Seminar

Parkinson's disease

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Parkinson's disease is the most common serious movement disorder in the world, affecting about 1% of adults older than 60 years. The disease is attributed to selective loss of neurons in the substantia nigra, and its cause is enigmatic in most individuals. Symptoms of Parkinson's disease respond in varying degrees to drugs, and surgery offers hope for patients no longer adequately controlled in this manner. The high prevalence of the disease, and important advances in its management, mean that generalists need to have a working knowledge of this disorder. This Seminar covers the basics, from terminology to aspects of diagnosis, treatment, and pathogenesis.

In 1817, James Parkinson published his famous monograph: "An essay on the shaking palsy". In this report, he described a neurological illness—now known as Parkinson's disease—consisting of resting tremor and a peculiar form of progressive motor disability. It is noteworthy that his penetrating observations were based on just six individuals, three of whom were merely seen on the streets of London. Here, we review this disease, covering basics as well as new and exciting aspects of diagnosis, treatment, and pathogenesis.

Terminology

Parkinsonism describes a syndrome characterised by rigidity, tremor, and bradykinesia, of which Parkinson's disease is the main cause. Parkinson's disease is usually asymmetric and responsive to dopaminergic treatment, with no historical or examination clues to suggest a cause for symptoms. Pathological findings show that nigral dopamine neurons are greatly diminished and Lewy bodies are present in the remaining neurons. Thus, to obtain a definite diagnosis of idiopathic Parkinson's disease, autopsy is needed. A patient's history and examination by skilled clinicians can predict the pathological findings with fairly high assurance.[1] Familial Parkinson's disease and familial parkinsonism are terms used to describe disease entities with either an autosomal dominant (with variable penetrance) or autosomal recessive pattern. Parkinson-plus syndromes refer to diseases that include parkinsonism combined with other clinical signs. These include dementia with Lewy bodies, multiple system atrophy, progressive supranuclear palsy, and corticobasal degeneration.[2]

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Epidemiology

The prevalence of Parkinson's disease in industrialised countries is estimated at 0·3% of the general population and about 1% of the population older than age 60 years.[3,4] People of all ethnic origins can be affected, and men are slightly more prone to the disorder.[5,6] In one study, the annual incidence of Parkinson's disease was about 13 cases per 100 000.[7] Mean age of onset of this disorder was estimated to be in the late 50s,[8] but is now thought to be in the early-to-mid 60s.[9] In people with young-onset Parkinson's disease, the initial symptom can arise between age 21 and 40 (sometimes 50) years, while the first symptom in juvenile-onset disease occurs before the age of 20 years.[10] Young-onset Parkinson's disease affects 5–10% of patients.[11]

Clinical features

The three cardinal features of Parkinson's disease are rest tremor, rigidity, and bradykinesia. Postural instability—sometimes judged a cardinal feature—is non-specific and is usually absent in early disease, especially in the younger patient. Although motor features define the disorder, various non-motor features typically are seen, including autonomic dysfunction, cognitive and psychiatric changes, sensory symptoms, and sleep disturbances.

A resting tremor with a frequency of 3–5 Hz (classically resembling pill-rolling) is the first symptom in 70% of Parkinson's disease patients. Tremor is usually

Search strategy and selection criteria

We searched PubMed for English language articles on Parkinson's disease from 1998 to 2004, with the key phrase "Parkinson disease" and other keywords or phrases including: "treatment", "therapy", "epidemiology", "diagnosis", "etiology", "pathogenesis", "imaging", "positron emission tomography", "single photon emission computed tomography", "genetic", "environment", "neuroprotection", "deep brain stimulation", "transplantation", and many other keywords relevant to every section. We also reviewed books on Parkinson's disease or movement disorders published in the same period. We reviewed selected references from articles retrieved by the initial search. The contents of this article are based on reviewed published work, our judgment, consultation with experts in the area of Parkinson's disease, and on feedback from reviewers.

Panel 1: **Clinical diagnostic criteria for idiopathic Parkinson's disease**[19,20]

Clinically possible
One of:
- Asymmetric resting tremor
- Asymmetric rigidity
- Asymmetric bradykinesia

Clinically probable
Any two of:
- Asymmetric resting tremor
- Asymmetric rigidity
- Asymmetric bradykinesia

Clinically definite
- Criteria for clinically probable
- Definitive response to anti parkinson drugs

Exclusion criteria
- Exposure to drugs that can cause parkinsonism such as neuroleptics, some antiemetic drugs, tetrabenazine, and reserpine, flunarizine, and cinnarizine
- Cerebellar signs
- Corticospinal tract signs
- Eye movement abnormalities other than slight limitation of upward gaze
- Severe dysautonomia
- Early moderate to severe gait disturbance or dementia
- History of encephalitis, recurrent head injury (such as seen in boxers), or family history of Parkinson's disease in two or more family members
- Evidence of severe subcortical white-matter disease, hydrocephalus, or other structural lesions on MRI that may account for parkinsonism

asymmetric at disease onset and worsens with anxiety, contralateral motor activity, and during ambulation. Resting foot tremor is much less common than hand tremor as a presenting sign.

Rigidity is the raised resistance noted during passive joint movement that is uniform throughout the range of motion of that joint. It can have a cogwheel quality even without tremor, but is usually more pronounced in the more tremulous limb. Rigidity is enhanced by contralateral motor activity or mental task performance.

