

Parkinson's disease

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Parkinson's disease is a common progressive bradykinetic disorder that can be accurately diagnosed. It is characterised by the presence of severe pars-compacta nigral-cell loss, and accumulation of aggregated α -synuclein in specific brain stem, spinal cord, and cortical regions. The main known risk factor is age. Susceptibility genes including α -synuclein, leucine rich repeat kinase 2 (*LRRK-2*), and glucocerebrosidase (*GBA*) have shown that genetic predisposition is another important causal factor. Dopamine replacement therapy considerably reduces motor handicap, and effective treatment of associated depression, pain, constipation, and nocturnal difficulties can improve quality of life. Embryonic stem cells and gene therapy are promising research therapeutic approaches.

Introduction

James Parkinson hoped that his monograph entitled *An Essay on the Shaking Palsy*, in which he detailed six patients with "involuntary tremulous motion with lessened muscular power, in parts not in action even when supported, with a propensity to bend the trunk forward and to pass from a walking to a running pace", would persuade nosologists that he had described an unrecognised disorder.^{1,2} In acknowledgment of the London apothecary's clear description, Jean Martin Charcot, the father of neurology, proposed that the syndrome should be called *maladie de Parkinson* (Parkinson's disease).

The incidence of the disease rises steeply with age, from 17.4 in 100 000 person years between 50 and 59 years of age to 93.1 in 100 000 person years between 70 and 79 years, with a lifetime risk of developing the disease of 1.5%.^{3,4} The median age of onset is 60 years and the mean duration of the disease from diagnosis to death is 15 years, with a mortality ratio of 2 to 1.⁵ Because of ageing of western populations, an increased frequency above the current 1 in 800 can be anticipated. The precise mode of death is difficult to identify in most cases, but pneumonia is the most common certificated cause. Although good evidence exists that men are about 1.5 times more likely than women to develop Parkinson's disease, this difference is not the same across different studies, and is more pronounced in, and might be restricted to, people older than 70 years of age in western populations.⁶

Parkinson's disease is not related to race or creed, and literary and historical precedents before the publication of Parkinson's monograph make it unlikely to be a postindustrial condition.⁷ The cause remains as elusive as when it was first described in 1817, but important genetic and pathological clues have recently been found.

Pathogenesis

Although Parkinson's disease is regarded as a sporadic disorder, remarkably few environmental causes or triggers have so far been identified.⁸⁻¹⁰ Similar to other neurodegenerative diseases, ageing is the major risk factor, although 10% of people with the disease are younger than 45 years of age. The incidence seems to decrease in the ninth decade of life,⁹ which could be artifactual or related to underdiagnosis of elderly people

of that age, or could be a real decline, similar to what happens in some other neurodegenerative diseases (eg, motor neuron disease). Never smokers are twice as likely to develop Parkinson's disease,^{11,12} and men and postmenopausal women who are not taking hormone replacement, who take no or very low quantities of daily caffeine, seem to be at increased (about 25% more) risk.^{13,14} These findings might be related to dopamine's role in reward pathways and to low premorbid novelty seeking personality traits¹⁵ rather than to any neuroprotective effect of tobacco smoke, nicotine, or caffeine.^{15,16} Some studies, however, have shown the inverse association between risk to develop the disease and smoking.¹⁷ Both nicotine and caffeine increase striatal dopamine release, and the enzyme monoamine oxidase, which can increase oxidative stress, is inhibited in the brains of smokers.¹⁸

Caffeine is an adenosine A2 receptor antagonist, and it is of interest that some compounds in this class have shown potential as anti-parkinsonian drugs.¹⁹ Studies on the smoking history of discordant identical twins with Parkinson's disease have also indicated that the differences in smoking habits between affected and unaffected siblings cannot be adequately explained by confounding genetic or familial factors.²⁰ Weak associations between Parkinson's disease and head injury, rural living, middle-age obesity, lack of exercise, well-water ingestion, and herbicide and insecticide exposure (paraquat, organophosphates, and rotenone) have also been reported.^{21,22} Environmental toxins (eg, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine [MPTP], cyanide, carbon disulphide, and toluene) can produce a similar but not identical clinical picture.²³

Search strategy and selection criteria

We searched PubMed for papers published in English between 1998 and 2008 with the terms "Parkinson's disease" and "gene therapy", "implantation", "treatment", "diagnosis", "imaging", "epidemiology", "pathology", and "genetics". We also reviewed historical textbooks and monographs. We have used the American Academy of Neurology (AAN) treatment guideline parameters, the Movement Disorder Society Evidence Based Review (EBR), and the National Institute for Health and Clinical Excellence (NICE) guidelines on Parkinson's disease to write the therapeutics section.

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	Pathological aggregates	Comments
Parkinsonism		
Parkin	Substantia-nigra degeneration but usually no Lewy bodies	Recessive, young onset
<i>PINK1</i>	No pathology reported	Recessive, young onset
<i>DJ-1</i>	No pathology reported	Recessive, young onset
<i>ATP13A2</i>	No pathology reported	Recessive young onset
Parkinson's disease		
α -synuclein	Lewy bodies	Dominant point mutations and duplications. Genetic variability contributes to disease
<i>LRRK-2</i>	Usually Lewy bodies	Dominant mutations
<i>GBA</i>	Lewy bodies	Dominant loss of function mutations increase risk

GBA=glucocerebrosidase. *LRRK-2*=leucine rich repeat kinase 2. *PINK1*=PTEN-induced putative kinase 1.

