Parkinson's disease – a brief practical approach

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Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease, and affects about 1% of the population over 65 year of age. Although the incidence of PD rises with advancing age, juvenile onset PD (onset under 40 years of age) is well recognised and is associated with identifiable genetic mutations in a significant proportion of cases.

The cause of PD remains unknown. One possibility is that affected individuals may have inherited a predisposition to developing PD and that some environmental exposure may trigger the start of neuronal degeneration. The recent identification of a number of genetic mutations in families with several affected members, has enhanced our understanding of the pathogenesis of neuronal degeneration in PD. These gene mutations result in a number of possible abnormalities including abnormal protein folding/aggregation, defective protein clearance, defective cell resistance to oxidative stress, mitochondrial dysfunction – such abnormalities may contribute to pathogenesis.

Clinical features

The onset of symptoms in PD is often insidious. Patients and their families may pass off the slowness of movement as being a sign of old age, or 'rheumatism'. Usually a family member notices that the patient has slowed up, become stooped or simply 'aged' quickly. This slowness of movement or bradykinesia is the *sine qua non* of PD. Bradykinesia is readily observed by the patients expressionless face, soft voice, small spidery handwriting, stooped posture and absent arm swing with gait testing. Tremor, which is present in 70% of PD patients at the time of diagnosis, characteristically is present only at rest. Some patients also have an action tremor that interferes with eating and other activities. Tremor is a frequent source of embarrassment for patients, especially as it tends to worsen when the patient is under stress or anxious. In addition to tremor and bradykinesia, patients with PD have increased muscle tone or rigidity. Postural instability, tested by standing behind the patient and pulling back the shoulders (having first alerted the patient), tends to occur as the illness advances.

Disturbed sleep is common in PD. This may be multifactorial, due to nocturnal akinesia, nocturia, tremor or the presence of a parasomnia. Patients' sleeping partners may report symptoms of restless legs syndrome or periodic limb movements of sleep or REM sleep behaviour disorder. This latter syndrome consists of patients acting out their dreams, often shouting and thrashing about, apparently, in an attempt to repel attackers. All of these sleep disturbances are common in PD and contribute to a poor night's sleep, leading to a poor day thereafter. Low doses of clonazepam (0.5 mg nocte) are particularly effective for patients with REM sleep behavior disturbance.

The presence of prominent postural instability, falls (especially backward falls) or cognitive impairment at the time of diagnosis or within a year or two thereafter suggests that the patient has a form of PD that differs from the more common idiopathic form. Table 2 provides a number of 'red flags' that should alert that the patient may have atypical parkinsonism.

Treatment

The goal is to keep patients in the mainstream of life. It is important to enquire about patients' routine, work and leisure practices when coming to a decision regarding initiation of treatment. It may be useful to ask "are there any activities that you used to do which you have had to give up?" Patients may have been keen card players but discontinued because of difficulty holding them or because of embarrassment at the presence of tremor. Many patients will not volunteer this kind of information unless it is specifically sought after. If there is a suggestion that the patient is withdrawing from society, either as a direct result of their Parkinsonism or as a result of secondary depression this must be taken as evidence of serious disability, and treated aggressively.

In patients with minimal symptoms, it is reasonable to start therapy with rasagiline, selegiline, amantadine, dopamine agonists or an anticholinergic drug. However, some of these drugs may be poorly tolerated in the elderly. Rasagiline and selegiline block one of the main dopamine degradation pathways by inhibiting the B isoform of monoamine oxidase (MAO-B). The theoretical risk of interaction with the selective serotonin reuptake inhibitors (SSRIs), tri-cyclic antidepressants (TCADs) and non-selective MAO is rarely encountered in clinical practice, and no special diet is required.

Amantadine has a mild symptomatic effect which is often short-lived. The usual maintenance dose is 100 mg tds. Amantadine may cause pedal oedema and should be used with caution in patients with renal impairment; it is also associated with *livedo reticularis*. Anticholinergic drugs are especially useful for treating tremor, rigidity and dystonia, although they confer a substantial risk of serious side effects in older patients, especially confusion, memory impairment, blurred vision, urinary retention and constipation.

For most patients over the age of sixty, the appropriate initial therapy is with a levodopa preparation. A favourable response to levodopa confirms the diagnosis of idiopathic PD. As mentioned above, the drug is administered with an inhibitor of the enzyme dopa decarboxylase (carbidopa; Sinemet and Duodopa, or benserazide; Madopar) in order to prevent conversion of levodopa to dopamine in the peripheral circulation. Both Sinemet and Madopar are available as immediate release or controlled release preparations.