Bradykinesia is the most disabling symptom of early Parkinson's disease. It initially manifests by difficulties with fine motor tasks such as doing up buttons or handwriting and reduced arm swing while walking. Limb bradykinesia can be tested by finger tapping, alternating forearm pronation and supination, foot tapping, and fist closing and opening.[12]

Postural instability refers to the gradual development of poor balance, leading to an increased risk of falls. It can be tested by pulling the patient backwards to check for balance recovery (retropulsion test). Gait becomes slower, with shuffling, and turning is en bloc. Freezing is characterised by difficulty initiating gait or striking gait hesitation on turning or arriving at a real or perceived obstacle. Postural and gait abnormalities are rarely prominent early in the course of Parkinson's disease.

Autonomic dysfunction is generally manifest by constipation, urinary urgency and frequency, and orthostatic hypotension.[13] Dementia develops in about 40% of individuals with Parkinson's disease,[14] although in one study that followed up patients until death, it was noted in more than 80% of end-stage patients.[15] The combination of dementia and the drugs used to treat parkinsonism can lead to hallucinations and psychotic behaviour in some individuals. Depression is common, affecting nearly half of patients.[16] Sensory symptoms arise in Parkinson's disease in various patterns.[17] Disturbed sleep is common in this disorder and has many different causes, including nocturnal stiffness, nocturia, depression, restless legs syndrome, and REM (rapid eye movement) sleep behaviour disorder.[18]

Diagnostic criteria

A definite diagnosis of Parkinson's disease needs autopsy. However, clinical diagnosis of this disorder has become more rigorous, with gradations of diagnostic certainty, including clinically possible, clinically probable, and clinically definite Parkinson's disease (panel 1).[19] Sustained improvement of motor symptoms with levodopa is generally a feature of clinically definite disease.[20] Panel 1 shows exclusion criteria for idiopathic Parkinson's disease, which suggest an alternative diagnosis.[19,21]

Differential diagnosis of Parkinson's disease

The clinical diagnosis of Parkinson's disease relies heavily on history, physical examination, and improvement of symptoms and signs with dopaminergic treatment. The differential diagnosis of this disorder includes normal ageing, essential tremor, drug-induced parkinsonism, the Parkinson-plus syndromes, vascular parkinsonism, and normal pressure hydrocephalus.[22] Less common entities with parkinsonism include dopa-responsive dystonia,[23] juvenile-onset Huntington's disease,[24] and pallidopontonigral degeneration.[25]

Normal ageing

To define normal ageing is difficult.[26] Slowness of movement, stooped posture, stiffness, and postural instability are common in elderly people.[27] Pathologically, ageing is associated with loss of pigmented neurons in the substantia nigra but in a pattern that differs from that seen in Parkinson's disease.[28,29] Asymmetric motor signs and a more accelerated rate of symptom progression seen in Parkinson's disease differentiates it from normal ageing. A trial of levodopa can assist in distinguishing Parkinson's disease from changes due to normal ageing, which will not substantially improve with this drug.

Essential tremor

Essential tremor is characterised by action tremor that typically interferes with drinking from a cup rather than resting tremor.[30] It tends to be bilateral but frequently asymmetric, and in half of patients there is a family history. The frequency of essential tremor is higher (8 Hz) than that of Parkinson's disease, but it falls with age. In severe cases, essential tremor can be present at rest, making its differentiation from parkinsonian tremor quite difficult. Presence of rigidity, bradykinesia, and response to dopaminergic treatment help to differentiate Parkinson's disease from essential tremor. However, to complicate matters, some patients with Parkinson's disease have a postural rather than a rest tremor, or both postural and rest tremor, and some individuals with longstanding essential tremor can develop parkinsonism.[31]

Drug-induced parkinsonism

Drug-induced parkinsonism usually arises after exposure to neuroleptics.[32] Antiemetic and promotility agents (promethazine, prochlorperazine, and metoclopramide), reserpine, tetrabenazine, and some calcium-channel blockers (flunarizine and cinnarizine) can also cause parkinsonism. Symptoms are symmetric, and drug-induced parkinsonism resolves when the drug is stopped, although resolution can take weeks to months.

Progressive supranuclear palsy

In progressive supranuclear palsy, oculomotor disturbance, speech and swallowing difficulties, imbalance with falls, and frontal dementia are predominant.[33] Patients have symmetric onset of parkinsonism, early postural instability, severe axial rigidity, absence of tremor, and a poor response to dopaminergic treatment. Supranuclear gaze palsy, especially of downgaze, is the defining characteristic. Blepharospasm and eyelid opening apraxia are also typical.

Corticobasal degeneration

Corticobasal degeneration manifests with pronounced asymmetric parkinsonism and cortical signs.[34] Asymmetric limb dystonia and limb apraxia occur, and corticospinal tract signs are noted. Cortical myoclonus, early oculomotor and eyelid abnormalities, cortical sensory signs (eg, extinguishing to double simultaneous stimulation), and the alien limb phenomenon can be present. Patients respond poorly to dopaminergic drugs.

Multiple system atrophy

Multiple system atrophy is the current term for grouping the previously separate entities olivopontocerebellar atrophy, Shy-Drager syndrome, and striatonigral degeneration.[2] It presents with parkinsonism, cerebellar, autonomic (orthostatic hypotension, bladder and bowel dysfunction, temperature dysregulation), and pyramidal dysfunction in various combinations.[35] Multiple system atrophy-P (formerly striatonigral degeneration) is characterised by symmetric parkinsonism without tremor and early, pronounced postural instability. Multiple system atrophy-C (formerly olivopontocerebellar atrophy) manifests with cerebellar signs and parkinsonism. Corticospinal tract signs and respiratory stridor can be recorded in all categories of multiple system atrophy. A poor response to dopaminergic treatment is seen.