Table: Genes associated to L-dopa-responsive parkinsonism

Genetic studies have shown that several mutations in seven genes are linked with L-dopa-responsive parkinsonism (table). Six pathogenic mutations in leucine rich repeat kinase 2 (*LRRK-2*)—a kinase encoding the protein dardarin—have been reported, and the most common of these—the Gly2019Ser mutation—has a worldwide frequency of 1% in sporadic cases and 4% in patients with hereditary parkinsonism, making it as common as multiple system atrophy and progressive supranuclear palsy.^{24,25} In north African Arabs, almost a third of all patients diagnosed with parkinsonism have an *LRRK-2* mutation, which is also common in Ashkenazi Jews (28% of hereditary cases) and in Portuguese people.²⁵ The clinical presentation closely resembles sporadic Parkinson's disease, but patients tend to have a slightly more benign course and are less likely to develop dementia. A person who inherits the Gly2019Ser mutation has only 28% risk of developing parkinsonism when younger than 60 years of age, but the risk rises to 74% at 79 years of age.²⁵ Both point mutations and gene triplications of α -synuclein also cause a parkinsonian syndrome indistinguishable from Parkinson's disease, but these are much rarer.^{26,27} Duplications of α -synuclein have rarely been found in sporadic Parkinson's disease.²⁸

Loss-of-function mutations in four genes (*parkin*, *DJ-1*, *PINK1*, and *ATP13A2*) cause recessive early onset parkinsonism (age of onset <40 years). *Parkin* mutations are the second most common genetic cause of L-dopa-responsive parkinsonism, whereas mutations in the other three genes are rare. All these mutations lead to a disease that has a more benign course than Parkinson's disease, responds well to dopaminergic drugs, and frequently presents with gait disorder, rest tremor of the legs, and limb dystonia. Early behavioural disturbances are commonly reported, but prominent bulbar symptoms, dementia, and hyposmia are unusual. Additional features, including a supranuclear gaze palsy and prominent pyramidal signs, are typical of Kufor-Rakeb syndrome.²⁹

PINK1 shares the same mitochondrial pathway as *parkin*.^{30,31} A dysfunction of mitochondria could be the key reason for at least some of the autosomal recessive forms of parkinsonism.³² Defects in protein handling by the ubiquitin proteasome system, leading to the aggregation of cytotoxic proteins, has also been linked to several mutations in proteins such as α -synuclein and *parkin*. Accumulation of unwanted proteins, exceeding the capacity of the proteasomes to clear them, leads to proteolytic stress, which could then result in Parkinson's disease and familial forms of parkinsonism.³³ The ubiquitin ligase *parkin* protein mediates the engulfment of dysfunctional mitochondria by autophagosomes.³⁴ Failure to remove dysfunctional mitochondria may therefore be an important pathogenetic factor.

Homozygous loss of function of glucocerebrosidase (*GBA*) causes Gaucher's disease, whereas its heterozygous loss of function increases the risk of developing Parkinson's disease more than five fold.³⁵ The relation between this rare inborn error of metabolism, which is common in Ashkenazi Jews, and Parkinson's disease is still unclear, although the few people with Gaucher's disease who survive into adult life have had parkinsonism, and Lewy bodies have been found in their brains.^{35,36} The percentage of cases affected by severe *GBA* mutations is 29% in Jewish Parkinson's disease patients (mean age 68 years) and 7% in young (20–45 years old) healthy controls. This result shows that the risk of developing Parkinson's disease is increased 13 times if one carries a severe *GBA* mutation, which reduces the mean age of Parkinson's disease onset from 60 to 55 years of age.³⁷ Ashkenazi Jews with Parkinson's disease have a 30% probability of carrying either a *GBA* or a *LRRK-2* mutation; therefore, these susceptibility genes should be regarded as important risk factors in this ethnic group.^{37,38} In the UK, about 4% of Parkinson's disease patients have a *GBA* mutation.

Mendelian genes and *GBA* mutations cause parkinsonism in about 6% of patients in the UK. It is speculated that α -synuclein, *LRRK-2*, and *GBA* are implicated in a common biochemical pathway that is important in the pathogenic process. Whether this pathway is associated with other postulated causal mechanisms, including oxidative stress, glutamate excitotoxicity, mitochondrial dysfunction, neuroinflammation, and apoptosis also remains to be clarified.

Clinical features

Parkinson's disease commonly presents with impairment of dexterity or, less commonly, with a slight dragging of one foot. The onset is gradual and the earliest symptoms might be unnoticed or misinterpreted for a long time. Fatigue and stiffness are common but non-specific complaints. Work colleagues or family members might notice a lugubrious stiff face, a handgrip

appearance, a flexion of one arm with lack of swing, a monotonous quality to the speech, and an extreme slowing down. These changes are rarely noticed by the patient. The early physical signs are often erroneously ascribed to old age, misery, introspection, or rheumatism, and a lag of 2–3 years from the first symptoms to diagnosis is not unusual.

Once the diagnosis has been confirmed, patients and their families often start to remember potentially relevant symptoms and signs going back more than a decade. Early difficulties with coordination might have been blamed on faulty equipment, such as a keyboard that keeps typing a letter twice; a towel that does not dry properly; or a self-winding watch that keeps stopping despite reassurances from the manufacturer. Each neurologist has his anecdotes about unusual clinical presentations. Kinnier Wilson, a distinguished neurologist who worked at the National Hospital for Nervous Diseases (Queen Square, London) and whose name has been associated with hepatolenticular degeneration, described the case of a colleague who remained abnormally still in his seat during a medical conference, and another of a friend who commented that his first symptom was that he could walk more easily on a pebbled beach than in a crowded street.³⁹ Loss of sense of rhythm and a tendency to swim in circles are two personal recollections. Early motor symptoms can be subtle and easily missed. A change in a patient's writing can be present for several years before diagnosis, with a tendency to slope usually in an upward direction and for the writing to get progressively smaller and more cramped after a line or two.

