Parkinson Disease

This diagnosis is made in individuals with progressive L-DOPA-responsive signs of parkinsonism (tremor, rigidity, and bradykinesia) in the absence of a toxic or other known underlying etiology. Familial forms of PD with autosomal dominant or autosomal recessive inheritance exist. Although these make up a limited number of cases, they have contributed to our understanding of the pathogenesis of the disease.

Morphology. The typical macroscopic findings are pallor of the substantia nigra (compare Fig. 28-40A and B) and locus ceruleus. On microscopic examination, there is loss of the pigmented, catecholaminergic neurons in these regions, associated with gliosis. Lewy bodies (Fig. 28-40C) may be found in some of the remaining neurons. These are single or multiple, cytoplasmic, eosinophilic, round to elongated inclusions that often have a dense core surrounded by a pale halo. Ultrastructurally, Lewy bodies are composed of fine filaments, densely packed in the core but loose at the rim; these filaments are composed of α-synuclein. Lewy bodies may also be found in the cholinergic cells of the basal nucleus of Meynert, which is depleted of neurons (particularly in patients with abnormal mental function), as well as in other brainstem nuclei including the locus ceruleus and the dorsal motor nucleus of the vagus.

Molecular Genetics.

More than a dozen genetic loci for PD have been identified through linkage studies. The five genes currently known to be clearly associated with the disease point to a complex set of possible disease mechanisms.\[53\] \[54\] The first gene to be identified as a cause of autosomal dominant PD encodes α-synuclein, an abundant lipid-binding protein normally associated with synapses that is also a major component of the Lewy body. Mutations in α-synuclein are rare; they take the form of point mutations and amplifications of the region of chromosome 4q21 that contains the gene. The occurrence of disease caused by changes in gene copy number implies a gene dosage effect, similar to what has been observed with APP in AD, and suggests that polymorphisms in the α-synuclein promoter that alter its expression may influence the risk of PD. Mutations in the gene encoding LRRK2 (leucine-rich repeat kinase 2) are a more common cause of autosomal dominant PD and are found in some sporadic cases of the disease. Several of these pathogenic mutations increase the kinase activity of LRRK2, suggesting that gains in LRRK2 function contribute to the development of PD.

A juvenile autosomal recessive form of PD is caused by loss of function mutations in the gene encoding parkin, an E3 ubiquitin ligase with a wide range of substrates. The pathology of parkin-linked PD is similar to that of α-synuclein–linked or sporadic PD except that Lewy bodies are absent in most cases. Other cases of autosomal recessive PD are the result of mutations in the gene encoding DJ-1, a protein involved in regulating redox responses to stress; or the gene encoding the kinase PINK1, which appears to regulate normal mitochondrial function.

Pathogenesis.

No unifying pathogenic mechanism has emerged yet from these diverse genetic and biochemical clues, and many possibilities have been suggested, including a misfolded protein/stress response triggered by α-synuclein aggregation; defective proteosomal function due to the loss of the E3 ubiquitin ligase parkin; and altered mitochondrial function caused by the loss of DJ-1 and PINK1. Intriguingly, other lines of evidence also point to a role for mitochondrial dysfunction; for example, levels of mitochondrial complex I, a component of the oxidative phosphorylation cascade, are reduced in the brains of patients with sporadic PD, and some models of experimental PD are produced by the administration of mitochondrial inhibitors.

The dopaminergic neurons of the substantia nigra project to the striatum, and their degeneration in PD is associated with a reduction in the striatal dopamine content. The severity of the motor syndrome is proportional to the dopamine deficiency, which can, at least in part, be corrected by replacement therapy with L-DOPA (the immediate precursor of dopamine). Treatment does not, however, reverse the morphologic changes or arrest the progress of the disease; moreover, with progression, drug therapy tends to become less effective and symptoms become more difficult to manage. An acute parkinsonian syndrome and destruction of neurons in the substantia nigra follows exposure to MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), discovered as a contaminant in the illicit synthesis of psychoactive meperidine analogues. The use of this toxin in experimental animals has proved highly useful in studies of therapeutic interventions for PD, including transplantation. Epidemiologic evidence has also suggested pesticide exposure as a risk factor for PD, while caffeine and nicotine may be protective.

Clinical Features.

In addition to the signs of parkinsonism, autonomic dysfunction is common, as is some impairment of cognitive function. Parkinson disease is sometimes accompanied by a dementia, either early in the course of the illness or as a late additional morbidity. While L-DOPA therapy is often extremely effective in symptomatic treatment, it does not significantly alter the intrinsically progressive nature of the disease. Over time, L-DOPA becomes less able to help the patient through symptomatic relief and begins to lead to fluctuations in motor function on its own. Given the well-characterized biochemical defect in PD, it has been the focus of early therapeutic trials for neural transplantation and gene therapy.\[55\] Other current neurosurgical approaches to this disease include the strategic placement of lesions elsewhere in the extrapyramidal system to compensate for the loss of nigrostriatal function and placement of stimulating electrodes (deep brain stimulation).\[56\]

Dementia with Lewy Bodies

About 10% to 15% of individuals with PD develop dementia, with increasing incidence with advancing age. Characteristic features of this disorder include a fluctuating course, hallucinations, and prominent frontal signs. While some affected individuals have pathologic evidence of AD (or, less frequently, other degenerative diseases associated with cognitive changes) in combination with the findings of PD, in others
the most prominent histologic correlate appears to be the presence of Lewy bodies in a wide range of cortical locations. These inclusions are less distinct than those observed in the brainstem but similarly contain predominantly α-synuclein. Immunohistochemical staining for α-synuclein also reveals the presence of abnormal neurites, which contain aggregated protein—called Lewy neurites even though he never saw them! In this setting, the gross pathologic findings typically include depigmentation of the substantia nigra and locus ceruleus, paired with relative preservation of the cortex, hippocampus, and amygdala. The burden of cortical Lewy bodies is usually extremely low, and the mechanism by which this disease wreaks havoc on cognitive functioning is not clear. It has been suggested that Lewy body diseases represent a continuum; there is evidence that Lewy bodies and Lewy neurites are found first in the medulla, progress over time to reach the midbrain (when it becomes manifest as PD), and can eventually progress across the nervous system to reach the cortex (and manifest as dementia with Lewy bodies).