Parkinson's disease

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Abstract

Parkinson's disease (PD) is a common neurodegenerative condition, affecting 2–3% of those >65 years of age. Although it is classically defined as a movement disorder, patients also experience a range of non-motor symptoms, reflecting pathology that is more widespread than originally thought and affecting the peripheral and autonomic nervous system as well as the brainstem and cortex. Some non-motor symptoms can occur years before motor problems emerge, and there is interest in better defining this prodromal state to enable future disease-modifying therapies to be used at an early stage. Patients differ in the extent of non-motor and motor symptoms at presentation, and in the speed at which these evolve. This is at least partly because of genetic factors and is to some extent predictable in early disease. In this article, we discuss the natural history of PD and provide an update on its genetic and pathological basis before reviewing motor and non-motor symptomatology. We discuss currently available therapies and their complications, before going on to review new therapeutic developments and the need to target these precisely to particular disease subtypes that are now better defined at an early disease stage.

Keywords Genetics; heterogeneity; Lewy bodies; Parkinson's disease; therapy

Key points

- Parkinson's disease (PD) is a multisystem disorder with prominent non-motor features, some of which occur as a prodrome to the motor symptoms; eliciting these may facilitate earlier diagnosis
- PD is clinically very heterogeneous, which at least partly relates to inherited genetic factors
- Levodopa remains the most effective and best tolerated oral therapy for the motor symptoms of PD, despite its long-term complications
- Early stratification of patients, based on clinical and genetic factors that predict their likely prognosis, is important to allow better targeting of new therapies
- New therapies undergoing clinical trials include cell-based transplant therapies and gene therapies to directly replace striatal dopamine, and vaccine therapies to prevent the spread of α-synuclein aggregates through the brain

Introduction

Parkinson's disease (PD) is defined as a movement disorder caused by a loss of dopamine-producing cells in the substantia nigra. However, it is more complex than this, both clinically and pathologically. In addition to the well-described motor features of bradykinesia, rigidity, tremor and postural instability, non-motor features including cognitive impairment, depression, hallucinations, autonomic features and sleep problems form a significant symptomatic burden. The importance of non-motor symptoms in PD is acknowledged in the newly developed Movement Disorder Society clinical diagnostic criteria for PD, in which the absence of non-motor features within the first 5 years is a 'red flag' against the diagnosis.[1]

Here, we discuss the typical motor and non-motor symptoms of PD and their pathological basis and treatment. There is considerable variability in the extent of these symptoms and their speed of evolution. This clinical and pathological variability has important implications for selecting the optimal therapies targeted to disease subtype.

Epidemiology and natural history

PD has an incidence of 13 per 100,000 person–years. It is most prevalent in older people, affecting 2–3% of those >65 years of age, but it can begin as early as the third or fourth decade, particularly in inherited cases (see below).

Although many symptoms can be controlled effectively with dopaminergic medications for the first few years after diagnosis, non-dopa-responsive symptoms emerge as the disease progresses; these are generally irreversible and have a major impact on quality of life. Two such key milestones in the natural history of PD are postural instability and dementia, with average times to onset of approximately 5 years and 10 years from diagnosis, respectively. Some patients have a relatively benign course, approximately a quarter surviving without postural instability or dementia at 10 years into their illness.[2] Mortality in PD is reported to be slightly higher than expected for age, but not all studies concur. Pneumonia is the most common cause of death, which may be related to aspiration secondary to swallowing difficulties. However, in most patients dying with PD, the cause of death is not directly related to the PD.[2]

Genetic basis

Around 3–5% of sporadic PD cases are caused by a single genetic variant inherited in a Mendelian fashion. Among familial

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cases, 30% have a monogenic cause (Table 1). Although the vast majority of PD cases are 'idiopathic', genome-wide association studies have identified numerous susceptibility genes and loci (at least 24) that contribute to disease risk; these are being explored in terms of their mechanistic role in the disease process.