Dementia with Lewy bodies

Dementia with Lewy bodies is characterised by progressive parkinsonism and early dementia.[36] Little or no resting tremor is reported. Early cognitive and psychiatric features are noted. Hallucinations, REM sleep behaviour disorder, and psychosis can be present, even before dopaminergic treatment. Motor symptoms do not improve, and psychiatric symptoms are exacerbated by small doses of these drugs. These patients also strikingly deteriorate with neuroleptics, even those people whose parkinsonism has a low propensity to worsen. Cognitive function can improve with central cholinesterase inhibitors.[37]

Vascular parkinsonism and normal pressure hydrocephalus

Vascular parkinsonism is attributable to multiple infarcts in the basal ganglia and the subcortical white matter.[38,39] Gait difficulty is a typical presentation. A wide-based shuffling gait is very suggestive of this entity. Tremor is usually absent. Brain imaging shows extensive small-vessel disease. Dementia, pseudobulbar affect, urinary symptoms, and pyramidal signs frequently accompany vascular parkinsonism. No therapeutic response is seen to dopaminergic treatment. Normal pressure hydrocephalus can produce a similar picture.[40]

Neuroimaging

Parkinson's disease is mainly diagnosed clinically, and in typical cases no laboratory test or neuroimaging is necessary. However, when the patient's history or clinical findings are atypical, MRI can be helpful in detection of other causes such as vascular parkinsonism.[38]

Functional neuroimaging of the nigrostriatal dopaminergic pathway has become an important method for quantification of functional dopaminergic terminals in the striatum.[41] Parkinson's disease is characterised by decreased striatal 6-[^{18}F]-fluoro-L-dopa (F-DOPA) uptake, measured by positron emission tomography (PET).[42] This reduction is more pronounced in the putamen than in the caudate nucleus. Diminished binding to the monoamine vesicular transporter with tetrabenazine, to the dopamine transporter with methylphenidate by PET,[43] and to this transporter by single photon emission CT (SPECT) with [^{123}I]-2-[β]-carbomethoxy-3-[β]-(4-iodophenyl)-tropane ([β]-CIT)[44] is also reported in patients with Parkinson's disease.

Functional neuroimaging is mainly used experimentally and has become a part of therapeutic trials that include disease progression as an outcome measure.[41,45] Despite the decline in F-DOPA and dopamine transporter ligand retention with disease progression, functional neuroimaging is not an unequivocal marker of neurodegeneration. Changes seen with neuroimaging can represent pharmacological changes induced by treatment.[46] For this reason, much controversy exists about the interpretation of neuroimaging findings of trials.[47,48] Imaging of dopamine terminals with [β]-CIT is available in Europe as a diagnostic test in patients in whom the clinical diagnosis is unclear.[49]

Cause and pathogenesis

The underlying pathological finding in Parkinson's disease is injury to the dopaminergic projections from the substantia nigra pars compacta to the caudate nucleus and putamen (striatum). Intraneuronal Lewy bodies and Lewy neurites are the pathological hallmarks of the disease. Clinical signs of Parkinson's disease are evident when about 80% of striatal dopamine and 50% of nigral neurons are lost.[50] Lewy bodies are not confined to the substantia nigra and can be seen in cortex, amygdala, locus ceruleus, vagal nucleus, and the peripheral auto-

Gene locus (HUGO-approved name)	Chromosome locus	Gene product	Mode of inheritance
PARK1 (SNCA)	4q21.3	α synuclein	Dominant
PARK2	6q25.2-q27	Parkin	Recessive
PARK3	2p13	Unknown	Dominant
PARK4	4p15	Unknown	Dominant
PARK5 (UCHL1)	4p14	UCHL1*	Dominant
PARK6	1p35-p36	PINK1†	Recessive
PARK7	1p36	DJ1 protein	Recessive
PARK8	12p11.2-q13.1	Unknown	Dominant
PARK10	1p32	Unknown	Dominant

*Ubiquitin C-terminal hydrolase L1. †PTEN-induced kinase 1.

Genes linked to familial Parkinson's disease

nomic nervous system.[51,52] Lewy bodies and neurites in these non-motor areas could account for many of the non-motor symptoms.

Setting aside the few individuals with Parkinson's disease who have a known gene mutation or exposure to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), the cause of this disorder is unknown. Parkinson's disease is probably a result of multiple factors acting together, including ageing, genetic susceptibility, and environmental exposures.[53]

Role of ageing

Pathologically, ageing is associated with a decline of pigmented neurons in the substantia nigra pars compacta.[28] Incidental Lewy bodies are reported in up to 16% of elderly asymptomatic people at autopsy.[50] Results of some F-DOPA PET studies have shown a subtle age-related fall in F-DOPA uptake,[54] while others have not.[55] In a SPECT study,[56] an age-related decline in striatal dopamine transporters was reported, but no difference was noted between the caudate and putamen, a pattern that differs from that seen in Parkinson's disease. Although the incidence of Parkinson's disease increases with age, this disorder is generally accepted not to be simply an acceleration of ageing.

Role of genetic predisposition

Most people with Parkinson's disease do not have a family history. About 15% of patients have a first-degree relative with the disease, typically without a clear mode of inheritance.[57] Nine genetic loci associated with autosomal dominant or recessive parkinsonism have been identified (table). However, general environmental exposures can also account for familial patterns.[58]

Findings of most twin studies do not show enhanced concordance in monozygotic twins.[59,60] In PET studies, the concordance rate has been suggested to be greater than estimated by clinical methods.[61] Results of a twin study showed little concordance in twins when Parkinson's disease develops after age 50 years, but complete concordance in monozygotic twins for disease onset before this age.[62] This finding suggests that genetic susceptibility plays a more significant part in early-onset than in late-onset disease.

