

Clinical review

Science, medicine, and the future

Parkinson's disease

A H V Schapira

Parkinson's disease is the commonest neurodegenerative disease after Alzheimer's disease, with an estimated incidence of 20/100 000 and a prevalence of 150/100 000. It is characterised clinically by asymmetric onset of bradykinesia, rigidity, and, usually, resting tremor. The cause of the most common clinical features is the death of dopaminergic neurones in the substantia nigra of the midbrain. Lewy bodies are present in a proportion of surviving neurones. At the pathological level there is overlap with other neurodegenerative disorders including Alzheimer's disease, and this has been used to support the view that these diseases may share some common pathogenetic mechanisms.

Parkinson's disease causes substantial morbidity and results in a shortened life span. It also has considerable economic consequences, including loss of earnings, cost of care, and cost of drug treatment (currently calculated at \$1.1bn (£700m) worldwide). A major problem for researchers and clinicians is that, by the time patients' symptoms become sufficiently apparent for them to seek help, about 70-80% of their dopaminergic neurones may have already died. The length of the presymptomatic phase or incubation time of the disease may vary depending on the cause (fig 1). The main challenges in the treatment of Parkinson's disease are therefore (a) to protect dopaminergic neurones so that either the disease is prevented or its progression is slowed and (b) to provide treatment early to "rescue" neurones at risk.

Aetiology and pathogenesis

It is becoming clear that Parkinson's disease is probably not one disease but several with common clinical, pathological, and, possibly, biochemical end points. Although the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is the only environmental agent identified so far that is known to be capable of causing parkinsonism (and has done so within 14 days of exposure), other environmental factors such as use of pesticides and herbicides have been linked with an increased risk of disease.

There is increasing evidence for a genetic component in the cause of Parkinson's disease. Several population based studies have found an increased risk (2-3 fold) of developing Parkinson's disease in first degree relatives of a patient.¹ Furthermore, mutations in the α -synuclein gene on chromosome 4^{2 3} and the

Predicted developments

Research into the causes of Parkinson's disease are likely to show that multiple genetic and environmental factors are involved

Disease of early onset is more likely to be genetic

Modifying the use of drugs already available will improve control of symptoms

New drugs acting on both dopaminergic and non-dopaminergic transmitter systems will become available over the next 10 years

Clinical trials of new drugs with neuroprotective and neurorescue properties are in progress

University
Department of
Clinical
Neurosciences,
Royal Free and
University College
Medical School and
Institute of
Neurology,
University College
London, London
A H V Schapira,
*professor of clinical
neurosciences*
schapira@rthsm.
ac.uk

BMJ 1999;318:311-4

parkin gene on chromosome 6⁴ have been identified in families showing autosomal dominant and recessive parkinsonism respectively. These families have somewhat atypical disease—early onset, mild or absent tremor, and, in families with the parkin mutation, no Lewy bodies. A further gene (on chromosome 2), again causing autosomal dominant parkinsonism,⁵ is of particular interest as several affected members of the different families identified had features characteristic of idiopathic Parkinson's disease, including age of onset, symptoms, and clinical course. The defect on chromosome 2 seems to have relatively low penetrance (a gene's ability to cause a disease) and might therefore be of more relevance to apparently sporadic disease. Although the α -synuclein mutations have not been identified in sporadic Parkinson's disease, much research is now focused on trying to understand how mutations in different genes can result in specific patterns of neuronal cell death and the clinical features of parkinsonism.

How neurones die in Parkinson's disease

Some biochemical abnormalities have been identified in the affected brain region in Parkinson's disease that provide clues to how genetic or environmental factors may induce cell death. There is much evidence of increased oxidative stress and free radical damage in

the substantia nigra. There is also evidence for a defect of mitochondrial energy production (complex I deficiency).⁶ In a group of patients with this mitochondrial deficiency it has been shown that the abnormality was determined by their mitochondrial DNA.⁷ Other studies have shown that there may be abnormal

calcium handling in dopaminergic neurones and that the gliosis that accompanies nigral cell death may also have an inflammatory component.⁸

The Lewy bodies found in Parkinson's disease and others, including motor neurone disease, are neuronal intracytoplasmic inclusions. In Parkinson's disease they seem to be collections of protein filaments including ubiquitin and α -synuclein (which is also a component of the amyloid plaques of Alzheimer's disease). This has led to the suggestion that Parkinson's disease, and possibly other neurodegenerative diseases, may be caused by a fault in intracellular protein degradation that in turn results in protein accumulation. How such a defect in protein handling results in cell death is not known; possibilities include a "black hole" effect of protein attraction, aggregation, clogging of the cytoplasm, and impairment of intracellular function.

