Disorders of the basal ganglia and their modern management

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Parkinson’s disease

Epidemiology and genetic aspects

Parkinson’s disease (PD) is a common disorder, particularly among the elderly, with a prevalence of 100–200 per 100,000 in the general population\(^1\). In most patients, PD is sporadic, but rare genetic forms exist. Causative mutations have recently been identified on the \(\alpha\)-synuclein gene on chromosome 4, responsible for Lewy body-positive, autosomal dominant PD, and the parkin gene on chromosome 6, responsible for Lewy body-negative autosomal recessive juvenile parkinsonism. An increased familial risk for PD has also been shown in monozygotic as opposed to dizygotic twins when onset is below the age of 50\(^2\).

Diagnosis

Clinically, PD is characterised by the classical triad of bradykinesia, rigidity and frequently tremor, but with advancing disease postural instability and other features become evident. The diagnosis is clinical, based on these criteria and on the exclusion of other atypical features such as dementia at onset, cerebellar or pyramidal signs.

Treatment

Figure 1 is a simplified illustration of the major neuronal pathways within the basal ganglia in a normal individual. The principal pathological correlate of the motor disorder of PD is degeneration of the dopaminergic nigrostriatal neurons leading to impaired dopaminergic neurotransmission in the basal ganglia. The treatment of PD therefore concentrates either on replacing dopamine, on dopaminergic stimulation in the striatum or on surgically inactivating certain deep brain structures (see Table 1).

Antiparkinsonian drugs

Levodopa preparations. The mainstay of antiparkinsonian treatment in terms of efficacy, remains levodopa, given together with a peripheral decarboxylase inhibitor to reduce peripheral side effects and enhance efficacy. However, long-term treatment with levodopa is, sooner or later, complicated by the development of fluctuations in motor response and abnormal involuntary movements. Controlled-release (CR) levodopa preparations are absorbed more slowly than standard preparations (delaying onset of action), but give a longer ‘tail’ of plasma concentration (delaying offset of action). Their relative bioavailability is only 70% of that of standard preparations, so some patients are often inadvertently underdosed after switching to CR preparations. They can also worsen dyskinesias and give a less predictable response in some patients. Two large multicentre trials\(^4,5\)

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**Fig. 1. Major neuronal pathways within the basal ganglia in a) a normal individual and b) an individual with Parkinson’s disease (much simplified illustrations).** In crude terms, the substantia nigra pars compacta (SNPC) may be regarded as an ‘accelerator’ for movement, and the subthalamic nucleus (STN) and internal pallidum (GPI/substantia nigra pars reticulata (SNPR) as ‘brakes’. The consequence of nigral cell loss in Parkinson’s disease is to ‘remove the foot from the accelerator’ which, along the line in the outflow pathways, results in ‘braking’ of the ventrolateral thalamus (VL THAL) and hence of the motor cortex (CS = corpus striatum; putamen and caudate); DA = dopamine; \(D_1\) and \(D_2\) = dopamine receptors; GABA = gamma-aminobutyric acid; GPE = external pallidum; + = excitation; − = inhibition; green = inhibitory pathways; mauve = excitatory pathways. (Adapted from Ref 3.)
of CR versus standard preparations of Sinemet and Madopar as de novo treatment have failed to show any clinically significant delay or reduction in the development of fluctuations or dyskinesias in the CR groups. CR preparations are most consistently helpful when given at bedtime for night-time immobility. A more rapid onset of action can sometimes be achieved with dispersible levodopa – particularly useful to ‘kick in’ in the morning.

Dopamine agonists. Dopamine agonists, which act directly on striatal dopamine receptors and have a longer duration of action than levodopa preparations, frequently help smooth response fluctuations, and may delay their onset when used as monotherapy. A number of different dopamine agonists are currently available, including the newly licensed long-acting cabergoline and the non-ergot derivatives ropinirole and pramipexole. It remains to be shown whether these drugs are generally superior to the older dopamine agonists bromocriptine and pergolide. The only subcutaneously applicable antiparkinsonian drug, the dopamine agonist apomorphine, can rapidly reverse off periods or, if given via a continuous pump, can smooth severe fluctuations of motor response.