The discovery of five genes and four other gene loci in familial Parkinson's disease (table) has greatly enhanced interest in the genetic contribution to this disorder. The single gene abnormalities identified thus far cause very few cases.[63] However, the discovery of these genes and their products has already expanded our understanding of the potential mechanisms of neurodegeneration in both familial and sporadic Parkinson's disease.[64]

The first gene linked to familial disease (*PARK1*; HUGO-approved name *SNCA*) was that coding for the α synuclein protein recorded in a large Italian-American kindred (Contursi family).[65] A missense mutation (Ala53Thr) was detected in the α synuclein gene. Subsequent to this discovery, the same mutation was noted in other families of Italian or Greek background,[66] suggesting a founder effect. A second mutation (Ala30Pro) in the α synuclein gene was identified in a small German pedigree.[67] The exact function of the α synuclein protein—so named because it seemed to localise to synaptic terminals and nuclei—is unknown, but it is a major component of Lewy bodies.[68]

The second gene linked to an autosomal recessive juvenile-onset form of Parkinson's disease (*PARK2*) was that coding for the parkin protein.[69] Several different parkin mutations cause autosomal recessive disease,[70] and these could account for up to half of early-onset cases of the disorder and perhaps even a higher proportion of juvenile-onset Parkinson's disease.[71] Heterozygous mutations in parkin might also confer a risk for parkinsonism.[72] Pathological findings in young-onset Parkinson's disease with the parkin mutation show cell loss in substantia nigra pars compacta and the locus coeruleus, but typically without Lewy bodies. The discovery that parkin is an ubiquitin-protein ligase,[73] and that α synuclein is ubiquitinated by parkin,[74] lends support to the hypothesis that failure of the ubiquitin-proteasome system is the common denominator in the pathogenesis of Parkinson's disease.[64]

The third gene linked to inherited Parkinson's disease (*PARK5*; HUGO-approved name *UCHL1*) codes for the ubiquitin C-terminal hydrolase L1. This mutation was reported in two German siblings.[75] This enzyme hydrolyses bonds between ubiquitin molecules and provides monomeric molecules necessary to label abnormal proteins for proteasomal degradation. Since only one family with two affected individuals has been identified with this mutation, its importance is somewhat controversial.[76]

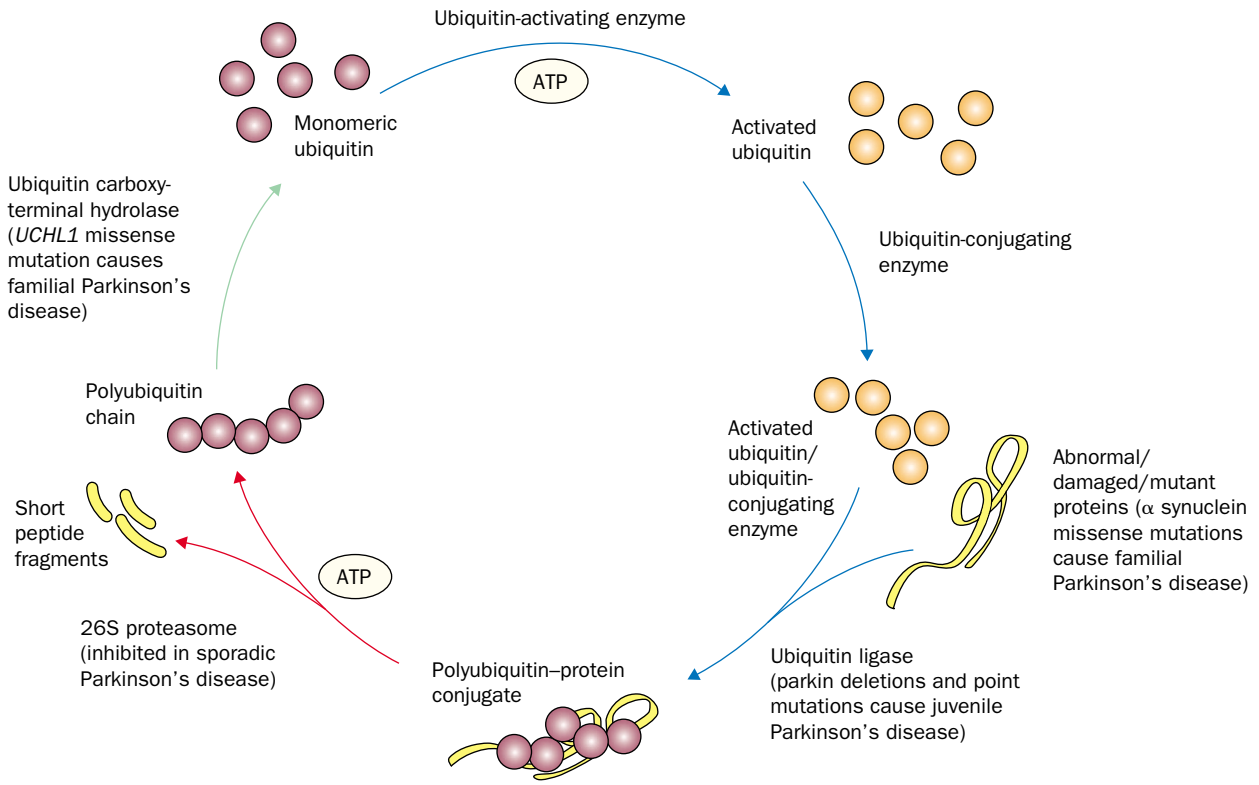
The fourth gene (*PARK7*) is located close to the region for *PARK6* on chromosome 1p36, but no overlaps exist between markers for these two genes.[77] *PARK7* is linked to an autosomal recessive early-onset form of Parkinson's disease.[78] This gene codes for the DJ1 protein, which might be implicated in the response to oxidative stress.

