# 449 Parkinson's Disease and Other Movement Disorders

C. Warren Olanow, Anthony H.V. Schapira, Jose A. Obeso

## PARKINSON'S DISEASE AND RELATED DISORDERS

Parkinson's disease (PD) is the second commonest neurodegenerative disease, exceeded only by Alzheimer's disease (AD). Its cardinal clinical features were first described by the English physician James Parkinson in 1817. It is noteworthy that James Parkinson was a general physician who captured the essence of this condition based on a visual inspection of a mere handful of patients. It is estimated that approximately 1 million persons in the United States, 1 million in Western Europe, and 5 million worldwide suffer from this disorder. PD affects men and women of all races, all occupations, and all countries. The mean age of onset is about 60 years. The frequency of PD increases with aging, but cases can be seen in patients in their 20s and even younger. Based on the aging of the population and projected demographics, it is estimated that the prevalence of the disease will dramatically increase in the next several decades.

Clinically, PD is characterized by rest tremor, rigidity, bradykinesia (slowing), and gait impairment, known as the "cardinal features" of the disease. Additional features can include freezing of gait, postural instability, speech difficulty, autonomic disturbances, sensory alterations, mood disorders, sleep dysfunction, cognitive impairment, and dementia (Table 449-1).

Pathologically, the hallmark features of PD are degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc), reduced striatal dopamine, and intracytoplasmic proteinaceous inclusions known as Lewy bodies that primarily contain the protein alpha synuclein (Fig. 449-1). While interest has primarily focused on the dopamine system, neuronal degeneration with inclusion body formation can also affect cholinergic neurons of the nucleus basalis of Meynert (NBM), norepinephrine neurons of the locus coeruleus (LC), serotonin neurons in the raphe nuclei of the brainstem, and neurons of the olfactory system, cerebral hemispheres, spinal cord, and peripheral autonomic nervous system. This "nondopaminergic" pathology is likely responsible for the development of nondopaminergic clinical features listed in Table 449-1 characterized by their lack of satisfactory response to dopaminergic replacement therapy. There is evidence that Lewy body pathology first begins in the peripheral autonomic nervous system, olfactory system, and dorsal motor nucleus of the vagus nerve in the lower brainstem, and then spreads in a predictable and sequential manner to affect the upper brainstem and cerebral hemispheres (Braak staging). These studies suggest that degeneration of dopamine neurons develops in a mid-stage of the disease. Indeed, epidemiologic studies suggest that clinical symptoms reflecting this nondopaminergic degeneration, such as constipation, anosmia, rapid eye movement (REM) behavior sleep disorder, and cardiac denervation, can precede the onset of the classic motor features of PD.

**TABLE 449-1 CLINICAL FEATURES OF PARKINSON'S DISEASE**

| Cardinal Motor Features | Other Motor Features | Nonmotor Features |
|---|---|---|
| Bradykinesia | Micrographia | Anosmia |
| Rest tremor | Masked facies (hypomimia) | Sensory disturbances (e.g., pain) |
| Rigidity | Reduced eye blinking | Mood disorders (e.g., depression) |
| Gait disturbance/ postural instability | Soft voice (hypophonia) | Sleep disturbances (e.g., RBD) |
| | Dysphagia | Autonomic disturbances |
| | Freezing | Orthostatic hypotension |
| | | Gastrointestinal disturbances |
| | | Genitourinal disturbances |
| | | Sexual dysfunction |
| | | Cognitive impairment (MCI/ dementia) |

***Abbreviations:*** RBD, rapid eye movement behavior disorder; MCI, mild cognitive impairment.

### DIFFERENTIAL DIAGNOSIS

Parkinsonism is a generic term that is used to define a syndrome manifest as bradykinesia with rigidity and/or tremor. It has a differential diagnosis (Table 449-2) that reflects damage to different components of the basal ganglia. The basal ganglia are comprised of a group of subcortical nuclei that include the striatum (putamen and caudate nucleus), subthalamic nucleus (STN), globus pallidus pars externa (GPe), globus pallidus pars interna (GPi), and the SNc (Fig. 449-2). Among the different forms of parkinsonism, PD is the most common (approximately 75% of cases). Historically, PD was diagnosed based on the presence of two of three parkinsonian features (tremor, rigidity, bradykinesia). However, postmortem studies found a 24% error rate when diagnosis was based on these criteria. Clinicopathologic correlation studies subsequently determined that parkinsonism associated with rest tremor, asymmetry, and a good response to levodopa was more likely to predict the correct pathologic diagnosis. With these revised criteria (known as the U.K. Brain Bank Criteria), a clinical diagnosis of PD is confirmed pathologically in as many as 99% of cases. A more complete definition of PD is now needed to incorporate the fact that there is widespread pathology beyond the dopaminergic system, nondopamine and nonmotor clinical features, and a premotor stage of the disease.

Imaging of the brain dopamine system in PD with positron emission tomography (PET) or single-photon emission computed tomography (SPECT) shows reduced uptake of striatal dopaminergic markers, particularly in the posterior putamen with relative sparing of the caudate nucleus (Fig. 449-3), reflecting the degeneration of nigrostriatal dopamine neurons. Imaging can be useful in patients where there is diagnostic uncertainty (e.g., dystonic tremor, essential tremor) or in research studies, but is rarely necessary in routine practice because the diagnosis can usually be established on clinical criteria alone. This may change in the future when there is a disease-modifying therapy and it is important to make the diagnosis as early as possible. Genetic testing is not routinely used at present, but can be helpful for identifying at-risk individuals in a research setting. Mutations of the *LRRK2* gene (see below) have attracted particular interest because they are the commonest cause of familial PD and are responsible for approximately 1% of typical sporadic cases of the disease. Mutations in *LRRK2* are a particularly common cause of PD in Ashkenazi Jews and North African Berber Arabs. The penetrance of the most common *LRRK2* mutation ranges from 28 to 74% and is strongly correlated to the age of the carrier, with 50% affected by age 60 years. Mutations in the *parkin* gene should be considered in patients with onset prior to 40 years of age.

**Atypical and Secondary Parkinsonism** Atypical parkinsonism refers to a group of neurodegenerative conditions that usually are associated with more widespread neurodegeneration than is found in PD (often involvement of striatum and/or globus pallidus as well as the SNc). As a group, they present with parkinsonism (rigidity and bradykinesia) but have a slightly different clinical picture than PD, reflecting differences in the underlying pathology. In these conditions, parkinsonism is typically characterized by early speech and gait impairment, absence of rest tremor, no motor asymmetry, poor or no response to levodopa, and an aggressive clinical course. In the early stages, they may show some modest benefit from levodopa and be difficult to distinguish from PD. Pathologically, neurodegeneration typically involves degeneration of the SNc but occurs without Lewy bodies (see below for individual conditions). Neuroimaging of the dopamine system is usually not helpful, because dopamine depletion can be seen in both PD and atypical parkinsonism. By contrast, metabolic imaging of the basal ganglia/thalamus network (using 2-F-deoxiglucose PET) may be helpful, showing a pattern of decreased activity in the GPi with increased activity in the thalamus, the reverse of what is seen in PD.