Table 1. The medical and surgical treatment of Parkinson’s disease.

| Indication                | Treatment                                                                 |
|---------------------------|---------------------------------------------------------------------------|
| No functional impairment  | No symptomatic treatment                                                  |
|                           | Neuroprotective role of selegiline unproven                               |
| Early functional impairment: | Start with levodopa preparation                                          |
| old (>70 years)           | Try to delay levodopa if possible by using:                              |
| young (<50 years)         | anticholinergics                                                         |
|                           | dopamine agonists                                                        |
|                           | selegiline                                                               |
|                           | amantadine                                                               |
|                           | When levodopa is needed, consider combination with an agonist            |
| Intermediate (50–70 years) | Optimal approach uncertain                                                |
| Fluctuations and dyskinesias: | Attempt to smooth peaks and troughs of                                  |
|                           | dopaminergic stimulation with:                                            |
|                           | fractionated levodopa doses                                              |
|                           | controlled-release levodopa                                              |
|                           | selegiline                                                               |
|                           | COMT inhibitor                                                           |
|                           | adjunctive dopamine agonists                                             |
|                           | amantadine                                                               |
|                           | apomorphine sc ‘rescue’ injections or pump                               |
|                           | If severe problems despite above measures:                               |
|                           | deep brain stimulation/lesioning of:                                      |
|                           | thalamus* for tremor and rigidity                                        |
|                           | pallidum* for dyskinesias>parkinsonism                                   |
|                           | subthalamic nucleus for parkinsonism and dyskinesias                      |

* now largely superseded by subthalamic nucleus as target of choice in Parkinson’s disease.

Enzyme inhibitors:

- Monoamine oxidase inhibitors. Selegiline, which was associated with an increased mortality in one study but not in others, has mild antiparkinsonian efficacy when given alone, and may improve wearing-off when added to levodopa therapy. A new buccally absorbed formulation, which does not undergo first-pass metabolism and therefore produces less selegiline metabolites, has been marketed recently.

- Drugs in the new category of catechol-O-methyltransferase (COMT) inhibitors, comprising tolcapone (central and peripheral COMT-inhibitor, recently suspended in the UK due to hepatic complications) and entacapone (peripheral COMT-inhibitor), prolong the elimination half-life, and hence the duration of action, of levodopa. As a result, doses of levodopa may need to be reduced by 20–40%.

Peak-dose dyskinesias and motor response fluctuations are usually managed by titrating combinations of the above medications in order to even out peaks and troughs of dopaminergic stimulation. Beginning- and end-of-dose dyskinesias, which are related to intermediate levels, are however much more difficult to treat.

Surgical treatment

Lesioning and deep brain stimulation. In addition to medical treatment of PD, stereotactic surgery, targeting the thalamus for tremor, the internal pallidum mainly for dyskinesias, and the subthalamic nucleus (STN) for all aspects of parkinsonism, has experi-
enced a renaissance. Both lesioning and deep brain stimulation (DBS) (which effectively inhibits structures stimulated at high frequency) have been successfully used in patients with advanced PD no longer satisfactorily controlled by medical treatment. DBS may carry a lower morbidity than lesioning (controlled comparative studies are needed), but is more costly and requires indefinite follow-up. Today, the optimal procedure is probably either lesioning or DBS of the STN; this allows major reductions in levodopa dosage, and hence improves not only parkinsonism but also dyskinesias, and off period dystonia and freezing.

Neural grafting. Transplantation of human fetal nigral neurons has been shown to have beneficial effects in several studies, but remains experimental. Most recently, implants of fetal porcine nigral cells are being investigated.

Non-motor problems in Parkinson’s disease

In addition to the problems of mobility, many patients with PD, especially those with advanced disease, develop other problems which need to be addressed, such as depression, dementia, other neuropsychiatric disturbances, postural hypotension, and urinary dysfunction. Dementia with Lewy bodies may present with either parkinsonism, dementia, or both. This is probably the second commonest cause of dementia after Alzheimer’s disease (AD), and accounts for many cases previously labelled ‘plaque only’ AD.