The fifth gene (*PARK 6*) has been found to be associated with mutations in PINK1 (PTEN [phosphatase and tensin homolog deleted on chromosome ten]-induced kinase 1). PINK1 is located in the mitochondria and might exert a protective effect on the cell.[79]

Role of environmental exposure

In 1983, Langston and colleagues[80] reported a series of patients who developed acute levodopa-responsive parkinsonism after exposure to MPTP, a toxic side product in the clandestine synthesis of a pethidine analogue. MPTP freely crosses the blood-brain barrier and is converted to MPP^+ within the brain by astrocytes.[81] MPP^+ is selectively taken up by dopaminergic cells and inhibits mitochondrial complex 1 in the respiratory chain.[82] MPTP is the only environmental agent that has been directly linked to development of levodopa-responsive parkinsonism that is clinically indistinguishable from Parkinson's disease. However, similar chemicals abound, lending support to hypotheses that substances in the environment might contribute to this disorder.[83] Indeed, pesticide exposure, living in rural areas (in industrialised countries), and drinking well water have all been linked to Parkinson's disease.[84]

Conversely, certain environmental exposures seem to lessen the risk of Parkinson's disease. Cigarette smoking is inversely associated with risk of developing this



Degradation of abnormal proteins by ubiquitin-proteasome system

Blue section shows ATP-dependent identification and labelling of abnormal proteins with multiple ubiquitin molecules (ubiquitination) as a signal for ATP-dependent degradation by the 26S proteasome complex (proteolysis; red section). Green section shows recovery (deubiquitination) and subsequent recycling of ubiquitin molecules from polyubiquitin chains that are released from proteins. Also depicted are ways in which potential defects in the system can cause parkinsonism. Reprinted from reference 64 with permission from Macmillan Magazines and the authors.

disorder.[85] Possible explanations include a neuroprotective effect of a substance in cigarette smoke, possibly carbon monoxide, which is a free radical scavenger, or reduced appetite for smoking in people at risk for this disease. Findings of a study of caffeine and Parkinson's disease showed that the risk of this disease was inversely related to intake of caffeine from coffee and non-coffee sources.[86] No clear explanation exists for this inverse relation.

Infection has also been suggested in the pathogenesis of Parkinson's disease.[87–89] The epidemic of encephalitis lethargica was temporarily correlated with the influenza pandemic of 1918, leading to the presumption of a causative association. A subset of affected individuals developed post-encephalitic parkinsonism. More recent analysis with RNA detection methods on autopsy material has disputed this association.[90] Post-encephalitic parkinsonism is clinically and pathologically distinct from Parkinson's disease.[91,92]

Mechanisms of neurodegeneration

Neurodegeneration could be related to mitochondrial dysfunction, oxidative stress, excitotoxicity, apoptosis, and inflammation.[83] The discovery of mutations in the genes coding for α synuclein, parkin, and ubiquitin C-terminal hydrolase L1 in familial Parkinson's disease suggests that the failure of the ubiquitin-proteasome system is the common final pathway of neurodegeneration.[64] Ubiquitin molecules are normally attached to damaged proteins as a signal for degradation (figure). Ubiquitin-protein conjugates are degraded by the 26S proteasome, which is a multisubunit protease.

Mutant α synuclein protein tends to misfold, aggregate, and resist degradation by the ubiquitin-proteasome system.[93] Parkin is a ubiquitin ligase that catalyses the ligation of ubiquitin to proteins targeted for degradation. Polyubiquitin chains that are released from the degraded proteins are disassembled back into ubiquitin monomers by ubiquitin C-terminal hydrolase L1 to re-enter this cycle (figure). Mutations in parkin and ubiquitin C-terminal hydrolase L1 are also likely to interfere with normal protein degradation.

Lewy bodies contain various proteins that might have been destined for degradation but were not broken down.[64] The substantia nigra pars compacta of patients with Parkinson's disease contains high amounts of oxidised and nitrated proteins that are resistant to proteasomal degradation.[94] Amplified concentrations of nitrated proteins also suggest a contribution from excitotoxicity.[95] A reduction in mitochondrial complex 1 activity in the substantia nigra pars compacta of Parkinson's disease patients[96] would produce more free radicals to damage cell constituents and impair protein degradation, which needs energy. Therefore, mitochondrial injury, complex 1 deficiency, oxidative stress, and excitotoxicity are not inconsistent with the hypothesis that the ubiquitin-proteasome system malfunctions in Parkinson's disease. However, the exact mechanism by which abnormal protein accumulation leads to neuronal death is unknown.

Medical treatment

In an evidence-based review of treatment options for Parkinson's disease, data were surveyed for slowing disease progression, providing symptomatic relief of motor and non-motor symptoms, and preventing motor fluctuations and dyskinesia.[97] Here, we discuss salient features of the above-mentioned topics.