Cells may die either by necrosis or apoptosis. Necrosis involves the disintegration of a cell and its organelles and its subsequent removal by phagocytosis through an inflammatory response. Apoptosis is characterised by chromatin condensation, DNA fragmentation, cell shrinkage, relative sparing of organelles, and lack of an inflammatory response. Apoptosis may be programmed, as during embryogenesis, or occur in response to a toxic stimulus. The mitochondrion has recently been shown to have a critical role in the cascade of events that lead to apoptotic cell death.⁹ There is now evidence for apoptotic cell death in the brain tissue of patients with Parkinson's disease at the time of death.¹⁰

This observation may have important implications for developing disease modifying treatment. Apoptotic cell death is relatively rapid. If apoptosis is active at the time of patients' death, it suggests that a proportion of neurones may have been in a pre-apoptotic phase and tipped over into apoptosis by the agonal state. If true, this would offer the opportunity not only to protect nigral neurones but possibly to "rescue" them (fig 2). Many of the biochemical events that precipitate and participate in apoptosis have been defined. Interestingly, both complex I inhibition and oxidative stress (both present in brain tissue affected by Parkinson's disease) may cause apoptotic cell death.

Present treatment options

Drug treatment

With the exception of fetal nigral implants, all treatment currently available for Parkinson's disease is only symptomatic. Because of this, and the potential long term complications of certain drugs, an important principle in treatment is to prescribe drugs only when the symptoms of Parkinson's disease interfere with function to a substantial degree.

Levodopa is the most commonly used treatment for Parkinson's disease. It is always combined with a dopa decarboxylase inhibitor to reduce peripheral side effects and enhance absorption. The development of motor complications with levodopa limits its general usefulness. Direct acting dopamine agonists have been available for some years, but some evidence suggests that those developed more recently have better efficacy and are associated with fewer side effects. Selegiline is a monoamine oxidase B inhibitor and so prolongs the action of dopamine at the synapse. There is evidence

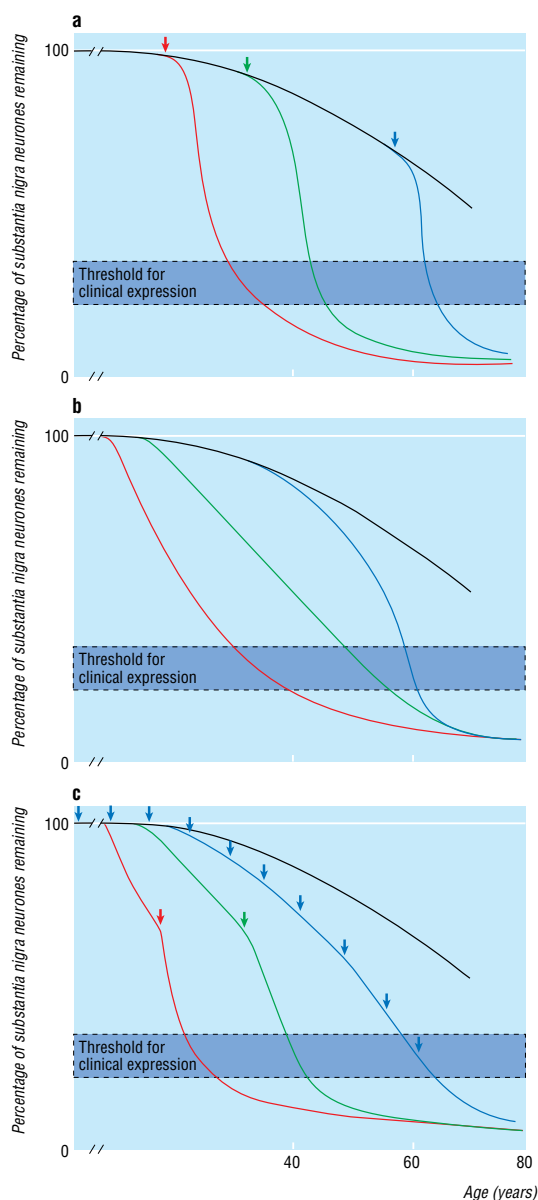


Fig 1 Putative time courses for loss of dopaminergic neurones from substantia nigra relative to different aetiologies of Parkinson's disease. (a) Environmental cause of disease: the environmental insult (arrows) can occur at any time and results in rapid loss of neurones superimposed on age related loss (black line). (b) Genetic cause of disease: the rate of cell death is not known, although patients tend to present at younger age than usual, and rate may vary according to gene defect and patient's genetic background (red, green, and blue lines). (c) Interaction of environmental and genetic causes: genetically induced high rate of cell death (red line) couple with severe point exposure to environmental factor (arrow) results in early presentation; less severe genetic and environmental effects (green line) result in more gradual cell death; and genetic susceptibility superimposed on lifetime exposure to common toxins (blue line) may cause slow cell loss with later presentation of disease

