Parkinson’s disease
clinical features and diagnosis

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Parkinson’s disease (PD) is a progressive neurodegenerative disorder, caused by the loss of dopaminergic neurones in the substantia nigra. The disease is characterised by tremor, rigidity, akinesia and postural instability. Although PD is predominantly a movement disorder, patients also experience non-motor symptoms including psychiatric problems, sleep disorders, dysfunction of the autonomic nervous system and sensory disturbances.

James Parkinson, an English surgeon and apothecary, published the first formal description of the symptoms of PD in 1817 in “An essay on the shaking palsy”. Later, the French neurologist Jean-Martin Charcot credited Dr Parkinson’s findings by referring to the disease as “La maladie de Parkinson”.

Quality of life for patients with PD is severely affected by both motor effects (eg, disabling tremor, falls) and non-motor symptoms (eg, anxiety, depression). Input from a multidisciplinary team can improve outcomes for patients and carers.

Epidemiology
About 5.2 million people suffer from PD worldwide. It is more common in Europe and North America than in Africa; this could reflect a difference in life expectancy since PD is, mainly, a disease of older people.

In the UK there are approximately 60,000–108,000 people affected by PD (based on a prevalence of 100–180 per 100,000). The annual incidence in the UK is between four and 20 per 100,000 people, and a typical GP surgery with 6,000 patients could expect to have between six and 11 patients with PD on its list.

The average age of onset is 65 years. Young-onset PD, defined as appearance of the condition under the age of 40 years, accounts for about 5–10% of all cases.

Causes
The cause of PD remains largely unknown. Although the condition is more prevalent in older people, age is not the only factor contributing to the development of PD. It has been suggested that a combination of an inherited susceptibility and exposure to environmental risk factors could cause PD and this warrants further research.

Genetics
There is little doubt that genetic factors contribute to the development of PD, but their significance has yet to be established clearly. Advances in genetic research have enabled the identification of 12 genes associated with PD (PARK1 to PARK11, and NR4A2). Each gene mutation expresses different clinical features, with some overlap. This contributes to a hypothesis that...

SUMMARY
Parkinson’s disease (PD) is a progressive neurological disorder that results from the loss of dopaminergic neurones in the substantia nigra. The cause of this neuronal damage remains largely unknown, but it is believed to be associated with both genetic and environmental factors.

PD is characterised by motor and non-motor symptoms. The main motor features are rigidity, tremor, bradykinesia and hypokinesia. Non-motor symptoms include: neuropsychiatric conditions (eg, dementia, depression and hallucinations); autonomic disturbances (eg, constipation, postural hypotension); sleep disorders; and sensory symptoms (such as pain).
PD is an umbrella term for several neurodegenerative diseases. A person has a 2.5–3 times higher risk of developing PD if a first-degree relative has the disease. However, familial PD is rare (<5%). Twin studies have shown that age of onset plays an important role — onset after the age of 50 years is less likely to be genetically influenced.

Environment Several non-genetic risk factors for PD have been suggested, based on presumed pathogenic pathways. However, the evidence of an association between environmental risk factors and development of PD is weak and the literature should be interpreted with caution. Suggested environmental factors include exposure to pesticides (eg, MPTP), herbicides or heavy metals (manganese, copper).

Conversely, cigarette smoking is negatively associated with the development of PD. Other factors that are proposed to reduce the risk of PD include coffee consumption, drinking alcohol and physical activity.

Pathophysiology The discovery of dopamine as a neurotransmitter in the 1950s by Arvid Carlsson and colleagues led to the identification of the role of dopamine in the pathophysiology of PD. Professor Carlsson observed a high level of dopamine in the basal ganglia, an area of the brain important for movement. In his experiments, animals that were given reserpine (a drug that depletes dopamine) subsequently developed symptoms similar to PD.

There are three pathological hallmarks of PD: the presence of Lewy bodies; neuronal death in the pars compacta of the substantia nigra; and the loss of pigmented neurons (neuromelanin) in pigmented brainstem nuclei.

Lewy bodies, named after the German pathologist Fritz Heinrich Lewy, are protein aggregates of abnormal α-synuclein and other neurofilaments within the neuronal cytoplasm. The exact role of Lewy bodies in the pathophysiology of PD has yet to be established but they are believed to be pathogenic in PD, leading to neuronal cell death. Nevertheless, the presence of Lewy bodies can be asymptomatic and not associated with PD. Lewy bodies are also found in other neurodegenerative diseases (eg, Lewy body dementia, Alzheimer’s disease, multisystem atrophy). The number of Lewy bodies increases with age, which correlates with the increasing incidence of PD among older people.

Degeneration of dopaminergic neurones in the substantia nigra pars compacta leads to profound depletion of dopamine within the brain. Compensatory mechanisms are so effective that the clinical symptoms of PD only develop when 80% of dopaminergic neurones have degenerated.

Symptoms The clinical features of PD are classified into two groups — motor symptoms and non-motor symptoms. The classic motor features are:

- Resting tremor — fine rhythmic movement (frequency 4–6Hz) and often one of the first signs of PD, initially seen in one upper limb and typically involving both upper limbs at later stages of the disease; involvement of the thumb and the index finger is known as “pill-rolling”
- Bradykinesia — slowness of movement, usually in the upper body
- Hypokinesia — poverty of movement, including impassive facial expression and loss of arm swing when walking and progressing to general difficulty with fine movements
- Rigidity — the feeling of resistance to passive movement, which begins unilaterally and progresses to bilateral rigidity in advanced disease; the term “lead pipe” is used to describe continuous resistance, whereas “cogwheel” rigidity refers to more jerky rigidity caused by superimposed tremor

Other motor symptoms that develop in later stages of PD include motor freezing and postural and gait instability. Postural disturbances can include stooped posture, poor balance and stumbling, which frequently lead to falls. Gait becomes slow with shuffling and festination (involuntary quickening).