Atypical parkinsonism

The most common causes of atypical parkinsonism are multiple system atrophy (MSA) and progressive supranuclear palsy (PSP). These are two distinct disorders with more extensive characteristic pathological abnormalities involving the basal ganglia, but also involving other areas of the central nervous system which account for additional clinical features. Both are frequently misdiagnosed, and many of these patients die with an incorrect diagnosis of PD.

Diagnosis An important characteristic in both conditions is a poor or declining response to levodopa, but some patients with MSA may, at least initially, show a good response. Other clues to the diagnosis of MSA include:
- cerebellar features
- early and prominent autonomic failure
- urogenital dysfunction
- pyramidal signs.

Features of PSP include:
- early impairment of postural stability with falls
- a vertical supranuclear gaze palsy
- prominent axial rigidity, often with relatively preserved limb mobility
- early dysarthria or dysphagia.

The diagnosis of MSA and PSP, like that of PD, is primarily clinical. However, investigations that can help support the clinical diagnosis, and exclude other symptomatic causes of parkinsonism, are magnetic resonance imaging of the brain, sphincter-electromyography (EMG), and (in MSA) autonomic function tests.

Key Points

**Dystonia**
- Exclude ‘curable’ causes (though lifelong treatment will be needed)
  - Wilson’s disease (treatment: penicillamine)
  - dopa-responsive dystonia (treatment: levodopa)
  - paroxysmal kinesigenic dyskinesia (treatment: carbamazepine)
- Exclude structural causes (especially in hemidystonia)
- Check DYT 1 gene in classical ‘Oppenheim’ phenotype, if patient wishes
- After levodopa, try slowly increasing doses of anticholinergics (other drugs much less likely to help)
- Consider focal injections of botulinum toxin (especially for neck, orbicularis oculi and larynx)
- Consider neck surgery and pallidotomy in severe cases

**Treatment**

As mentioned above, treatment is usually disappointing in these disorders due to the extent of degeneration in multiple areas. Amantadine can sometimes provide benefit when levodopa fails. However, the most important forms of help for these patients are physiotherapy, speech therapy, occupational therapy, and treatment of postural hypotension and urinary dysfunction.

**Essential tremor**

Essential tremor (ET) is characterised by a postural and/or kinetic tremor of the hands, with optional additional involvement of other body parts. Up to 4% of the population may have ET, but affected subjects are often unaware of their tremor, while those who are aware rarely consult a doctor (particularly a specialist) because of it. Additionally, differentiation from dystonic or parkinsonian tremor can be difficult. Inheritance is often autosomal dominant, and ET is most likely a genetically heterogeneous disorder. Linkage to regions on chromosomes 2 and 3 has already been identified in two families.

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Chorea

Hereditary

Huntington's disease (HD) is the archetypal cause of hereditary chorea, and is associated with dementia, psychiatric manifestations, and a relentlessly progressive course. It is an autosomal dominantly inherited CAG repeat disorder. A genetic test for the abnormal expansion in the responsible gene on chromosome 4 is now available for diagnosis and, after appropriate counselling, as a predictive test in at-risk adults. A family history may however be lacking, particularly when onset is at a late age or if the transmitting parent died young. Rarer inherited causes include dentatorubropallidolusyan atrophy, caused by a trinucleotide CAG repeat expansion on chromosome 12 and which can be tested for, and neuroacanthocytosis. Other movement disorders also occur in HD, and juvenile cases (with longer repeat expansions) are more likely to have predominant parkinsonism and dystonia rather than chorea (Westphal variant).

Chorea may be reduced by administration of neuroleptics and/or tetrabenazine, but these drugs should be used sparingly as they often concomitantly worsen underlying parkinsonism and depression. The most disabling features of HD are usually neuropsychiatric, including personality change, psychosis and depression, which may need specific treatment. Potentially disease-modifying treatments such as fetal striatal tissue transplantation and anti-excitotoxic drug regimens are under experimental investigation.

Sporadic

The differential diagnosis of sporadic chorea includes Sydenham's chorea, pregnancy, drugs, thyrotoxicosis, polycythemia rubra vera, vascular disease (usually as hemichorea/hemibalism), systemic lupus erythematosus, the lupus anticoagulant syndrome and new variant Creutzfeldt-Jakob disease.