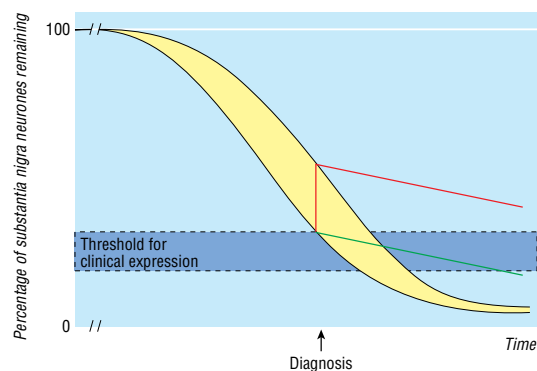


Fig 2 Neurorescue and neuroprotection in Parkinson's disease. Effective neurorescue at diagnosis (red line) will restore damaged neurones that are at risk of death (shaded area between curves) to normal function, and age related loss will probably be attenuated with continuing treatment. Neuroprotection (green line) will prevent further neuronal loss other than by attenuated age related loss

that the early use of selegiline delays a patient's need for additional treatment by 9-12 months. Concerns about the safety of selegiline remain controversial.

The newly developed catechol-*O*-methyltransferase (COMT) inhibitors increase the availability of levodopa to the brain, and their action is complementary to that of the dopa decarboxylase inhibitors. There are concerns about the hepatotoxicity of tolcapone, whereas entacapone, another catechol-*O*-methyltransferase inhibitor, seems safer in this respect. Antimuscarinic drugs and amantadine remain viable alternatives to dopamine related drugs, although their use is often limited by side effects and tolerance.

Surgery

The medical management of Parkinson's disease has its limitations, and new surgical techniques with low morbidity have emerged as a viable alternative for carefully selected patients. Pallidotomy may reduce contralateral dyskinesias and improve bradykinesia and rigidity, and thalamotomy may improve tremor. Deep brain stimulation to the globus pallidus or subthalamic nucleus may substantially improve contralateral symptoms including tremor.¹¹ Fetal nigral implants improve the symptoms of Parkinson's disease considerably, and postmortem examination of brains of transplanted patients (who had died later of unrelated causes) demonstrated outgrowth and new synaptic formation from the transplanted tissue.¹² Despite its benefits, the application of surgery in treating Parkinson's disease is limited: procedures carry some risk of injury and death, long term effects are unknown, and benefits are only unilateral unless surgery is undertaken on both sides of the brain.

Future treatment prospects

Immediate prospects

The first priority is to maximise the efficacy and safety of the treatments currently available. It has been suggested that levodopa may be toxic and accelerate the death of dopaminergic cells.¹³ There is no *in vivo* evidence to support this, and a recent paper suggests that levodopa might have a trophic effect on dopamin-

ergic neurones.¹⁴ Nevertheless, there is clear evidence that after two to three years of treatment with levodopa, an increasing proportion of patients (about half at five years) begin to experience fluctuations and dyskinesias. This probably relates to the pulsatile stimulation of dopamine receptors that occurs with levodopa and to postsynaptic changes.

The frequency of these complications is substantially less with dopamine agonists, and, at least in animal models, they may not occur if levodopa is not used. Thus, there is a strong argument for starting symptomatic treatment of Parkinson's disease with a dopamine agonist. It is critical that the dose is increased gradually, and many neurologists favour covering the first two weeks of treatment with domperidone, an antiemetic with no extrapyramidal side effects. The newer agonists seem able to control symptoms in a substantial proportion of patients when used alone—for at least up to the first four years of treatment. Levodopa will be required as the disease progresses and symptoms worsen.

Medium term prospects

Preventing or delaying the onset of fluctuations and dyskinesias would be a major advance in treatment, and trials are under way to assess the effectiveness of early monotherapy with a dopamine agonist. A similar study using controlled release levodopa with a catechol-*O*-methyltransferase inhibitor in previously untreated patients would be needed to answer whether a more sustained activation of dopamine receptors results in a lower dyskinesia rate.

Drugs with new forms of action, such as dopamine reuptake inhibitors and adenosine antagonists, have proved promising in animal and early clinical studies. Adenosine A_{2A} receptors are present in high concentration in the striatum—the area to which the dopaminergic neurones of the substantia nigra project. The A_{2A} receptors are localised on neurones containing γ -aminobutyric acid and enkephalin, which also have dopamine receptors. Adenosine A_{2A} stimulation has a negative effect on motor function, whereas antagonists (such as caffeine) can increase locomotor activity, particularly when dopamine receptors are decreased or blocked. Thus, adenosine A_{2A} antagonists may present a new treatment for Parkinson's disease if their efficacy and safety are proved.