Careful assessment of the family history of patients with Parkinson's disease might also help to identify other affected first-degree relatives. Early loss of smell is occasionally spontaneously reported but many patients are unaware of hyposmia until they are formally tested.⁴⁰ Disturbed sleep—including shouting out, flailing movements of arms and legs, and falling off the bed during dreaming—might only be noticed if the patient's spouse is specifically questioned. These symptoms suggest rapid eye movement (REM) sleep disorder and, if severe, might need to be treated with clonazepam.⁴¹

Complaints within the first 2 years of the disease of falls (especially backwards), fainting, urinary incontinence, prominent speech, disturbed swallowing, amnesia, or delirium should raise the possibility of an alternative diagnosis.

The use of dopamine antagonists, such as prochlorperazine for giddiness, metoclopramide for dyspepsia, chlorpromazine for bipolar depression, calcium-channel blockers, such as flunarizine, cinnarizine, and sodium valproate used to control epilepsy or migraine, should be limited because all these medications can cause reversible parkinsonism. Herbal remedies such as the western Pacific sedative kava⁴² or the Indian snake root *Rauwolfia serpentina* can

also cause parkinsonism.⁴³ The increasing purchase of herbal medications over the internet and the rise of generic formulations of dubious purity have exposed people to a greater risk of noxious unregulated products.⁴⁴

The patient's occupation, and smoking, caffeine, and alcohol habits should be noted together with any history of illicit drug use. A past history of severe head injury, encephalitis, toxin exposure, or hypertension and cerebrovascular disease might be important as secondary causes.

In the late stages of Parkinson's disease, the face of patients is masked and expressionless, the speech is monotonous, festinant, and slightly slurred, and posture is flexed simian with a severe pill rolling tremor of the hands (figure 1). Freezing of gait for several seconds can happen when attempting to enter the consulting room and, when starting to move again, the patient tends to move all in one piece with a rapid propulsive shuffle. These motor blocks lead to falls. All dextrous movements are done slowly and awkwardly, and assistance might be needed for dressing, feeding, bathing, getting out of

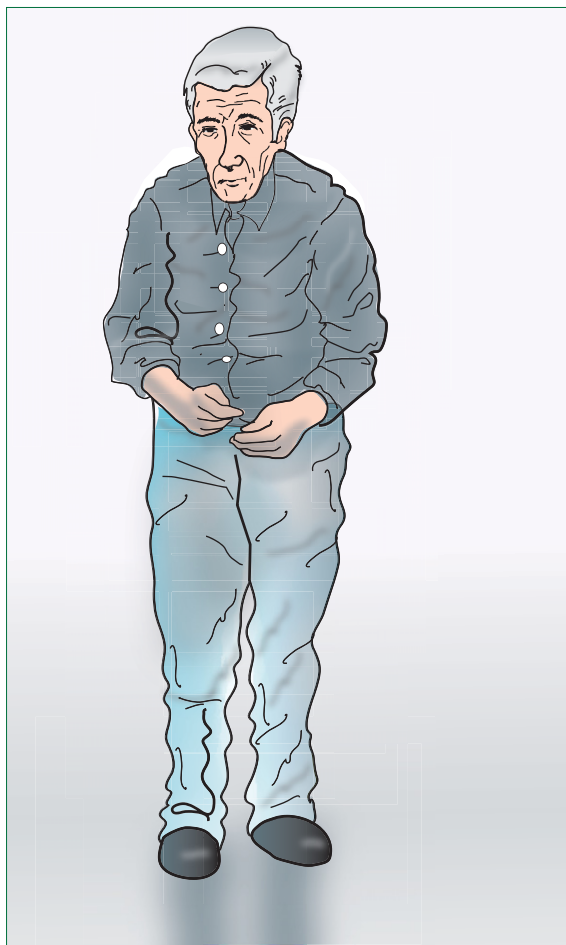


Figure 1: Illustration of the slightly anxious frozen face and characteristic flexed posture of a Parkinson's disease patient (courtesy of Nathalie Lees)

chairs, and turning in bed. Constipation, chewing and swallowing difficulties, drooling of saliva, and urge incontinence of urine are common complaints; urinary catheterisation and percutaneous gastrostomy are sometimes needed in the terminal phase.

Risk of dementia exists, particularly in those patients who present with prominent gait and speech disorders, depression, and a poor response to L-dopa. The greatest risk factor for dementia, however, is the age of the patient and not the duration of the disease.^{45,46} Visuospatial difficulties, disturbances of attention and vigilance, delirium, and executive dysfunction are more common in Parkinson's disease than in Alzheimer's disease. Dementia with Lewy bodies, which presents with dementia, delirium, and well formed visual hallucinations, is a clinical syndrome with similar pathological features to Parkinson's disease.⁴⁷ Bradykinesia and rigidity are common in dementia with Lewy bodies; therefore, later in its course it might be indistinguishable from Parkinson's disease with associated dementia.

Diagnosis

The diagnosis of Parkinson's disease cannot be made without the detection of unequivocal bradykinesia, although individuals with monosymptomatic rest tremor who have abnormalities of striatal dopamine on functional imaging exist. Bradykinesia might be apparent as soon as the patient enters the consulting room or when the patient undresses to be examined. Facial expression can be immobile and rigid, and the ability to express emotions is slow. The speech might also be slow, quiet, and lacking in rhythm and melody. Repetitive finger movements need to be assessed. Rapid repetitive finger tapping of the index finger on the thumb for about 20 s on each hand is the most popular test, but this should be done together with piano-playing movements and the sequential touching of each finger on the thumb. If there are still doubts, the patient should be asked to carry out finger tapping simultaneously with both hands. Bradykinesia in the leg is assessed by fast foot tapping and asking the patient to walk. Good clinical practice is to ask the patient to write a few lines of longhand script, although the correlation between abnormalities of finger tapping and micrographia is not always present. Bradykinesia is confirmed with the demonstration of slowness, and a progressive reduction of speed and amplitude on sequential motor tasks.

