

Empirical clustering of symptoms can help expose nonintuitive relations between symptoms that may produce novel treatment approaches. For example, daytime hallucinations in patients with PD are sometimes treated by adding extended-release levodopa at bedtime. This approach became standard after it was discovered that a subset of patients who had hallucinations also complained of poor nighttime sleep resulting from tremors. This discovery has allowed numerous patients to avoid being placed on antipsychotics and other medications that may have more deleterious effects upon their level of functioning.

Autonomic Nervous System Failure

PD is characterized by symptoms relating to autonomic nervous system dysfunction, for example, orthostatic hypotension, constipation, urinary frequency and urgency, erectile dysfunction and vaginal tightness, and sweating abnormalities. Olfactory deficits often are an early sign/symptom of PD. One European study found olfactory deficits in 97% of people with a clinical diagnosis of PD. A 5-year prospective study suggested that olfactory deficits may help predict the development of PD. For each unit of improvement on an odor-discrimination test, the risk of PD was cut by 19%;
however, because only 5 of 361 subjects developed PD during the observation interval, additional research is needed before olfactory deficits can be considered a reliable indicator of incipient PD.

**Sleep Disturbances**

Sleep disturbances are common in PD, but their cause is unclear. In one study, 42% of individuals with PD had sleep problems compared with 12% of controls. Specific symptoms included insomnia in 32%, nightmares in 32%, and excessive daytime sleepiness in 15%. The rates of these symptoms in controls were 5% to 6%.

Depletion of dopamine has been hypothesized as one process that promotes disrupted sleep in people with PD. Markers of neuronal degeneration (e.g., Lewy bodies [LBs], Lewy neurites, and α-synuclein) can be found in the brainstem nuclei in both people with PD and people without PD who experience rapid eye movement sleep behavior disorder (RBD). These findings dovetail with clinical observations that both RBD and forms of PD (“parkinsonisms”) typically begin in the sixth decade of life and suggest that parkinsonism and RBD are physiologically and anatomically linked.

Other factors common to PD that also likely contribute to sleep disturbances include restless leg syndrome, stimulant effects of PD medications, anxiety, reduced bed mobility with inability to make oneself comfortable (sleep cycle dysregulation caused by poor sleep hygiene), reduced activity levels and exercise, frequent nocturia, and nocturnal disorientation caused by cognitive impairment or vivid dreams. Treatment with benzodiazepines can provide temporary relief from sleep disturbances, but their use should be monitored carefully because of the potential for abuse and worsened cognitive impairment.

**Environmental Risk and Protective Factors**

Studies consistently suggest that there are environmental risk factors for PD, although the magnitude of the associations varies. One meta-analysis, based on 11 to 16 studies (depending on the exposure considered), reported an elevated risk for PD with exposure to rural residence (odds ratio [OR] 1.56, 95% confidence interval [CI] 1.18–2.07), use of well water (OR 1.26, 95% CI 0.97–1.64), living on a farm/exposure to farm animals (OR 1.42, 95% CI 1.05–1.91), and pesticide exposure (OR 1.85, 95% CI 1.31–2.60). Interest in pesticides and herbicides as risk factors for PD is high. In a meta-analysis of case-control studies conducted in North America, Europe, and Asia, 17 of 19 studies reported positive associations between pesticide/herbicide exposure and PD (combined OR 1.94, 95% CI 1.49–2.53). Exposures that may protect against the development of PD—most commonly, cigarette smoking (nicotine intake) and coffee drinking (caffeine intake)—also have been examined. In a comprehensive meta-analysis, Hernán and colleagues examined 48 smoking-related studies and 13 coffee-related studies conducted in North and South America, the Caribbean, and Europe (mainly case-control studies, but also included some prospective cohort studies). These authors reported strong protective effects for “ever” versus “never” smokers (OR 0.59, 95% CI 0.54–0.63) and for past smokers (OR 0.39, 95% CI 0.32–0.47). Coffee drinkers (compared with nondrinkers) also derived some protection (OR 0.69, 95% CI 0.73–0.84). There were fewer studies of coffee drinking, but they were relatively consistent in showing reduced risk for PD.

**Neuropathology**

Neuropathological analyses of postmortem brains of patients with PD have demonstrated significant neuronal loss in the substantia nigra (SN); however, striatum, which receives inputs from the SN, usually appears normal. LBs and Lewy neurites are the pathognomonic features of PD. LBs are small inclusion structures (Fig.), mainly comprising various densely packed proteins, among them, α-synuclein and ubiquitin. LBs may result from ineffective protein degradation, leading to an accumulation and sequestration of proteins for disposal, which can no longer be accomplished. LBs displace other organelles.
within the neuron. Lewy neurites often accompany LBs, but they represent damaged neuronal fragments (Fig.).