Neuroprotection

Vitamin E, selegiline, and coenzyme Q10 have been studied as potential neuroprotective agents to slow down disease progression. Vitamin E was not beneficial in a large multicentre trial of patients with early Parkinson's disease.[98] Selegiline was initially touted as being neuroprotective. However, the effectiveness of this drug in delaying initiation of levodopa treatment is at least partly attributable to symptomatic relief of motor symptoms rather than neuroprotection.[99] The putative neuroprotective effects of the selective monoamine oxidase B inhibitors remains an open question.[100,101]

Findings of a pilot study suggest that high-dose coenzyme Q10 might slow symptom progression in early Parkinson's disease,[102] although these results need to be confirmed in larger studies with longer follow-up. Although glutathione is given intravenously at many centres, no controlled studies have lent support to its efficacy either in symptomatic relief or in neuroprotection.

Results of randomised controlled trials of dopamine agonists versus levodopa in early Parkinson's disease, which used functional imaging of the dopaminergic system, have suggested a slower rate of nigrostriatal neuronal loss in patients who were started on dopamine agonists compared with those who first took levodopa.[41,45] The interpretation of imaging findings in these trials is debatable,[47,48] leaving the question of neuroprotection by dopamine agonists unresolved.

Neurotrophic factors have been suggested as potential symptomatic and neuroprotective agents in Parkinson's disease.[103] In a randomised double-blind trial of glial cell line-derived neurotrophic factor given to patients by an implanted intracerebroventricular catheter, this factor did not improve motor symptoms.[104] One potential explanation for the lack of efficacy was that the neurotrophic factor did not reach the target tissues. In an open-label study, five patients with Parkinson's disease received infusions of glial cell line-derived neurotrophic factor via catheters directly into their putamen. After 1 year, improvements in motor scores and activities of daily living were noted.[105] No irrefutable evidence exists for a neuroprotective agent that slows the progression of Parkinson's disease at the cellular level.[106]

Symptomatic treatment of motor symptoms

Symptomatic treatment is begun when symptoms become bothersome or cause disability. Anticholinergics can be used in young patients in whom tremor is the major symptom. The many side-effects of this type of drug limit usefulness in older patients. Amantadine, which has weak antiparkinson actions, is sometimes used for initial therapy. However, the more definitive treatment of early Parkinson's disease is with either a dopamine agonist or levodopa.

Because dopamine agonist monotherapy rarely causes dyskinesia,[107,108] treatment of early Parkinson's disease in the younger and healthier patient generally begins with dopamine agonists. In view of its enhanced adverse effect profile in elderly people, levodopa is the preferred initial drug in the older and frailer population. Furthermore, levodopa is less expensive than agonists. The agonists have less antiparkinson efficacy than levodopa, but agonist monotherapy is usually sufficient to control parkinsonism for the first couple of years. No direct comparisons have been done of the effectiveness of dopamine agonists. Despite different potencies, these drugs are of similar effectiveness and have few differences in side-effect profile at their respective therapeutic doses.[109] However, use of non-ergot agonists might avoid the rare but serious retroperitoneal, pulmonary, and cardiac-valve fibrosis associated with long-term treatment with ergot drugs.[110]

Common side-effects of dopamine agonists include nausea, hypotension, leg oedema, vivid dreams, hallucinations (especially in the older population with cognitive deficits),[111] somnolence,[112] and sudden sleep attacks.[113] Domperidone, a dopamine antagonist that does not cross the blood-brain barrier and does not worsen parkinsonism, helps to reduce nausea. If one dopamine agonist is not tolerated, another should be tried, since individual differences might exist in susceptibility to adverse events.[111]

Levodopa remains the most potent antiparkinson drug and is the backbone of treatment throughout much of the disease course. Most patients started on dopamine agonist therapy will need the addition of levodopa within 5 years.[108] This drug is combined with carbidopa or benserazide to prevent peripheral conversion to dopamine by dopa-decarboxylase. Side-effects of levodopa are similar to those of dopamine agonists, except that somnolence, hallucinations, and leg oedema are less common with levodopa than with dopamine agonists. Adding extra carbidopa or domperidone might reduce levodopa-induced nausea.

A complication of long-term levodopa treatment is motor fluctuations. Initially, patients note that they feel the effects of a dose of levodopa wear off and they become slower and more tremulous. With time, the individual can fluctuate between periods of mobility and immobility. To begin with, these fluctuations are predictable, termed wearing-off or end-of-dose fluctuations, but they can become unpredictable with sudden switches between mobility and immobility, referred to as on-off phenomena.[114] About a quarter to half of patients taking even low-dose levodopa develop motor fluctuations after 5 years.[115,116] Prevalence of these fluctuations in young-onset Parkinson's disease is even higher—more than 90% at 5 years.[117]

Dyskinesia emerges over months to years of long-term levodopa treatment and can take several patterns.[118] Peak-dose chorea is the most usual form of dyskinesia, but dystonia can also occur alone or in combination with chorea. Diphasic dyskinesia refers to dyskinesia that is worse or only present at the beginning and end of a dose cycle. The patient can develop painful dystonia at the end of a levodopa dose cycle (off-period dystonia).

