# Parkinson's disease

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## Abstract

Parkinson's disease (PD) is the second most common neurodegenerative condition affecting patients in the UK after Alzheimer's disease. It is broadly classified as a 'movement disorder' with a variety of clinical features, including bradykinesia, rigidity and tremor. Traditionally, focus has fallen on the treatment of 'motor' complications, such as tremor and mobility problems, although these features are only a small part of the clinical phenotype. In reality, PD is better defined as a multisystem neurodegenerative disorder causing a large number of motor and non-motor complications, and both aspects will be covered in this update. Although dopamine deficiency is the hallmark of the disease, other neurotransmitters involved in both motor and non-motor features of PD include acetylcholine, serotonin and noradrenaline. Diagnosis remains largely clinical and there are many potential pitfalls for the unwary clinician. Successful treatment relies heavily on a multidisciplinary approach with introduction of pharmacological therapy in a gradual, incremental and monitored setting. In the absence of definite disease-modifying agents, therapy remains symptomatic and complications increase as time progresses. Many of the most disabling complications are non-motor, and management of advanced PD is both complex and challenging. One of the most devastating non-motor consequences of PD is the development of Parkinson's disease dementia, which develops in up to 80% of subjects over time. The search for disease-modifying agents to both delay the onset of PD and reduce the burden of cognitive impairment is therefore of paramount importance.

**Keywords** basal ganglia; bradykinesia; dementia; dopamine; dyskinesia; extrapyramidal; non-motor symptoms; Parkinson's disease; tremor

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## What's new?

- In addition to dopamine, other neurotransmitters involved in both motor and non-motor features of Parkinson's disease (PD) include acetylcholine, serotonin and noradrenaline
- Advances in genetics help in understanding the disease process in both sporadic and familial PD
- The search for disease-modifying agents to treat PD is of paramount importance
- Most people with PD will develop dementia in PD over time, if followed up for long enough
- Around 14% of patients, mainly those on dopamine agonists, experience some symptoms of impulse control disorder

## Definition

Defining Parkinson's disease (PD) is difficult because of the variability of signs and symptoms present. Broadly speaking, patients exhibit signs of parkinsonism — bradykinesia, tremor and rigidity — although these clinical features are not unique to PD. Another common term used to describe such symptoms is 'extrapyramidal' — separating the clinical features from disorders of the motor cortex and pyramidal tracts. The most common form of PD is often referred to as 'idiopathic' to help distinguish it from the rarer genetic forms of PD and atypical extrapyramidal disorders.

## Epidemiology

PD is the second most common neurodegenerative disorder in the UK after Alzheimer's disease (AD) and, given our ageing population, will become increasingly important in future years. In the UK, prevalence in the general population is 0.3%, with an estimated incidence of 8–18 per 100,000 person years.[1] Both these figures increase with age, and prevalence is estimated at 1% in the over 60s and 4% in the over 80s.[2,3] In other words, an average GP practice will see between two and four new cases per year, and an average Premiership football crowd will contain 12–15 sufferers.

## Pathology and pathogenesis

Pathological examination of the brains of PD patients reveals abnormal protein aggregations of $\alpha$-synuclein, often collected into intracellular inclusions (Lewy bodies). In addition, there is marked loss of dopaminergic cells in an area of the brainstem known as the substantia nigra, leading to degeneration of projections to other regions of the brain. Most of these projections terminate in the putamen and globus pallidus, although there are also projections to the cerebral cortex, thalamus and other areas of the brainstem. Dopamine deficiency is the hallmark of PD but many other neurotransmitters are also affected in the condition, including acetylcholine, serotonin and noradrenaline. This degeneration ultimately leads to dysfunction of a complex network of excitatory and inhibitory feedback loops, resulting in the symptoms seen in PD (Figure 1). Neurodegeneration involving these other transmitters is likely to be