The goal of therapy should be to restore the patient to normal function, using the minimum dose of levodopa. The clinical effects of levodopa may take several weeks to become apparent, and the temptation to increase either the frequency or strength of the daily dose should be resisted, especially in younger patients who carry the greatest risk of developing motor fluctuations and dyskinesias. In older patients, the risk appears to be substantially less and in fact these patients may require larger doses initially for a clinical effect to become apparent. Most patients will show a clear response to a total daily levodopa dose of 600 mg; patients who show no clinical improvement at 1000 mg/day almost certainly do not have idiopathic PD, and other causes of Parkinsonism should be entertained.

The usual maintenance levodopa dose for initial therapy is 100 mg tds of an immediate release preparation. The dispersible preparation of madopar is best avoided in early disease due to its short half-life. Controlled-release preparations of levodopa are also best avoided as initial therapy, as their bioavailability is less than that of the immediate-release preparations; hence it might be difficult to ascertain in patients with sub-optimal responses whether their poor response is a result of subtherapeutic levodopa dosing or that they are resistant to levodopa therapy (suggesting that the underlying diagnosis is not idiopathic PD).

The risk of transient nausea from levodopa can be offset by pre-treating patients with domperidone (Motilium) 10mg tds for the first three days of treatment. For patients with severe nausea, the dosage escalation phase of levodopa may need to be much slower. It is important to remember that nausea is almost universally transient, and the physician should not conclude that the patient is 'allergic' to the drug on the basis of initial GI upset. Metoclopramide (Maxolon) and prochlorperazine (Stemetil) are centrally acting dopamine antagonists and must be avoided in PD. Once nausea subsides, patients should be instructed to take the medication on an empty stomach, preferably one hour before meals. This is necessary as levodopa is absorbed in the intestine via a saturable transport system which is shared with other large neutral amino acids; hence large amounts of dietary protein will inhibit absorption of levodopa. Taking levodopa on an empty stomach is probably less important for patients with early PD, but becomes critical for patients who have developed motor fluctuations who experience 'dose failures'; in many of these cases, the apparent failure of levodopa to work relates simply to inadequate absorption.

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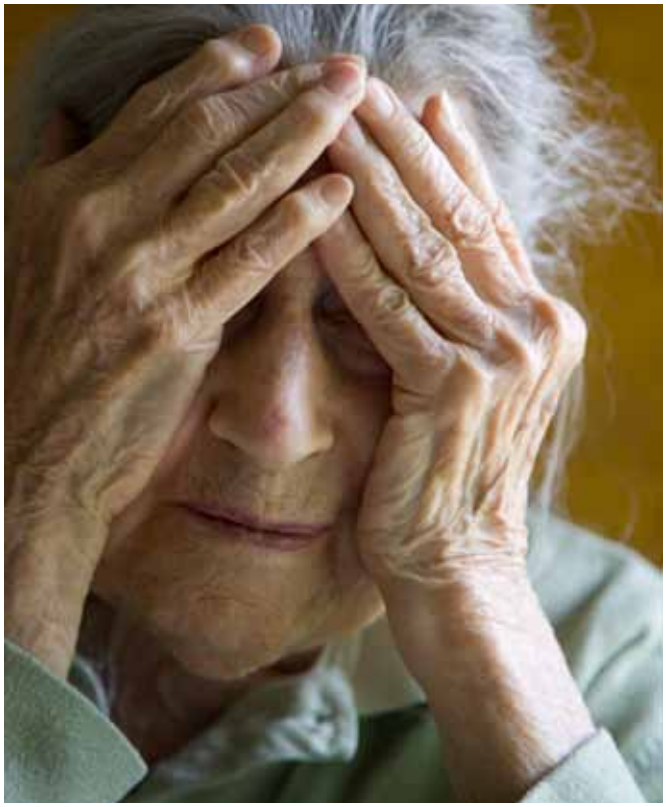

Non-pharmacological therapy
For patients whose activity level is curtailed by motor symptoms, an evaluation by a physiotherapist with experience in treating PD is invaluable, particularly if the patient is concurrently starting drug therapy. A home exercise and aquatherapy are also useful modalities of treatment. Patients should be encouraged to remain informed about the disease and any therapeutic developments, possibly through involvement in a support group. It must be emphasised that support groups are not for everyone, and, while many patients feel empowered and better informed through such groups, other patients become despondent seeing fellow patients with advanced disease. It is useful to educate patients about the spectrum of disease, and that it is not incompatible with a long and fulfilling life in many cases.