Some researchers have embraced the theories of Heiko Braak and colleagues to explain the progression of PD. In their “dual-hit hypothesis,” an unknown, possibly viral pathogen, enters the brain directly through an olfactory route (this would account for the early, prodromal olfactory deficits seen in people with PD) and follows a pathway ending in the temporal lobe. As a second pathway, swallowing nasal secretions introduces the pathogen into the gut. The pathogen then enters the vagus nerve and through some transsynaptic transmission, reaches the SN via the medulla, pons, and midbrain. Supporting this view, LBs have been observed in the intestines, vagal nerve, and brain structures that are susceptible to LB pathology (most important, the SN). This model is based on cross-sectional pathological analyses of brains pre-screened to contain synuclein pathology and has been cited in >1500 studies. These perspectives are not without their critics. Dickson and colleagues observed α-synuclein in multiple brain regions simultaneously in the same tissue samples, calling into question Braak’s predictable progression of α-synuclein through a caudal-rostral route. Furthermore, Kalaitzakis and colleagues note that the widespread and multisystem distribution of neuropathology in brains with PD is not limited to α-synuclein pathology; thus, a significantly biased view of PD progression can result when focusing solely on synuclein pathology.

Heterogeneity

PD is increasingly recognized as a family of disorders. Some parkinsonian syndromes are widely accepted in the field. They frequently have different evolving clinical presentations seemingly related to differing neuropathological substrates seen at autopsy of the brain. Key differential diagnostic features are summarized in Table 1.

Medical Management

The AAN practice parameters identify PD as a core neurologic disease. General neurologists tend to provide disease-specific care for people with PD, but consultation with a movement disorders specialist often can be helpful.

Diagnosis and Prognosis

Idiopathic (“classic”) PD is diagnosed by the criteria described earlier in this review. Distinguishing classic PD from other parkinsonian syndromes can be challenging. In their evidence-based practice parameter recommendations, the AAN Consensus Committee concluded that the following symptoms may support a diagnosis of a parkinsonian syndrome (eg, corticobasal degeneration, multisystems atrophy, progressive nuclear palsy, DLB, PDD) rather than PD: falls, poor response to levodopa, symmetry of motor manifestations, rapid progression, lack of tremor, and dysautonomia. Relatively poor efficacy of levodopa and amphetamine also suggests the possibility of a parkinsonian syndrome. Poorer scores on tests of olfaction may also help distinguish PD from other parkinsonian syndromes. In several studies, poorer olfaction was more often seen in people with PD than in people with multisystems atrophy, progressive nuclear palsy, corticobasal degeneration, and essential tremor.

Investigators also have studied predictors of disease progression in PD as assessed by motor progression, nursing facility placement, and shorter survival time. In an evidence-based review, Suchowersky and colleagues concluded that more rapid motor progression in PD was predicted by older

<table>
<thead>
<tr>
<th>Condition</th>
<th>Motor symptoms predate dementia (&gt;1 y)</th>
<th>Hallucinations</th>
<th>Rigidity (± With cog-wheeling)</th>
<th>Lateralized motor symptoms</th>
<th>Restricted down gaze/slow saccadic eye movements</th>
<th>Prominent gait disturbance</th>
<th>Apraxia and cortical sensory loss</th>
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<tr>
<td>Parkinson disease with dementia</td>
<td>+</td>
<td>+</td>
<td>+ With cog-wheeling</td>
<td>+</td>
<td>+ Typical at onset</td>
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<tr>
<td>Dementia with Lewy bodies</td>
<td></td>
<td>+ Early course</td>
<td>+</td>
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<tr>
<td>Progressive supranuclear palsy</td>
<td>±</td>
<td>Neck &gt; limb</td>
<td>+</td>
<td>+ Falls early in course</td>
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<tr>
<td>Corticobasal degeneration</td>
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<td>Multisystem atrophy*</td>
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* = feature is uncommon; ± = symptom is variable; + = symptom is common.

*Dysautonomia is a defining feature of multisystem atrophy.
age at onset, associated comorbidities, rigidity, and bradykinesia as presenting symptoms and decreased dopamine responsiveness. Older age at onset, dementia, and decreased dopamine responsiveness predicted earlier nursing facility placement and survival.

Treatment of People with PD Who Have Motor Fluctuations and Dyskinesias

Treatment of PD is most frequently based on medical interventions and surgery, including deep brain stimulation (DBS). In using medical interventions, both the occurrence of motor fluctuations (ie, “on times,” when the medication is demonstrably effective, and “off times,” when drugs wear off and PD symptoms return) and dyskinesias (when drug treatment causes involuntary movements) should be considered. Levodopa combined with carbidopa is the gold standard treatment for PD; however, adjunctive therapies frequently are combined, with a goal of reducing motor fluctuations and dyskinesias. Compared with other dopamine agonists, entacapone and rasagiline were most effective in reducing off times, according to AAN practice parameter guidelines. Other agonists were efficacious, although less so, in reducing off times, but the quality of studies supporting this conclusion was lower. Evidence reviewed in the AAN practice guidelines did not establish the superiority of one medicine over another in reducing off times. Sustained-release carbidopa/levodopa and bromocriptine were not shown to reduce off times.