Parkinson's disease is also characterised by a coarse, slow, pill rolling tremor of the hands (4–6 cycles/s), which might be only evident when the hand is truly at rest, such as when the patient is asked to do fine finger movements with the other hand or to walk. Tremor of the hands can be abolished in the early stages by postural readjustments or use of the affected hand, and is aggravated by highly charged or emotional situations and cold weather. Young patients (<40 years of age) frequently present with tremor, which is more severe in

the legs, and noted on lying or sitting, whereas older patients (>70 years of age) might have tremor of the jaw, chin, lips, and tongue. Many patients also have a fast postural tremor of the outstretched hands resembling that seen in essential tremor but with a fractional delay before its emergence. The debate as to whether essential tremor increases the risk of subsequently developing Parkinson's disease remains unresolved. However, many neurologists have seen patients with a long history of essential tremor, with postural and kinetic tremor of the hands, sometimes with associated yes–yes head tremor, which progresses after many years into unequivocal Parkinson's disease.⁴⁸ Although the presence of rest tremor is helpful for the diagnosis of Parkinson's disease, a similar tremor can occur in some cases of dystonic and atypical tremor syndromes.⁴⁹

Flexion of the limbs and trunk is characteristic of Parkinson's disease, and some patients have transient fixed posturing of a hand after completing a motor task (catalepsy). Some patients have motor impatience with a difficulty in finding a comfortable position to rest their limbs, and few have striking mirror movements. Absent arm swing, with a mild flexion of the arm at the elbow, can be one of the earliest clues to diagnosis. Truncal difficulties can also be identified by asking the patient to stand up with arms folded, tandem walk for ten steps, and finally walk quickly down a corridor. Additional physical signs that can be noticed at the first consultation include foot dystonia in young patients, infrequent blinking with a slightly staring anxious expression, and a tendency to drag one leg when walking.

Parkinson's disease is by far the most common cause of bradykinesia and should always be the diagnosis if no specific and definite secondary cause can be identified.⁵⁰ A slow progression, unilateral presentation with asymmetrical signs, a pill rolling rest tremor, and good sustained response to L-dopa support the diagnosis, and they are included in panel 1.^{50,51} Recent minor research modifications of the widely used Queen Square Brain Bank criteria include the replacement of CT scanning with MR imaging in step 2 and the insistence of exclusion of cases with more than one first degree affected relative has also been challenged. Early hyposmia and late appearance of visual hallucinations are also suggestive of Parkinson's disease.^{52,53} Some patients who present with predominant gait and speech difficulties and have a modest response to L-dopa might be difficult to distinguish from those with multisystem atrophy parkinsonism or progressive supranuclear palsy parkinsonism. Vascular parkinsonism usually presents with severe gait initiation failure, a broad based shuffling gait, mild bradykinesia, rigidity of the arms, and subtle hypomimia. This clinical picture is sometimes referred to as lower half parkinsonism. Vascular risk factors include hypertension and a past history of mini strokes might exist. Patients with vascular parkinsonism have no rest tremor, their

Panel 1: Queen Square brain bank clinical diagnostic criteria**Step 1 Diagnosis of parkinsonian syndrome**

Bradikinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude or repetitive actions)

And at least one of the following:

- Muscular rigidity
- 4–6 Hz rest tremor
- Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction

Step 2 Exclusion criteria for Parkinson's disease

- History of repeated strokes with stepwise progression of parkinsonian features
- History of repeated head injury
- History of definite encephalitis
- Oculogyric crises
- Neuroleptic treatment at onset of symptoms
- More than one affected relative
- Sustained remission
- Strictly unilateral features after 3 years
- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic involvement
- Early severe dementia with disturbances of memory, language, and praxis
- Babinski signs
- Presence of a cerebral tumour or communicating hydrocephalus on CT scan
- Negative response to large doses of L-dopa (if malabsorption excluded)
- MPTP exposure

Step 3 Supportive prospective positive criteria of Parkinson's disease

Three or more required for diagnosis of definite Parkinson's disease:

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting the side onset most
- Excellent response (70–100%) to L-dopa
- Severe L-dopa-induced chorea
- L-dopa response for 5 years or more
- Clinical course of 10 years or more
- Hyposmia
- Visual hallucination

olfaction is normal, and the response to L-dopa is usually poor. MRI shows extensive subcortical white-matter ischaemic changes. Some rare subacute onset vascular parkinsonism cases are the result of a motor hemiparesis from a lacunar stroke in the basal ganglia. As the corticospinal signs recede, parkinsonism appears in the same limbs. These cases, which closely resemble Parkinson's disease, respond to L-dopa³⁴ and

sometimes have a complete absence of nigrostriatal dopamine uptake in the contralateral striatum, with normal transporter uptake on the ipsilateral side.⁵⁵ Coexistent cerebrovascular disease can also modify the clinical picture of Parkinson's disease in elderly patients.

Multiple system atrophy parkinsonism and progressive supranuclear palsy parkinsonism are sometimes confused with Parkinson's disease, but are much rarer; for every case of atypical parkinsonism, there are at least 20 cases of Parkinson's disease. Multiple system atrophy parkinsonism typically presents in the sixth decade of life with urinary incontinence and syncope, and with early erectile failure in men. Some years later, a rapidly progressive gait disturbance, slowness and stiffness, and speech and swallowing problems appear, and the patient can lose the ability to sweat. Difficulty to distinguish multiple system atrophy from Parkinson's disease arises when autonomic failure is not prominent and when a good response to L-dopa with dyskinesias is seen.⁵⁶ Few patients with Parkinson's disease also have cardiovascular autonomic failure.