The primary cause of motor fluctuations is the short half-life of levodopa (90–120 min). Treatment for these fluctuations focuses on trying to improve absorption, altering timing of doses, and prolonging the effect of every dose. A high protein meal can reduce levodopa absorption and limit its ability to cross the blood-brain barrier.[119] Spreading of protein intake throughout the day might help to reduce motor fluctuations. Prolongation of effects of every dose of levodopa can be achieved with controlled release forms of levodopa but at the expense of making absorption somewhat more unpredictable. Catechol-*O*-methyltransferase inhibitors such as entacapone or tolcapone relieve end-of-dose wearing off by lengthening the half-life of circulating levodopa.[120] Tolcapone is the most potent inhibitor, but because of a few cases of fatal liver failure it is now unavailable in many countries.[121] Dopamine agonists enhance effectiveness of levodopa and help to reduce off time.[122]

Dyskinesia is largely related to use of levodopa and can be exacerbated by any strategy used to treat motor fluctuations by enhancement of this drug's effects. Impairment can be lessened by reduction of the dose of levodopa, but this decrease generally leads to loss of control of parkinsonism. Sometimes, this effect can be

counteracted by addition of a dopamine agonist. Amantadine can suppress dyskinesia,[123] perhaps through antagonism of the N-methyl-D-aspartate glutamate receptor.[124] Pulsatile dopaminergic stimulation is postulated to underlie dyskinesia,[125,126] and is the basis of an unproven strategy to reduce peaks and troughs by use of adjunctive agents and thereby prevent or reverse dyskinesias.[127]

Symptomatic treatment of non-motor symptoms

Autonomic dysfunction in patients with Parkinson's disease includes symptomatic orthostatic hypotension, constipation, urinary symptoms, and sexual dysfunction. Reduction of the dose of antiparkinson drugs, enhancement of salt and fluid intake, and addition of fludrocortisone or midodrine are treatment options for hypotension. Aggressive management of constipation entails escalation of water and fibre intake, addition of fibre supplements (eg, psyllium), and use of stool softeners, suppositories, and enemas. Urinary urgency can be treated with peripheral anticholinergic drugs (oxybutynin and tolterodine) or α adrenergic-blocking agents (prazosin and terazosin). Unfortunately, anticholinergics worsen constipation and α adrenergic-blocking agents exacerbate hypotension. Male erectile dysfunction in Parkinson's disease has been successfully treated with sildenafil, although close blood pressure monitoring is needed.[128]

Depression in Parkinson's disease is usually treated with a selective serotonin reuptake inhibitor.[16] No controlled head-to-head studies have been done to suggest one drug is superior to another in Parkinson's disease. Tricyclic antidepressants can exacerbate orthostatic hypotension. In hypotensive patients, venlafaxine may be the drug of choice because it increases blood pressure.[129]

Disorders of sleep in Parkinson's disease include daytime somnolence and sleep attacks, night-time awakenings attributable to overnight rigidity and bradykinesia, REM sleep behaviour disorder, and restless legs or periodic limb movements.[18] Daytime somnolence and sleep attacks have been linked to dopamine agonists and patients should be warned of these adverse effects.[112] Elimination of the agonist or even use of a stimulant might be necessary.[130] Night-time awakenings and restless legs can be alleviated with a bedtime dose of long-acting levodopa or addition of entacapone. Low-dose clonazepam is very effective in treatment of REM sleep behaviour disorder.[131]

Psychosis is rare in untreated Parkinson's disease and is thought to be mostly drug-induced. Dopamine agonists are more likely to cause hallucinations than is levodopa.[111] The first step in management is to discontinue the agonist or anticholinergic drug and to use the lowest levodopa dose possible. However, addition of an atypical neuroleptic is sometimes necessary. Clozapine is the only neuroleptic with proven efficacy in a randomised, double-blind, controlled study in patients with Parkinson's disease.[132] However, because of potentially fatal agranulocytosis, blood count must be measured every week or biweekly. Therefore, quetiapine has become the most popular atypical neuroleptic in Parkinson's disease, in view of the absence of agranulocytosis and fewer extrapyramidal adverse effects than risperidone and olanzapine.[133]

Findings of several open-label studies have suggested that dementia and psychosis in Parkinson's disease can be treated with central cholinesterase inhibitors.[134] In a randomised, double-blind, controlled study, rivastigmine was effective in dementia with Lewy bodies.[37] Results of a small randomised controlled study showed that donepezil improved cognition in patients with Parkinson's disease.[135] At present, no evidence suggests one cholinesterase inhibitor is superior to another in Parkinson's disease patients with dementia.

Surgical options for treatment

Surgical ablation of deep brain structures to treat Parkinson's disease goes back six decades.[136] Before levodopa, thalamotomy was successful at reduction of contralateral tremor,[137] and pallidotomy variably improved motor symptoms in Parkinson's disease.[136] Functional neurosurgery was virtually abandoned with the introduction of levodopa in the late 1960s. However, complications of motor fluctuations and dyskinesia with long-term drug treatment led to a resurgence of surgical

Panel 2: **Proposed criteria for deep brain stimulation**[141,147]

Inclusion criteria

1. Clinically definite Parkinson's disease
2. Hoehn and Yahr stage 2–4 (moderate to severe bilateral disease, but still ambulatory when on)
3. L-dopa responsive with clearly defined off and on periods
4. Persistent disabling motor fluctuations despite best drug treatment with some combination of
   - At least 3 h of off period daily
   - Unpredictable off periods
   - Disabling dyskinesia
5. Intact cognition as measured by neuropsychological testing and no active psychiatric disturbances
6. Strong social support system and commitment from patient and family members to keep follow-up appointments