Sudden stopping or the inability to initiate movements is referred to as “freezing”. This is different from “switching off”, which is a motor complication of PD drug therapy where the treatment effect wears off before the next dose is due (see accompanying article, p368).

A greater awareness of non-motor features of PD is developing. Widespread use of the PD “non-motor symptoms scale” questionnaire has provided evidence that non-motor symptoms often have an equal or greater impact on quality of life than motor complications of PD. Patients may not be aware that non-motor symptoms are related to PD. Although non-motor symptoms are often difficult to control, it is important.
that they are addressed and treated to minimise their impact on quality of life. Non-motor clinical features include:

- Neuropsychiatric symptoms — dementia (24–31%), depression (30%), anxiety, visual hallucinations
- Autonomic — constipation, urinary incontinence, hyperhidrosis, sialorrhoea, postural hypotension (another cause of falls)
- Sleep disorders — rapid eye movement sleep behaviour disorder, restless leg syndrome, vivid dreams, narcolepsy
- Sensory symptoms — pain (dystonic and non-dystonic), paraesthesia

**Diagnosis**

Accurate diagnosis of PD relies on clinical examination and a thorough review of a patient’s history. No definitive laboratory or imaging tests are available to confirm the diagnosis until post-mortem.

There is a high error rate in the diagnosis of PD (24–35% of diagnosed cases are false positives) because of the lack of definitive laboratory or imaging tests to confirm diagnosis. Evidence suggests that the error rate is 47% in primary care compared with 6–8% in tertiary care and, therefore, if PD is suspected patients should be referred (preferably untreated) to a movement disorder clinic for diagnosis. The UK Parkinson’s Disease Society’s “brain bank criteria” (see Box 1, p366) can be used to aid diagnosis and ongoing patient review.

Additional investigations (outlined below) are not usually necessary, but may be useful if diagnosis is unclear.

**Levodopa challenge**

Improved symptoms in response to levodopa is one of the characteristics of PD; therefore administration of single doses has been suggested as a diagnostic test. However, the test is not recommended as a diagnostic tool because it carries a risk of: assessor bias; placebo effect from dose administration; and false negative results from patients who require higher doses for a longer period to elicit a response. The test is also not sufficiently specific (other conditions, such as multisystem atrophy and progressive supranuclear palsy, can respond to levodopa initially).

**Imaging**

Single photon emission computed tomography (SPECT) measures the uptake of radiolabelled tracers that bind to the dopamine transporter protein (DAT) in nigrostriatal nerve endings. A DAT scan will be abnormal for patients with PD, multisystem atrophy or progressive supranuclear palsy, but can be used to differentiate these conditions from essential tremor and drug-induced Parkinsonism (in which a DAT scan would be normal).

Other imaging techniques (eg, transcranial ultrasound of the substantia nigra) are currently not recommended because of high cost and lack of evidence. They are sometimes used in clinical trials.

**Genetic testing**

Specific genes that are associated with PD have been identified, but monogenic forms of the disease are rare and routine testing is therefore not recommended. Testing may be of value for patients with young-onset disease and with a strong family history of PD.

**Olfactory testing**

Impairment of sense of smell is one of the early symptoms of PD and is seen in 85% of patients. Testing for this is not recommended for diagnosis because of the lack of specificity of the symptom (other conditions such as Alzheimer’s disease also feature diminished sense of smell).

**Differential diagnosis**

Some neurodegenerative and Parkinsonian conditions (eg, multisystem atrophy, progressive supranuclear palsy, Wilson’s disease and cortico-basal degeneration) can present with symptoms similar to PD and this can complicate diagnostic accuracy. Evaluation of age of onset, family history, symmetry, eye movements, tremor, presence of dementia, onset and nature of falls, levodopa response, cardiovascular autonomic failure and bladder disturbance are helpful in differentiating these diseases.

Essential tremor is a symmetrical, task-related tremor of 8–10 Hz that occurs mainly in the arm and upper limbs. To differentiate between PD and essential tremor patients are often asked to complete a writing test. This usually reveals progressively bigger text written by a patient with essential tremor compared with patients with PD for whom the writing becomes smaller.

Drug-induced Parkinsonism is the second most common cause of Parkinsonian symptoms in older people (idiopathic is the most common).14 Drugs commonly
implicated are antipsychotics (typical antipsychotics more often than atypical) and antiemetics, due to their dopamine-blocking properties. Drug-induced Parkinsonism is also associated with amiodarone, calcium channel blockers, lithium and antiepileptics (eg, valproate and phenytoin). Drug-induced Parkinsonism is under-diagnosed and can lead to permanent symptoms in 15% of cases, even after withdrawal of the causative medicine; it is not clear whether these cases reflect an unmasking of underlying idiopathic PD.17

**Prognosis**

Rates of disease progression vary considerably among PD patients. PD in itself is not fatal — the cause of death for most people with PD is a secondary comorbid disorder (eg, pneumonia). This is believed to have led to discrepancies in the mortality rates reported in epidemiological studies. Overall, most studies conclude that PD does reduce life expectancy, with reported mortality hazard ratios varying from 1.5 to 2.16. Some 25–40% of patients with PD will develop dementia, which is thought to contribute heavily to the reduced life expectancy.24 Mortality rates associated with PD have remained largely stable. A decrease in mortality was noted in the late 1970s and early 1980s and this was followed by an increase back to previous levels (explained by the introduction of levodopa, which is believed to delay death by about five years).25

**References**