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Parkinson's disease

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Fifteen years ago the pathology of Parkinson's disease was thought to be neatly parcelled in the substantia nigra with deficiencies of the dopaminergic system in the nitro-striatal pathways. The elegant pathological simplicity previously envisioned is now known to be much more complex.

Pathology

The hallmark of Parkinson's disease was said to be the total or subtotal loss of nigral cells in the substantia nigra but this is also seen in normal ageing and is most marked in the dorsal part of the pars compacta while in idiopathic Parkinson's disease it is seen in the ventral part. Lewy bodies are seen in the brains of patients with idiopathic Parkinson's disease but their precise role is not clear.¹ They are also seen in the brains of 10% of elderly controls without Parkinson's disease but are more frequent in those with the disease.^{1,2} Whether they are a cause or a marker of disease is not yet clear.

The previous supposition that only dopaminergic pathways are involved is known to be wrong. Abnormalities in adrenergic, cholinergic, and serotonergic pathways have all been noted.³ The dopamine receptor has been analysed and subdivided and there are currently at least five dopamine receptor subtypes (D₁ to D₅) classified. Pharmacological agents with differing affinities for these receptors have been and are being developed.

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is known to produce a clinical syndrome very similar to Parkinson's disease.^{4–6} MPTP is converted by monoamine oxidase-B to the toxic metabolite MPP⁺ which inactivates mitochondrial complex I. Mitochondrial complex I is one of four complexes that convert pyruvate to adenosine triphosphate in the mitochondria. MPTP accumulates in the mitochondria of dopaminergic neurons and eventually kills them. In idiopathic Parkinson's disease levels of complex I are known to be depressed and mitochondrial defects have been reported in the brains,^{7,8} platelets⁹ and muscles¹⁰ of patients with Parkinson's disease. No MPTP-like substance has yet been identified in the environment but this pathological model involving an environmental cause as a potent factor is a tempting one.

Clinical features

Other features known to be of significance in addition to the classic triad of tremor, bradykinesia, and rigidity are impaired postural reflexes, shuffling gait, progression of physical signs, asymmetry at onset and response to dopaminergic agents. Dysarthria is common and dysphagia is increasingly recognised as a problem. Many methods are currently used to evaluate the degree of disability and severity of Parkinson's disease.^{11–14}

Other conditions may share features with idiopathic Parkinson's disease and need to be excluded. These include progressive supranuclear palsies, multi-system atrophy, exposure to toxins, Wilson's disease and Alzheimer's disease with extrapyramidal symptoms.

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Parkinson's disease

- Parkinson's disease is a complex pathological process, still not fully understood
- abnormalities are found in adrenergic, cholinergic, and serotonergic as well dopaminergic pathways
- MPTP poisoning provides a pathological model for further research
- signs of parkinsonism may be part of more widespread neurological disease
- present treatments help, but do not cure

Treatment

The mainstay of treatment is still levodopa with a peripheral decarboxylase inhibitor such as benserazide or carbidopa. This increases the bioavailability of levodopa to the brain, whilst reducing it in the rest of the body, allowing levels of dopamine to rise in the dopaminergic pathway. The combined treatment of levodopa and a decarboxylase inhibitor allows patients in the early and middle stages of their disease to lead a virtually normal life. Fluctuations in motor performance, the 'on-off' phenomenon, and dyskinesias with dopa treatment then seem to become progressive problems.^{15,16}

Dopamine receptor agonists have been developed both as an adjunct to existing levodopa therapy and as an alternative to try and delay the starting of definitive levodopa treatment. Bromocriptine and newer agents such as lisuride and pergolide differ in their affinity for D₁ and D₂ receptors and consequently have slightly differing effects. They have a role but they are expensive and are associated with confusion particularly in older patients.

Apomorphine by subcutaneous injection can be useful in a proportion of patients who are able to tolerate its side effects.¹⁷ Its principal side effect, severe nausea, can be diminished by pre-treatment with domperidone which has a peripheral and not a central action. Apomorphine can be useful in the diagnosis of Parkinson's disease, to try and reduce or abolish 'off' periods, and some patients are able to tolerate a continuous subcutaneous infusion. Apomorphine may be helpful in establishing whether a dose ceiling has been reached with oral therapy; if a subcutaneous injection of apomorphine produces further improvement while on oral treatment it would imply that the oral therapy could yet be increased.

Anticholinergic agents are still used but have a limited role. They may be useful for tremor and to a lesser extent rigidity but their side effects on vision, bladder and mental state can be prohibitive.

An alternative approach to increasing the brain levels of dopamine is to reduce its breakdown. Dopamine is broken down by monoamine oxidase and selegiline is a powerful monoamine oxidase group B inhibitor that was originally developed to minimise the 'on-off' phenomenon. There has been some evidence that use of selegiline in early Parkinson's disease may prolong the 'honeymoon' period and delay the need for the use of levodopa. The DATATOP study suggested that selegiline may delay the time to onset of definitive dopa treatment¹⁸ but a more recent study by the same group¹⁹ suggests that the choice of anti-parkinsonian agent in the early stages of disease may not be so critical. The role of other antioxidants such as vitamin E is still being explored.

Transplantation of human foetal dopaminergic tissue (embryonic mesencephalic tissue containing dopamine cells) into caudate and putamen has been described.²⁰⁻²⁴ Some benefit has been seen in a few patients, mostly in those patients with MPTP-induced Parkinson's disease.²⁴ However, it is clear that this will not be a treatment for all patients with Parkinson's disease; the duration of benefit is not clear, the degree of benefit is variable, and it is not clear which patients would be best suited for the procedure. None of the patients treated thus far have been over 65. Other problems include those related to the immunosuppression required after the procedure and the ethical dilemma of 'harvesting' foetal tissue.²⁵ While this clearly is an exciting step in the treatment of Parkinson's disease it is still at an early stage.

The future

Much work is being done in seeking the cause and the molecular biology of Parkinson's disease. Work done in animal studies concerning the role of glutamate receptor antagonists is yet to be applied to humans. Studies looking at clinical features such as the patterns of memory deficit, patterns of gait disturbance and the differentiation between early onset and late onset Parkinson's disease are also on-going.

In addition to decarboxylation, levodopa is metabolised by *O*-methylation and transamination. Selective catechol *O*-methyltransferase inhibitors are under development and their progress is well advanced.²⁶⁻²⁸ Their use may result in smaller doses of levodopa being useful for longer periods. Neuroprotective agents such as antioxidants are also under investigation. With these developments the future prospects for the treatment of Parkinson's disease are very promising.

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