Progressive supranuclear palsy parkinsonism is a recognised clinical subtype of progressive supranuclear palsy, which closely resembles Parkinson's disease at presentation. It usually presents in the seventh or eighth decade, and autonomic failure is absent. Axial and bulbar symptoms can be more striking than in Parkinson's disease, and some patients have early prominent bradyphrenia and slowing of vertical saccades.⁵⁷ Both multiple system atrophy parkinsonism and progressive supranuclear palsy parkinsonism have a much more rapid progression than Parkinson's disease, with a mean duration from onset of disease to death of about 9 years.⁵⁸

Essential tremor is commonly misdiagnosed as Parkinson's disease, especially when the tremor is of large amplitude, starts in old age, and continues into the resting state. Bradykinesia is not present and the tremor is usually most intrusive on action or when holding the hands outstretched. The presence of an associated head or voice tremor, a family history of tremor in more than one first-degree relative, normal olfaction, and an improvement of symptoms with small amounts of alcohol support the diagnosis. Patients with dystonic and atypical tremor syndromes may have some cogwheel rigidity at the wrist and do not swing one arm when walking. The flurries of tremor and dystonia can also make it difficult to assess whether bradykinesia is really present or not.⁵⁹

In most cases, the diagnosis of Parkinson's disease can be made on clinical grounds and no ancillary investigations are needed. If doubt exists, a second opinion rather than several inconclusive investigations is advised. Few patients with dystonic tremor, atypical tremor, or even a severe retarded depression, closely resemble those with Parkinson's disease. Furthermore,

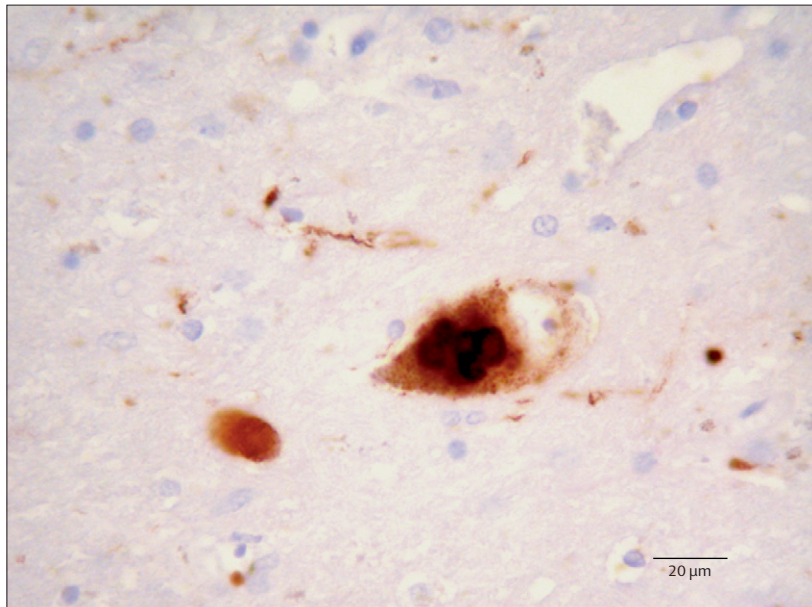


Figure 2: Light microscopy of a surviving neuron in the substantia nigra of a patient with Parkinson's disease. The neuron is full of α -synuclein Lewy bodies.

in some elderly people with gait disturbances and clumsiness or stiffness, and in others with diffuse subcortical ischaemia on MRI, parkinsonism can be suspected. In these specific situations, the demonstration of normal striatal dopamine-transporter uptake with dopamine transporter (DAT) SPECT can avoid inappropriate anti-parkinsonian treatment.⁶⁰ 4–14% of patients regarded as having early onset Parkinson's disease in recent large therapeutic trials had baseline scans without evidence of dopaminergic deficit (SWEDDS), and some of these with tremor on presentation who failed to respond to dopamine replacement and did not deteriorate on follow-up might have had dystonic tremor.⁶¹ DAT SPECT is also helpful in identifying juvenile parkinsonism, when the differential diagnosis lies between L-dopa-responsive dystonia and monogenetic parkinsonism.

In patients suspected to have Parkinson's disease who fail to respond to therapeutic doses of L-dopa (at least 600 mg/day) administered for 12 weeks, MRI scanning is needed to exclude rare secondary causes (ie, supratentorial tumours and normal pressure hydrocephalus) and extensive subcortical vascular pathology. Some patients thought to have Parkinson's disease develop late atypical features, which suggest an alternative neurodegenerative disorder. In these cases, 3-Tesla MRI with diffusion weighted sequences is showing promise in distinguishing multiple system atrophy parkinsonism (putaminal signal changes, hot cross bun sign, and pontine and cerebellar atrophy) from progressive supranuclear palsy parkinsonism (midbrain atrophy with so-called hummingbird and morning glory signs, and superior cerebellar peduncle atrophy).⁶² Patients with essential

tremor, vascular parkinsonism, multiple system atrophy, or progressive supranuclear palsy are also much more likely to have normal olfaction than those with Parkinson's disease, and the selective use of odour-identification tests, such as the University of Pennsylvania smell inventory test or the sniffin sticks, can be helpful in some clinical settings.⁶³

Neuropathological lesions

A region-specific selective loss of dopaminergic, neuromelanin-containing neurons from the pars compacta of the substantia nigra is the pathological hallmark of Parkinson's disease. However, cell loss in the locus coeruleus, dorsal nuclei of the vagus, raphe nuclei, nucleus basalis of Meynert, and some other catecholaminergic brain stem structures including the ventro tegmental area also exists.⁶⁴ This nerve-cell loss is accompanied by three distinctive intraneuronal inclusions: the Lewy body, the pale body, and the Lewy neurite. Lewy bodies are subdivided into classical (brainstem) and cortical types on the basis of their morphology. The brain-stem shape is a spherical structure measuring 8–30 μ m with a hyaline core surrounded by a peripheral pale-staining halo, and is composed ultrastructurally of 7–20-nm wide filaments with dense granular material and vesicular structures. Pale bodies are large rounded eosinophilic structures that often displace neuromelanin and are the predecessor of the Lewy body.⁶⁵ A constant proportion of nigral neurons (3–4%) contain Lewy bodies, irrespective of disease duration. This finding is consistent with the notion that, in contrast to neurofibrillary tangles, Lewy bodies are continuously forming and disappearing in the diseased substantia nigra.⁶⁶

