Pathogenic Mechanisms of Neurodegeneration in Parkinson Disease

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KEYWORDS

• Parkinson disease • α-Synuclein • Lewy bodies • Mitochondrial dysfunction

KEY POINTS

- Sporadic Parkinson disease (PD) represents an accelerated extreme of the normal spectrum of human senescence.
- Recent discoveries have shown that it is likely to result from the effect of many small but quantifiable genetic risk factors, in combination possibly with the effect of certain environmental insults.
- α-Synuclein is the presynaptic protein that constitutes the principal component of Lewy bodies, the pathologic hallmark of PD. Its transformation to fibrillar and oligomeric forms appears to be the key to its neuronal toxicity.
- Although its exact role in the etiology of sporadic PD is unclear, mitochondrial dysfunction appears to play a major role in its pathogenesis.
- The basis for the selective toxicity to dopaminergic cells that characterizes PD remains unclear.

HISTOLOGY, EPIDEMIOLOGY AND GENETICS OF SPORADIC PARKINSON DISEASE

Lewy bodies (LB), discovered in 1912 by Frederic Lewy, remain the pathologic hallmark of Parkinson disease (PD). Their distribution is thought to follow a sequential appearance within the dorsal motor nucleus, olfactory bulbs and nucleus, locus ceruleus, and subsequently, in the substantia nigra pars compacta (SNc).[1] Neuronal cell loss in PD appears first in the dopaminergic cells of the SNc. It has been estimated that dopamine levels in the striatum are reduced to approximately 60% to 70% of normal values at the time of diagnosis. Degeneration of non-dopaminergic neurons

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also occurs in PD, but usually later in the course of the disease. The cholinergic nucleus basalis of Meynert, the serotoninergic neurons of the raphe nucleus, and the hypocretin-containing neurons of the hypothalamus suffer neuron loss with advanced disease.[1]

Consistently, age is the greatest risk factor for sporadic PD.[2,3] In the United States, the age-adjusted incidence is 13.5 to 13.9 per 100,000 person-years.[2,4] Age-adjusted prevalence is approximately 115 per 100,000, estimated as 1.3 per 100,000 under age 45 years, and 1192.9 per 100,000 in patients aged 75 to 85 years.[4] Conversely, a prevalence study in Holland found 3100 cases per 100,000 aged 75 to 85 years and 4300 per 100,000 for those older than 85 years.[5] The pathological progression of PD occurs in advance of symptomatic motor PD, with the so-called premotor symptoms, including rapid eye movement sleep disturbance, constipation, subcortical cognitive impairment, and hyposmia potentially preceding it by decades.[6] Imaging with positron emission tomography (PET) suggests the preclinical period of cell loss within the SNc is around 8 years, with the greatest rate of decline in the early stages of the disease.[7] LB have been found within the brains of normal aged subjects,[8,9] perhaps the best indication that PD as a disease entity should be viewed as the accelerated extreme of the "normal" spectrum of senescence. Conversely, in dementia with LB, Lewy pathology with an extremely similar distribution to that in advanced PD[10] leads to a progressive subcortical dementia with or without Parkinsonism,[11] highlighting the variable penetrance of the motor PD phenotype and Lewy pathology's lack of specificity to it.

Although caution must be exercised when correlating the histological stigmata of PD with its clinical and, specifically, its motor signs, the PD phenotype remains remarkably robust. Genome-wide association studies (GWAS) correlate single-nucleotide polymorphisms (SNPs) within the genomes of disease carrying subjects and compare them to controls to calculate (expressed as an odds ratio) the risk associated with those SNPs.[12] The success of GWAS in the context of the PD phenotype attests to its specificity. GWAS studies have confirmed the importance of several gene loci, associated with mendelian forms of PD[13,14] (see later discussion). With the exception of *LRRK2*, truly mendelian pathogenic mutations are comparatively rare. However, haplotypes within the same gene loci confer a smaller PD risk with a much greater frequency. In addition, SNPs in novel loci, not previously associated with PD risk, have been identified and confirmed as risk factors for PD.[14] The most prominent example is the consistent recording of the microtubule associated protein τ (*MAPT*), more commonly associated with the pathogenesis of Alzheimer disease, as a major risk allele locus for PD, the implications of which on the established LB centric model of PD remain unclear.

Age and genetic predispositions aside, other environmental factors have been proposed as risk associations in the pathogenesis of sporadic PD. Consistently, chronic tobacco smoke inhalation and coffee drinking have been shown to reduce the risk for PD. In the case of the former, the relationship appears to be dose-dependent and occurs even when the added burden of mortality from the complications of smoking are taken into account.[15] Pesticide exposure, rural living, and farming seem to confer an increased risk of the development of PD, although it is not clear whether farming represents a confounding association with pesticide exposure.[16] Nonsteroidal anti-inflammatory drug exposure, traumatic brain injury, and several other environmental risk factors[17] have also been identified as contributory; however, the odds ratios (ORs) of any of these risks are not sufficient to cause PD in isolation. Their role in the pathogenesis of PD therefore seems likely to be small, probably in conjunction with a (or a combination of) predisposing genetic risk factor(s).