DBS is a surgical intervention that has received widespread attention and generated enthusiastic responses from patients and practitioners. In DBS, an electrode is surgically implanted in the subthalamic nucleus (STN), globus thalamus (GPI), or ventral intermediate nucleus, introducing continuous high-frequency electrical stimulation. DBS usually is indicated for patients with drug-related movements and fluctuations whose condition has not improved after undergoing all medical management regimens, who show a clear response to levodopa following a levodopa challenge, who do not have a parkinsonian syndrome, who have no other major medical conditions; and who are in the middle (and sometimes late) stages of the illness. Further indications include refractory tremor that is disabling and has cognitive impairment on comprehensive testing. Pahwa and colleagues concluded that the DBS of the STN reduces off times and dyskinseas, improves motor function, and reduces reliance on medications; however, insufficient data exist regarding stimulation of the globus thalamus and ventral intermediate nucleus.

Research has been conducted to identify predictors of responsiveness to DBS, but conclusions were drawn only about DBS implantation in the STN. Preoperative response to levodopa, younger age, and shorter disease duration (<16 years) may predict greater improvements. Pahwa and colleagues emphasized that patients should be counseled about the risks and benefits of DBS.

Evaluation and Treatment of Depression, Psychosis, and Dementia

In their evidence-based AAN practice parameter, Miyasaki and colleagues recommended using the Beck Depression Inventory I, the Hamilton Depression Rating Scale, and the Montgomery Asberg Depression Rating Scale to evaluate depression in PD. They concluded that evidence is insufficient to support the use of any particular rating scale for psychosis in PD.

The efficacy of medical therapies in treating depression in PD is equivocal. Amitriptyline is not recommended for use in older adults because it has anticholinergic properties that can interfere with dopaminergic therapies (Table 2). Benzodiazepines such as alprazolam, lorazepam, and diazepam may be used to treat anxiety; however, they may be poorly tolerated, worsen or induce confusion, and worse motor performance, and there is the potential for dependence with long-term use of this class of medications.

Clozapine is effective in treating psychosis in PD. By contrast, olanzapine is somewhat effective but should be avoided because of its concurrent negative effects on motor function. Cholinesterase inhibitors show promise in treating the symptoms of dementia in PD (with relatively short-term effects) as well as DLB. Following publication of the AAN parameter, rivastigmine has been approved by the Food and Drug Administration for the treatment of dementia associated with parkinsonism.

Some classes of medications commonly prescribed in the primary care physician setting are contraindicated for use in PD because they may cancel out the effects of medical interventions in PD or even worsen PD symptoms. Thus, primary care physicians should be aware that prescribing certain medications could be hazardous to the patient with PD or a PD-related syndrome (Table 2).

Neuroprotection and Alternative Therapies

There is increasing interest in neuroprotection and alternative therapies for PD. A practice parameter review found no effective neuroprotective treatment, no effect of vitamin or food additives on motor function, and no effect of manual therapies (eg, chiropractic, massage). Findings suggested, however, that exercise may help reduce motor symptoms and that voice training may increase volume.

Since publication of the practice parameter review in 2006, several studies have shown that movement interventions may have greater efficacy than previously believed. In a review of randomized controlled trials (RCTs) of exercise interventions, researchers found beneficial effects of exercise on physical functioning, leg strength, and walking speed. A popular speech-language pathology and occupational therapy program, LSVT BIG and LOUD, emphasizes making loud vocalizations and high intensity/amplitude movements to “retrain”...
Tai chi, a martial art involving slow, controlled movements and the maintenance of various postures, has emerged as a popular PD movement intervention. RCTs have shown that tai chi benefits gait, balance, and functional mobility, and that participants experience fewer falls.\textsuperscript{36,37}

**Genetics**

Research has increasingly focused on the role of genetics in PD. In sporadic PD, the leucine-rich kinase 2 (\textit{LRRK2}) gene has received the majority of attention, but its prevalence is low in the general population (\textless2\%).\textsuperscript{38} Other genes, such as \textit{Parkin}, \textit{PINK1}, and \textit{DJ1} also have been implicated in sporadic PD, but the data are slim. Klein and Schlossmacher\textsuperscript{38} contend that single-gene variants of PD are rare and that it is more likely that there is a complex interaction among genes that operate to increase or decrease PD susceptibility. Environmental exposures may then act to modify further the underlying neuropathology and phenotypic expression of PD. Klein and Schlossmacher suggest that clinicians weigh their curiosity against actual patient benefit when deciding for or against routine clinical PD genetic testing. We believe that benefit is low at this time.\textsuperscript{38}

**Conclusions**

The Parkinson’s Disease Foundation has estimated that the combined annual direct and indirect costs of PD in the United States is $25 billion.\textsuperscript{39}

With a growing number of baby boomers aging into their 60s and beyond, the prevalence of PD can only be expected to increase. PD also has significant negative effects on the quality of life of people and their caregivers, with much of the impact coming from the nonmotor symptoms of the disease. Fortunately, treatments are effective at limiting the disability associated with the disease. General practitioners play a vital role in recognizing the possible signs and symptoms of PD and referring their patients to specialists with access to the latest knowledge and clinical skills in pharmacological, surgical and nonpharmacological interventions.

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**References**