Exclusion criteria

1. Parkinson-plus syndromes
2. Atypical parkinsonism—eg, vascular parkinsonism
3. Drug-induced parkinsonism
4. Medical contraindications to surgery or stimulation (serious comorbid medical disorders, chronic anticoagulation with warfarin, cardiac pacemakers, etc)
5. Dementia or psychiatric issues (untreated depression, psychosis, etc)
6. Intracranial abnormalities that would contraindicate surgery—eg, stroke, tumour, vascular abnormality affecting the target area
7. Severe brain atrophy on imaging (makes target localisation difficult)
8. Serious doubt about patient's commitment to return for follow-up visits (several no-shows in the past, poor compliance record, etc)

treatment.[138] Unilateral pallidotomy improves mostly contralateral tremor and dyskinesia.[139] Bilateral pallidotomy is associated with important morbidity (dysphagia, abulia, aphonia, and cognitive deficits) and is not recommended.[140]

High frequency stimulation of deep-brain targets mimics ablative surgery, presumably by reduction of neural activity in tissue surrounding the electrode contact. However, deep-brain stimulation causes less irreversible brain trauma than ablative surgery. Furthermore, the functional lesion induced by high frequency stimulation can be sculpted by adjustments of the electrode configuration, stimulation intensity, pulse width, and frequency. Therefore, bilateral deep-brain stimulation has essentially replaced unilateral pallidotomy as the procedure of choice in Parkinson's disease.[141] However, situations exist in which thalamotomy or pallidotomy might be the appropriate procedure for a particular patient.

Adverse effects of surgery include brain haemorrhage, infarct, seizures, and death.[142,143] Other complications include lead breakage or other hardware failure, pulse-generator malfunction, and hardware infection.[144] Side-effects from the stimulation itself include worsening dyskinesia, paraesthesias, and subtle cognitive, mood, speech, phonation, and gait disturbances.[145] Stimulation-related side-effects can be reversed by adjustment of stimulation variables.

Unilateral thalamic deep-brain stimulation, similar to thalamotomy, relieves contralateral tremor, but does not relieve other symptoms of Parkinson's disease.[146] Bilateral stimulation of the internal globus pallidus or the subthalamic nucleus is much more effective at relief of motor symptoms than is thalamic stimulation.[147] Bilateral globus pallidus stimulation improves tremor and rigidity in the drug-off state and dyskinesia in the drug-on state.[148] Bilateral subthalamic nucleus stimulation improves tremor, rigidity, and bradykinesia, mostly in the drug-off state.[149] This effect allows a reduction in antiparkinson drugs.[150] Some researchers claim that bilateral subthalamic nucleus stimulation is superior to bilateral globus pallidus stimulation in patients with Parkinson's disease,[151] but debate continues about the best stimulation target for this disorder.[147]

The key to successful outcome from functional neurosurgery is appropriate selection of patients.[141] Strict inclusion and exclusion criteria should be used (panel 2).[147] Medical treatment must have failed to relieve motor fluctuations or dyskinesia. Dedication and commitment from the patient and family to maintain frequent follow-up visits is crucial.

Restorative (transplantation) treatment

The goal of transplantation is to restore neuronal tissue lost to neurodegeneration. Fetal mesencephalic tissue transplantation has shown successful graft survival on PET scanning and on autopsy.[152,153] In a randomised sham surgery controlled study, some improvement was noted in the drug-off state in young patients but disabling dyskinesia arose in many patients.[154] In a further randomised controlled study, no relevant motor improvement was recorded despite robust survival of dopamine neurons.[155] Most patients who underwent transplantation developed dyskinesia that persisted after withdrawal of dopaminergic treatment. Therefore, at present, fetal nigral transplantation is not a treatment option for Parkinson's disease. Stem cells might offer various means to restore dopaminergic circuitry. These cells could be differentiated into dopamine-producing cells or programmed to release neurotrophic factors such as glial cell line-derived neurotrophic factor.[156] The negative results from fetal tissue transplantation have dampened enthusiasm for stem-cells as dopaminergic precursors for neural grafting.

Conflict of interest statement

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Uses of error

The arrogance of youth

Richard Bayliss

"These casualty officers! Okay, I'll be down in a minute", I said scornfully as I handed the note back to the casualty porter.

It was 1943 and I was one of the hospital's resident assistant physicians. "What is this about?" asked my boss who had just held a ward round. "A casualty officer who says he has a patient with leprosy, God help us!" I replied. "I know a bit about leprosy. I saw some cases in the last war in Mesopotamia, " said my boss quietly. "Can I come with you?" he asked with his customary politeness. "Of course, sir. Please do, but the casualty officer has been qualified only 6 weeks," I said disparagingly.

We were met downstairs by the casualty officer who led us to the room where a 20-year-old man lay on a couch. "He is a waiter from Cyprus and has got a swelling on his nose," said the casualty officer. "I've taken a swab and the laboratory has stained it. It is here under the microscope and it shows Hansen's bacillus—*mycobacterium leprae.*"

My boss and I looked. I had never seen Hansen's bacillus before. Both of us examined the patient's nose. "Lovely" said my boss and turning to the patient, "You'll be cured of this, laddy".

I admitted the patient and next day, because of the need to have beds available for blitz casualties, arranged to send the patient with many others to another hospital. At twelve o'clock that morning I was summoned to the telephone. The medical superintendant of the other hospital was apoplectic with rage. "What do you mean by sending me a patient with leprosy?" he shouted, "And infecting all the other patients in the ambulance, not to mention all those in my ward? Are you out of your mind?" "No, sir," I said firmly. "I spoke last evening to the consultant adviser in leprosy to the Ministry of Health and he told me it was quite all right to send the patient down to you. You are working on out-of-date biblical misinformation, sir." There was an explosion at the other end of the telephone as it was put down.

The waiter did get better, and some months later he treated my boss and I to dinner. Foster humility and remember that your juniors may know more than you do.

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