An abnormal, post-translationally modified, and aggregated form of the presynaptic protein α -synuclein is the main component of Lewy bodies. α -synuclein antibodies stain Lewy bodies and Lewy neuritis, and have become the standard and most sensitive immunohistochemical method for routine diagnostic purposes (figure 2).⁶⁷ α -synuclein-positive, ubiquitin-negative punctate cytoplasmic staining can also be seen in pigmented brain stem neurons without Lewy bodies and in glial tissue, and represents the earliest stage of abnormal α -synuclein accumulation.⁶⁸

Cortical Lewy bodies lack the inner core and halo, and are especially common in small-to-medium-sized pyramidal neurons of layers V and VI of the temporal, frontal, parietal, insular cortices, cingulum, and entorhinal cortex. These bodies are present in small numbers in almost all cases of Parkinson's disease.⁶⁹ Extensive neocortical Lewy body pathology is common in patients with severe memory loss when additional Alzheimer-type changes are frequently seen.^{70–75} A substantial proportion of non-demented patients with Parkinson's disease also have widespread cortical Lewy body pathology; therefore, neocortical Lewy bodies are not necessarily the pathological correlate of dementia in

Parkinson's disease.⁷⁶⁻⁷⁸ The amount of associated cortical β -amyloid seems to be the key factor for the cognitive decline in Parkinson's disease.^{69,79-81} Pathological heterogeneity in Parkinson's disease with dementia is further supported by a study showing that a long course of parkinsonism before the onset of dementia is associated with a low plaque frequency and cortical Lewy body count, despite a great loss of choline acetyltransferase activity.⁸¹

The few patients with α -synuclein, *LRRK-2*, and *GBA* mutations who have had autopsy have all shown changes indistinguishable from those found in patients with Parkinson's disease.⁸² Some families with *LRRK-2* mutations also have tangle pathology and non-specific neuronal loss. In contrast, parkin mutations lead to nigral loss, restricted brain-stem neuronal loss, and absence of associated Lewy bodies or neurofibrillary degeneration. Heterozygous parkin carriers, however, have been associated with both Lewy body and neurofibrillary tangle pathology.⁸³⁻⁸⁵

In about 10% of people older than 60 years of age who have died without evidence of neurological disease, Lewy bodies are present in the brain. This condition has been named incidental Lewy body pathology and might be a presymptomatic early phase of Parkinson's disease.^{86,87} If this is true, then there are around ten times more people at risk of developing Parkinson's disease than ever manifest bradykinesia.⁸⁸ Braak and colleagues⁸⁹ have suggested that the progression of α -synuclein accumulation from preclinical to symptomatic, and subsequently to advanced disease, is not random but spreads along axonal pathways interconnecting vulnerable brain regions in a constant pattern that they have arbitrarily subdivided into six different stages. The investigators suggested that the disease process begins in the gastric autonomic plexus of Meissner and the olfactory nerve endings,^{89,90} and then spreads to specific regions of the medulla oblongata and the anterior olfactory nucleus. From the lower brainstem, the disease process gradually ascends into more rostral brainstem structures, so that the pars compacta of the substantia nigra becomes affected. Cortical pathology is restricted to the temporal mesocortex in the following stage of the disease, then extends into the neocortex and finally into the first-order sensory association neocortical areas and premotor areas. Lamina 1 spinal-cord neurons could also be involved in the early phase of the disease contributing to autonomic dysfunction.⁹¹ Several research groups have confirmed the value of this staging system, although at least 15% of patients with Parkinson's disease do not conform to this pattern.^{92,93} Whether these findings have any clinical relevance or correlate with the severity of regional neuronal cell loss remains unclear.

Fetal mesencephalic neurons grafted into the striatum of Parkinson's disease patients to restore dopaminergic transmission can develop Lewy body pathology,^{94,95} which raises the possibility that a combination of

several disease-specific factors present in the striatal microenvironment of the host could trigger host-to-graft propagation of α -synuclein pathology. Inflammation, oxidative stress, excitotoxicity, and loss of neurotrophic support of the grafted neurons could all be important factors.⁹⁵ A prion hypothesis implicating permissive templating has also been proposed, in which α -synuclein misfolding in one brain region could trigger α -synuclein aggregation in interconnected neuronal groups, and finally deposit abnormally misfolded protein in the genetically distinct grafted dopaminergic neurons.⁹⁶ A prion-like mechanism could also be the neurobiological basis for the stereotypic disease spread described by Braak and colleagues⁸⁹ and could be a target of future disease-modifying therapies.⁹⁵

Treatment

Parkinson's disease is still an incurable progressive disease, but treatment substantially improves quality of life and functional capacity. L-dopa, in combination with a peripheral dopa decarboxylase inhibitor (benserazide or carbidopa), is the most effective therapy and should always be the initial treatment option, whatever the age of the patient. Most people can be maintained over the first 5 years of the disease on 300–600 mg/day L-dopa. Although prediction of the therapeutic response in an individual is not possible, motor symptoms initially improve by 20–70%. Within a week or two of starting treatment, fatigue lessens, and bradykinesia, rigidity, and gait steadily improve over the following 3 months.⁹⁷ Tremor is often more difficult to treat, and in some patients it only disappears after several years of treatment, which might indicate a delayed pharmacological effect or evolution of the disease. Speech, swallowing, and postural instability can improve initially, but axial symptoms are generally less responsive and seem to escape more readily from long-term control.^{5,98} Early adverse events can include nausea, anorexia, and faintness, but L-dopa is generally well tolerated when it is gradually increased. Early neuropsychiatric problems can sometimes occur including hypomania, depression, and delirium, and a small number of patients with prominent tremor are unable to tolerate even small doses. The non-ergoline dopamine agonists (pramipexole, ropinirole, rotigotine, and piribedil) are efficacious drugs that, in contrast to L-dopa, when used as monotherapy do not provoke dyskinesias. They are a popular first-line treatment in patients under 55 years of age; however, L-dopa is usually necessary within 3 years of diagnosis. Dopamine agonists also cause early gastrointestinal and psychiatric side-effects, and ankle oedema, sleep attacks, and impulse control disorders (pathological gambling, hypersexuality, binge eating, and compulsive shopping) necessitate drug withdrawal in few patients.