Long term prospects

Neuroprotection may be defined as preventing neuronal cell death and maintaining function without necessarily affecting the underlying biochemical mechanisms involved in pathogenesis. At a clinical level, this would mean stopping the progress of the disease. Neurorescue could be considered a mechanism to reverse established metabolic abnormalities and restore normal neuronal function and survival. Clinically, this would result in an improvement in symptoms as well as a halt in the progress of the disease. Inevitably, there will be some overlap between neuroprotection and neurorescue, and their relative benefits will vary according to the stage of disease. The development of such treatments is obviously limited by our knowledge of the biochemical events that cause cell death; at present only a few candidate treatments are available.

Neuroprotection is perhaps best exemplified by strategies designed to prevent cells undergoing apoptosis. Up regulating apoptosis defence genes, such as bcl 2, or down regulating apoptosis promoting genes, such as bax, may be useful if effects can be targeted to nigral neurones. The role of the mitochondrion in the apoptotic pathway is also receiving attention as a possible site at which to direct neuroprotective agents. Cyclosporin A inhibits opening of the mitochondrial megapore, which is associated with loss of membrane potential and the start of apoptotic cell death. Both low dose cyclosporin A and its non-immunosuppressant analogue, *N*-methyl-4-valine cyclosporin, prevent the cell death in vitro induced by toxins that cause parkinsonism.¹⁵ There is also in vitro evidence that selegiline and its desmethyl metabolite have anti-apoptotic properties.¹⁶ However, apoptosis plays an important role in the immune system and in tumour surveillance. Anti-apoptotic treatment for Parkinson's disease will therefore have to be anatomically selective, probably achieved through metabolically targeted delivery systems such as conversion of an inactive precursor to active drug possible only through enzymes of the central nervous system.

Based on our current knowledge of pathogenesis in Parkinson's disease, drugs to prevent or reduce free radical damage or enhance mitochondrial energy production should be of value. Interestingly, there is a reciprocal relation between mitochondrial dysfunction and excess generation of free radicals—the mitochondrion normally produces over 95% of a cell's superoxide ions, and mitochondrial inhibition results in an increased release of these radicals. However, antioxidant treatment has already been attempted with vitamin E without apparent success.¹⁷ Nevertheless, this does not preclude the potential beneficial effects of other antioxidants such as selenium and ubiquinone, or a combination of such drugs. A recent trial has begun with patients using ubiquinone as a means both to increase mitochondrial energy production and decrease free radical release.

Glutamate toxicity is thought to play a role in excitotoxic cell death in Huntington's disease and motor neurone disease, and there is some evidence that this mode of cell death may also be important in Parkinson's disease. This raises the prospect that *N*-methyl-4-valine antagonists or drugs that reduce glutamate release or receptor interaction may be used in Parkinson's disease.

There is some evidence that inflammatory processes may play a role in nerve cell damage in Parkinson's disease, although it is not known whether this is primary or secondary. If this is important in pathogenesis anti-inflammatory drugs or those capable of modulating the immune system (such as non-steroidal anti-inflammatory drugs in Alzheimer's disease and interferon beta in multiple sclerosis) may be worth investigating.

While neuroprotection or neurorescue will be valuable to patients at any stage of disease, treatment will clearly be of most value in those with early disease. The recent advances in the genetics of Parkinson's disease offer the prospect of identifying and treating susceptible individuals before clinical features appear. At first, this may be relevant only to members of those rare families with inherited Parkinson's disease. However, as

our knowledge of the genetic component of Parkinson's disease and its relevance to apparently sporadic disease improves, the application of such treatment may be more extensive. Parkinson's disease is unlikely to be caused by genetic factors alone, so identifying possible environmental contributions to aetiology will be important, and their removal or modification will be an essential part of future treatment and prevention.

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Endpiece

New Year's Eve

Every man has two birth-days: two days at least, in every year, which set him upon revolving the lapse of time, as it affects his mortal duration. The one is that which in an especial manner he termeth *his*. In the gradual desuetude of old observances, this custom of solemnising our proper birth-day hath nearly passed away, or is left to children, who reflect nothing at all about the matter, nor understand anything in it beyond cake and orange. But the birth of a New Year is of an interest too wide to be pretermitted by king or cobbler. No one ever regarded the First of January with indifference. It is that from which all date their time, and count upon what is left. It is the nativity of our common Adam.

Charles Lamb, *The Essays of Elia* (1895)