Dystonia

The classification and nomenclature of the dystonias has recently been revised into four main categories:

- primary dystonia (only dystonia ± tremor)
- dystonia-plus (including dopa-responsive dystonia)
- secondary dystonia (eg cerebral palsy, drug-induced)
- heredodegenerative dystonia (eg Wilson's disease (WD)).

This review will consider dystonia, mainly according to its distribution.

Generalised dystonia

Generalised primary dystonia typically starts in childhood, often first affecting a leg. Other causes must first be excluded, particularly WD. Although the gene for WD on chromosome 13 has been isolated and sequenced, gene-specific diagnosis is not generally possible because of the many different mutations within this very large gene. The diagnosis still depends on measuring serum caeruloplasmin and copper excretion, slit-lamp examination of the eyes for Kayser-Fleisher rings and, if doubt remains, liver biopsy copper content.

In childhood- or adolescent-onset dystonia, it is also crucial to exclude dopa-responsive dystonia (DRD) which is potentially 'curable' by lifelong administration of levodopa. It has recently been recognised that the spectrum of DRD is wider than previously thought, and that many atypical variants exist, including apparent 'athetoid cerebral palsy' with developmental delay in infants. It is a dominantly inherited disorder (with incomplete penetrance) caused by a mutation in the GTP cyclohydrolase-1 gene (DYT 5) on chromosome 4. Genetic testing is, however, complicated by genetic heterogeneity, with a great number of different 'private' mutations causing DRD. In contrast, the dominant (and 30–40% penetrant) mutation (DYT 1 on chromosome 9), responsible for approximately 40% of all cases of typical early limb-onset primary dystonia (Oppenheim's dystonia), has recently been identified and can be tested for.

Genetic advances will undoubtedly revolutionise our understanding of this disorder and potentially lead to new treatments. At present, the treatment of patients with dystonia is largely symptomatic. When DRD has been excluded by a trial of levodopa (in the case of childhood or adolescent-onset dystonia), anticholinergics are the most successful drugs, particularly in children who tend to tolerate them better than adults. However, anticholinergics alone do not provide satisfactory benefit in most patients. Occasional patients derive some benefit from benzodiazepines, dopamine antagonists, levodopa, carbamazepine or baclofen. In the face of severe, sometimes life-threatening, 'dystonic storms', triple therapy with tetrabenazine, a neuroleptic and an anticholinergic may, by rendering patients akinetic, tide them over a severe exacerbation. Recently, pallidotomy has been shown to be effective in a few patients with severe generalised dystonia, and is currently under trial in some centres.

Focal dystonia

Isolated adult-onset cervical and cranial dystonia is not caused by the DYT 1 gene. There is usually little progression or spread, and most patients with spasmodic torticollis (ST/cervical dystonia), blepharospasm, or laryngeal dystonia ('spasmodic/spastic dysphonia') respond
to injections of botulinum toxin into the involved muscles. ST patients who lose an initial favourable response have often developed antibodies against botulinum toxin type A. New types of botulinum toxin (B, C, F) are currently under trial to help these patients, and posterior primary ramiectomy may be particularly useful. Other focal dystonia such as writer’s cramp and task-specific dystonia (eg ‘occupational cramps’) may also respond to botulinum toxin but EMG-guided identification of responsible muscles is often necessary for successful treatment.

**Paroxysmal dyskinesias**

Paroxysmal dyskinesias mainly comprise:

- stereotyped, short-lived (30–60 sec), often frequent attacks precipitated by sudden movements (kinesigenic) which are virtually ‘cured’ by long-term treatment with carbamazepine

- less frequent, longer lasting (minutes to hours) non-kinesigenic attacks that sometimes respond to levodopa.

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**USEFUL ADDRESSES**

**Parkinson's Disease Society**
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Tel: 0171 931 8080

**The Progressive Supranuclear Palsy Association**
The Old Rectory
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Tel: 01327 860 299

**Autonomic Disorders Association**
Sarah Matheson Trust
Pickering Unit
St Mary's Hospital
Praed Street
London W2 1NY
Tel: 0171 886 1520

**Huntington's Disease Association**
108 Battersea High Street
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**The Dystonia Society**
46–47 Britton Street
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**National Tremor Foundation**
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