The selective type B monoamine oxidase inhibitors, selegiline and rasagiline, are well tolerated and can be administered once daily but they are less efficacious than

either L-dopa or dopamine agonists. They seem to delay disease progression when started early in the course of the disease, and are proposed as disease-modifying agents.^{99,100} Two recent trials have shown that early treatment with 1 mg rasagiline daily compared with delayed treatment (6 months later) leads to some positive outcomes at 72 weeks, but the biological significance and clinical relevance of this finding need to be carefully assessed with a longer follow-up.¹⁰¹ Amantadine is another well tolerated drug that has mild anti-parkinsonian effects and can be used as initial treatment. The efficacy of each of these drugs, as well as their adverse-event profile, need to be fully explained to the patient when treatment options are being considered.^{102,103} Placebo-associated responses are particularly striking in patients with Parkinson's disease and could lead to an initial 20% improvement in motor scores. This improvement might be mediated through mesolimbic dopaminergic pathways.^{104,105}

Despite adjustments of the timing and dose frequency of L-dopa, motor fluctuations and adventitious involuntary movements (chorea, athetosis, and dystonia) can mark the long-term therapeutic benefit. The combination of a catechol-O-methyl transferase inhibitor (entacapone) or a monoamine oxidase inhibitor B (selegiline or rasagiline) with L-dopa could help to eliminate early wearing-off effects, and partial substitution with a dopamine agonist could also reduce L-dopa-induced dyskinesias.^{102,103} L-dopa is now available in combination with carbidopa and entacapone, and trials are underway to assess whether this triple therapy has advantages over immediate-release standard L-dopa to reduce the frequency of motor fluctuations when used from the beginning.

The use of a subcutaneous apomorphine penject as a rescue device for unpredictable refractory off periods can also be helpful in some instances, and its fast action helps to restore confidence in patients becoming insecure about leaving home. Amantadine, which has glutamate antagonist properties, is also an effective anti-dyskinetic agent in some patients,¹⁰⁶ and anticholinergic drugs can reduce painful dystonic phenomena in young onset cases.¹⁰⁷

If these approaches fail to control the on-off swings, then tolcapone—a catechol-O-methyl transferase inhibitor—should be used as second-line oral therapy. Monitoring of hepatic enzyme function is mandatory because of reported early rare fatalities from liver failure. Subcutaneous waking day apomorphine pump is a highly effective treatment for refractory motor fluctuations but success of this procedure relies on the early use of domperidone as an anti-emetic drug, support from nurse specialists, and skin hygiene. Orally administered anti-parkinsonian medication should be slowly but completely withdrawn over 3–12 months to obtain the best results for dyskinesia reduction and off periods. The major limitations of this approach are: eosinophilic panniculitis at the site of injection on the abdominal wall,

which can rarely ulcerate or become infected and lead to erratic drug absorption; sedation, which leads to reduced vigilance and cognitive blunting; and orthostatic hypotension. Haemolytic anaemia is a rare complication with both L-dopa and apomorphine in patients with Parkinson's disease, but can develop rapidly.¹⁰⁸ Enteric administration of a soluble formulation of L-dopa (duodopa) through gastro-jejunostomy is another highly effective medical option for patients who failed to, or are reluctant to, try the apomorphine pump. Some technical issues, including blocking or kinking of the tube and dislocation of the catheter, have been frequently reported, and infection of the stoma is another complication. If the jejunostomy device becomes disconnected, then gut perforation can rarely follow.¹⁰⁹ Furthermore, dietary neutral long-chain aminoacids at the blood-brain barrier could lead to switch-off states even when steady state plasma L-dopa concentrations are achieved.¹¹⁰

Both parenteral apomorphine and enteral L-dopa produce a steady delivery of dopaminergic drug to the brain and reduce refractory off periods of immobility and dyskinesias by more than 50%. However, the evidence is still weak for both approaches.¹¹¹ Sustained improvement in motor performance with a great reduction in drug-induced involuntary movements can also be achieved by functional neurosurgery with bilateral deep brain stimulation of the subthalamic nucleus or the internal segment of the globus pallidus.^{112,113} Behavioural problems including abulia, depression, reduced verbal fluency, weight gain, apraxia of eyelid opening, and difficulty with social adjustment have been reported after surgery.¹¹⁴ Infection needing replacement of the pacemaker is another common cause of morbidity, and rare fatalities have been reported from intracerebral haemorrhage and suicide.¹¹⁵

Short-term memory and vigilance can be improved by the use of centrally acting cholinomimetics and visual hallucinations can also lessen.^{116,117} Autonomic and psychological symptoms are responsible for morbidity. Panel 2 lists available therapeutic options used to deal with these problems.

In addition to cognitive decline in elderly patients, the other most pervasive and challenging late complication of Parkinson's disease is postural instability, which can lead to a mounting fear of falls with increasing immobilisation and dependency, and therefore increase the risk of depression, osteoporosis, and severe constipation. Most falls in patients with Parkinson's disease occur in a forward or sideways direction and are due to turning difficulties, gait and postural asymmetries, problems with sensorimotor integration, difficulties with multitasking, failure of compensatory stepping, and orthostatic myoclonus.¹¹⁸ Skilled physical therapy with cueing to improve gait, cognitive therapy to improve transfers, exercises to improve balance, and training to build up muscle power and increase joint mobility, is efficacious.¹¹⁹ Regular physical and mental exercise

should be encouraged at all stages of the disease. Benzodiazepines should be avoided wherever possible because they increase the risk of falling.