Probably the most important of these is *GBA* (the glucocerebrosidase gene). Homozygous mutations in this gene cause the lysosomal storage disorder Gaucher's disease, but heterozygous mutations are a risk factor for PD. These occur in 3–4% of patients compared with only 1% of controls, a finding that has increased interest in the role of lysosomal dysfunction in PD. These *GBA*-associated cases tend to progress rapidly with early cognitive decline. Other genetic factors reported to contribute to phenotypic heterogeneity in PD include the catechol-*O*-methyltransferase (COMT) Val(158)Met polymorphism, which influences executive cognitive function, and the microtubule-associated protein tau (MAPT) H1/H1 genotype and apolipoprotein E (APOE)-ε4 carrier status, both of which are associated with earlier dementia.

Pathology

Pathologically, PD is defined as a loss of dopaminergic cells in the substantia nigra with the deposition of intraneuronal aggregates of α-synuclein in so-called Lewy neurites and Lewy bodies. It is well established that Lewy pathology in PD involves not only dopaminergic cells, but also cholinergic, noradrenergic, serotonergic, histaminergic and glutaminergic cells, accounting for the wide clinical spectrum of symptoms and signs observed. This Lewy pathology develops along a stereotyped trajectory through the brain, beginning in the olfactory bulb and dorsal motor nucleus of the vagus, and spreading rostrocaudally through the brainstem into the midbrain tegmental nuclei. It then spreads to forebrain structures before reaching the anteromedial temporal cortex and finally more widespread regions of the neocortex. There is evidence that small aggregates of α-synuclein can spread trans-synaptically through these anatomically interconnected brain regions.

The mechanisms driving this spread of pathology and the reasons this occurs at different rates in different individuals are still unclear. The mechanisms of initiation of this process are also not fully determined, but recent observations of early pathology in the gastrointestinal tract as well as the olfactory bulb in prodromal PD cases suggest that an environmental pathogen might trigger the first conformational change in α-synuclein in these regions.[3]

Clinical features

Prodromal PD

The nigrostriatal degeneration that underlies the typical motor features of PD is thought to be preceded for many years by changes in the olfactory bulb, brainstem and peripheral enteric nervous system. It is therefore not surprising that some patients report prodromal symptoms dating back many years before the typical parkinsonian motor features become apparent. These include loss of sense of smell, constipation, rapid eye movement (REM) sleep behaviour disorder and mood changes, and their

Genes causing PD with Mendelian inheritance

Gene	Inheritance pattern	Clinical phenotype	Associated neuropathology
SNCA	AD	Early-onset rapidly progressive parkinsonism, dementia, behavioural impairment, autonomic dysfunction	Lewy body pathology in brainstem and cortex; neuronal loss in hippocampus
LRRK2	AD	Usually indistinguishable from idiopathic PD, but dementia less common	Nigrostriatal degeneration ± cortical pathology; Lewy bodies in majority with the G2019S mutation, but typically absent with rarer mutations
EIF4G1	AD	Late-onset slowly progressive L-dopa-responsive parkinsonism, cognition preserved	Lewy body pathology in brainstem and cortex
VPS35	AD	Tremor dominant L-dopa-responsive parkinsonism, variable cognitive and behavioural features	Pathology uncertain
Parkin	AR	Early onset L-dopa-responsive parkinsonism with dystonia and diurnal fluctuation, slowly progressive, no/minimal cognitive impairment	Nigrostriatal degeneration with minimal cortical involvement, no Lewy bodies
PINK1	AR	Early-onset L-dopa-responsive parkinsonism, slowly progressive, higher prevalence of affective and psychiatric symptoms	Lewy pathology and neuronal loss in substantia nigra pars compacta and nucleus basalis of Meynert, but sparing locus coeruleus (one case)
DJ1	AR	Early-onset L-dopa-responsive parkinsonism, slowly progressive, no/minimal cognitive impairment	Pathology uncertain

AD, autosomal dominant; AR, autosomal recessive.

Table 1

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