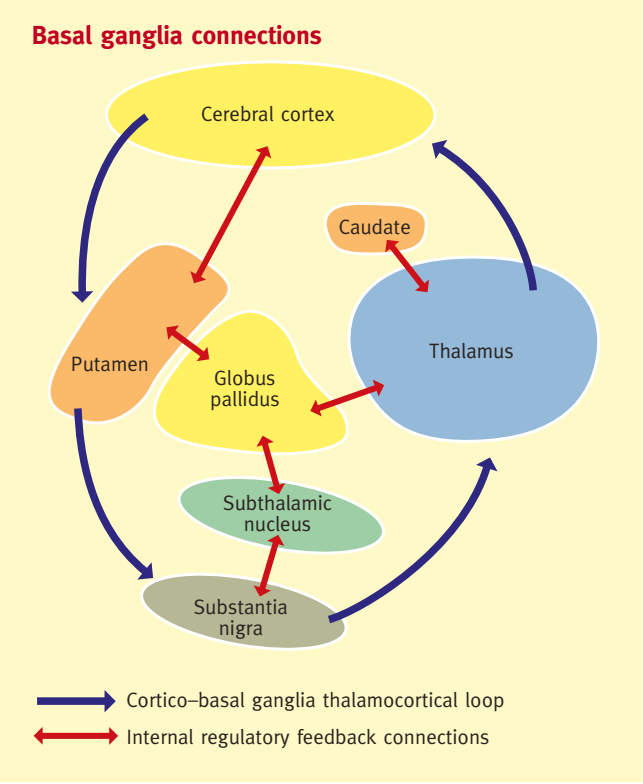


**Figure 1**

involved in the pathophysiology of non-motor symptoms, such as autonomic dysfunction, sleep abnormalities and neuropsychiatric features.

Genetic factors play a role in the development of PD, although true Mendelian inheritance is rare. It is thought that susceptibility genes in combination with a range of environmental factors play a role in the development of PD and around 90% of cases are sporadic, with no family history. Advances in genetics, and in particular, recent genome-wide association studies, have helped with understanding the underlying molecular biology of both sporadic and familial PD. The most common form of genetic PD is autosomal dominant and due to mutations in the gene for leucine-rich repeat kinase 2 (LRRK2),[4] which is clinically identical to idiopathic PD. Potential causative environmental factors are elusive although pesticide exposure has been consistently isolated as an independent risk factor. More recently, exposure to trichloroethylene, a solvent used in industry and in dry cleaning, has been linked to an increased risk of PD.[5] It seems likely that smoking is associated with a decreased risk of developing PD, although how much of this reduction is due to selective mortality in smokers is uncertain. Higher caffeine intake has also been reported to have an inverse correlation with risk of developing PD.[6]

Patients and relatives are often interested or concerned about these issues, and it is important to counsel them appropriately. Whilst there is a small (twofold) increase in relative risk of developing PD for first-degree relatives, this is not a condition that is 'passed on' in the truest sense of the phrase. We still have an incomplete understanding of the role that environmental factors play in the development of PD.

## Course of the disease

PD follows a progressive course with a highly variable tempo. There is no cure nor do we have treatments to reverse or retard the neurodegeneration. Treatment is therefore symptomatic and it is important that patients are aware of this. Putative disease-modifying effects of the monoamine oxidase type B inhibitor (MAOBI) rasagiline have been well publicized, but the results are by no means definitive.[7] There is a reduction in life expectancy associated with the diagnosis, with mortality hazard ratios of between 1.5 and 2.7. Most of the increased mortality is associated with the development of dementia in PD, accompanied by the numerous medical problems seen in this situation. Dementia is increasingly recognized as a complication of PD, with over 80% of patients succumbing after 20 years' disease duration and a sixfold increase in the risk of developing dementia compared with that in the general population.[8,9]

We are beginning to recognize clinical features in patients with PD that might predict a stormier course. In general terms, the later one develops the disease, the longer one has PD, and the more severe the disease is, the greater the likelihood of developing complications. In addition, the presence of neuropsychiatric features (depression and hallucinations) early on predicts worse outcome. Two main clinical phenotypes are now emerging:

- tremor-dominant PD patients
- those with a more marked postural instability and gait disorder (PIGD group).

The latter have a markedly increased risk of cognitive decline and dementia in later years.[10] Other factors that increase the risk of later dementia are increased age, presence of hallucinations and depression, being male and having baseline cognitive impairment.[11]

## Diagnosis

Despite advances in structural and functional brain imaging, the diagnosis of PD remains clinical. There is great potential for misdiagnosis and even in patients with advanced disease at tertiary referral centres neuropathological studies suggest an incorrect diagnosis in around 10% of cases.[12] In the real world, this diagnostic inaccuracy is likely to be higher. The cardinal clinical features are:

- bradykinesia (essential)

plus at least one of the following:

- rest tremor
- rigidity.

UK Brain Bank criteria (Table 1) are often used to aid diagnosis and, although not infallible, are at least applicable in a clinical environment. It is beyond the scope of this article to cover exhaustively all the clinical features of PD and the numerous potential differential diagnoses. We hope to provide a few clinical insights, however, to help you avoid the common pitfalls.

Rules of thumb are:

- tremor is not needed for a diagnosis of PD nor does the presence of tremor necessarily suggest PD
- parkinsonism describes the clinical features seen in PD, but it does not necessarily imply that the diagnosis is PD
- atypical features (Table 1) should make you question the diagnosis as should a poor response to treatment
- neurologists get it wrong too, and it is often better to leave the diagnosis open if you are not sure.