Future perspectives

Although life expectancy and control of bradykinesia and tremor have improved with new treatments for Parkinson's disease, postural instability and cognitive impairment have become increasingly important unmet therapeutic needs. Furthermore, no neuroprotective treatment can arrest the underlying disease process, and dopaminergic therapy is far from perfect in controlling motor handicap. Long-term physiological dopamine release can be achieved by fetal mesencephalic dopamine cell implantation.^{120,121} Although two randomised sham surgery controlled studies in the USA failed to meet their primary endpoint (ie, subjective global rating of the change in the severity of disease),^{122,123} some patients have done very well for more than 10 years after fetal graft. Good patient selection, a rigorous and selective dissection of the graft tissue, use of suspensions rather than pieces of graft, and long immunosuppression might improve the results. One issue, however, that will need to be solved if fetal implantation is to pave the way for stem-cell therapy is the avoidance of severe involuntary movements (runaway dyskinesias) reported in many successfully grafted patients. Stem cells, especially human embryonic stem cells, provide an unlimited supply of dopaminergic neurons and are capable of differentiating into dopamine neurons in the laboratory, although cell survival and behavioural improvement is limited and the potential risk of tumour formation remains.¹²⁴ These approaches, however successful, cannot directly address the associated dementia in elderly patients and it is not clear whether they can overcome the bulbar symptoms and postural instability that are typical in many patients later in the course of the disease.

Glial-cell-line-derived neurotrophic factor has potent neurotrophic effects in dopaminergic neurons in animal models. The ability to promote endogenous repair through targeted growth-factor delivery is attractive. However, a controlled trial with monthly intracerebroventricular bolus administration of glial-cell-line-derived neurotrophic factor gave negative results at 6 months.¹²⁵ Open-label studies with continuous intraputamenal glial-cell-line-derived neurotrophic factor infusions showed encouraging results after 3 months. These positive effects lasted for 2 years in some patients, and led to evidence of dopaminergic sprouting through improvement of fluorodopa putamenal uptake on PET. In one patient coming to autopsy after nearly 4 years of unilateral infusion, tyrosine-hydroxylase-immunopositive staining increased in nerve fibres.¹²⁶ This result led to a controlled trial of glial-cell-line-derived neurotrophic factor intraputamenal infusions in 34 patients with moderately advanced Parkinson's disease (mean age=46 years), which failed to confirm benefit at 6 months and showed the occurrence of anti-glial-cell-line-derived

Panel 2: Treatment of autonomic and psychological symptoms in Parkinson's disease

Insomnia

Adjust Parkinson's disease drugs, sleep hygiene techniques, or clonazepam

Depression

Serotonin and noradrenergic reuptake inhibitors or amitriptyline

Rapid eye movement behaviour disorders

Adjust Parkinson's disease drugs or clonazepam

Fatigue

Amantidine or selegiline

Day time sleepiness

Modafinil

Psychosis and hallucinations

Adjust Parkinson's disease drugs or antipsychotic (clozapine, quetiapine, and aripiprazole)

Constipation

Osmotic laxatives (macrogol)

Urinary urgency

Check drugs, anticholinergic bladder stabilisers, and desmopressin for nocturia

Impotence

Sildenafil, tadalafil, and vardenafil

Pain

Adjust Parkinson's disease drugs and muscle relaxants

Restless legs

Dopamine agonists

Orthostatic hypotension

Adjust Parkinson's disease drugs; increase water and salt intake; fludrocortisone, ephedrine, or midodrine

Drooling

0.5% atropine eye drops sublingually, scopolamine patch, or botulinum toxin injections into salivary glands

Excessive sweating

Adjust Parkinson's disease drugs, propantheline, propranolol, or topical aluminium creams

neurotrophic factor antibodies developing in three patients, and infection and catheter misplacement as postoperative complications.¹²⁷ The extent of glial-cell-line-derived neurotrophic factor delivery both for threshold concentration and spatial distribution might be crucial to the success of this approach.

Adenoviral and lentiviral vectors have been used to deliver the glial-cell-line-derived neurotrophic factor derivative neurturin and, in a separate clinical trial, a mixture of tyrosine hydroxylase, aromatic L-amino acid decarboxylase, and GTP cyclohydrolase 1. Gene transfer

of glutamate decarboxylase has also been used to inhibit the subthalamic nucleus and convert subthalamic-nucleus neurons projecting to the globus pallidus interna in toto an inhibitory pattern. Early encouraging feasibility and tolerability have been reported with all three approaches, but efficacy is still to be shown.^{128–130}

Other therapeutic initiatives, which are under investigation, include deep brain stimulation of the pedunculo-pontine nucleus for the treatment of freezing and falls,¹³¹ memantine for cognitive deficits, and adenosine A2 antagonists for motor symptoms and complications.¹³² Interest exists in the development of selective glutamate receptor antagonists, acting on 5-hydroxytryptamine 2A receptors, and long-lasting formulations of L-dopa.

Conclusions

Although shaking palsy remains as much an enigma as when James Parkinson first described its clinical features, the current knowledge of the disease continues to evolve and be challenged by scientific discovery. Severe damage to most catecholaminergic-containing nerve cells in the brain stem is a characteristic pathological finding, although damage is not restricted to these structures. Terms such as Lewy body disease or synucleinopathy can be helpful for molecular pathologists, but are inappropriate at the bedside. Further research on the function of the proteins identified by the susceptibility genes, the interplay of the disease process with normal ageing, and the nature of environmental triggers that unmask the disease process will be needed if we are to develop reliable biomarkers and a cure for this disabling movement disorder.

Conflicts of interest

AJL has received honoraria from Britannia, Novartis, Roche, GlaxoSmithKline, Boehringer Ingelheim, Solvay, Teva, Eli Lilly, Pfizer, Medtronic, Valeant, and Orion Pharma. The other authors declare that they have no conflicts of interest.

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