It should be expected that for the majority of patients, worsening of their condition as a result of *progression of disease* ought not to occur within the first 3 to 5 years of treatment. If a patient and their family return complaining of worsening of symptoms before this time, a careful search should be made for alternative explanations for the apparent worsening. The patient should be questioned about medications (compliance), wearing off phenomenon, sleep quality, depression and co-morbid medical conditions. Most causes of worsening symptoms can be attributed to one or a combination of the above factors. Teasing out the details of a complicated medication regimen requires patience of both patient and clinician.

Treatment of motor fluctuations
One of the early signs of the development of motor fluctuations in a patient is the wearing off phenomenon. Wearing off can be elicited by asking patients whether or not they feel the first tablet of the day kick in; this implies that there has been some decrement in the response to levodopa overnight, often with resulting nocturnal akinesia. This is best treated by the addition of a controlled release preparation of levodopa at night. For patients with more frequent wearing off between doses, the addition of entacapone, an inhibitor of one of the degradative enzymes of dopamine, catechol-o-methyl transferase (COMT) may be effective.

Freezing of gait is a common symptom in patients with advancing disease, and a frequent cause for falling forwards. Freezing is often manifested as difficulty initiating walking, or getting stuck in doorways. Patients may describe their feet as being like they are stuck in wet cement. It is important to ascertain whether the freezing is a manifestation of being off, or whether it is occurring regardless of the state of the patient's motor function. The latter is notoriously difficult to treat and usually refractory to medication. It may respond transiently to the use of visual cues, such as placing taped lines on the floor, or using a modified cane. For wearing off and 'off' – related freezing, the treatment is to augment the amount of dopamine available.

Treatment of dyskinesias
Dyskinesias typically occur as the plasma levels of levodopa reach a peak between doses; the movements are choreiform and random. Less common are dyskinesias which occur at the beginning of a dose interval or at the end (biphasic dyskinesias, also known as dyskinesia-improvement-dyskinesia [D.I.D]). This type of dyskinesia tends to be more dystonic in nature, with sustained posturing of an extremity. Unlike peak-dose dyskinesias, which are often not distressing to the patient, biphasic dyskinesias may be painful.

Treatment of refractory motor fluctuations/dyskinesias
It is widely believed that motor fluctuations and dyskinesias are the result of pulsatile stimulation of dopamine receptors in the striatum. In support of this is the experimental finding that by providing continuous dopaminergic stimulation using intravenous levodopa infusions, motor fluctuations do not develop. Unfortunately it has been difficult to provide a form of continuous dopaminergic stimulation that might be useful in the clinical setting. For patients with refractory motor fluctuations, use of apomorphine, a parenterally-administered short-acting dopamine agonist is a useful option.

Falls
Falls are common and often preventable in patients with PD. There are several possible causes including freezing and sudden 'off' periods, orthostatic hypotension and postural instability. The history may help determine the cause: backward falls are most often a result of postural instability, which is a symptom of relatively advanced PD. If backward falls occur within the first year or two of the diagnosis, an atypical form of Parkinsonism, such as progressive supranuclear palsy (PSP) or multiple systems atrophy (MSA) is possible. Serious consideration of the use of a wheelchair should be given to patients with backward falls. Orthostatic hypotension may be a result either of the Parkinsonism itself or the medications, especially selegiline and dopamine agonists. Falls due to freezing and off periods may respond to adjustment of the levodopa regimen as discussed above.

Surgical therapy for advanced PD
Surgical treatments for PD are not a new concept. Effective surgical interventions were available in the 1960s in the pre-levodopa era. It was found that placing lesions in the thalamus

(thalamotomy) or globus pallidus (pallidotomy) reversed many of the symptoms of PD, especially tremor and bradykinesia. This form of treatment was largely abandoned following the discovery of levodopa, but re-emerged in the 1990s once the long-term complications of levodopa therapy became apparent. More recently, surgical therapies have centered on electrically stimulating the thalamus, globus pallidus or subthalamus using deep brain stimulation (DBS). DBS works by inactivating those areas of the basal ganglia which are overactive in PD, possibly by overriding the normal neuronal electrical activity within those structures.

Non-motor manifestations of PD

Constipation

Constipation is almost universal in PD, and is in part medication related (especially anticholinergics) and in part due to autonomic dysfunction through gut hypomotility. The following approach may be helpful:

- Increase bulk in the diet: bran, psyllium (e.g. Metamucil), methylcellulose.
- Increase fluid intake to eight tumblers per day.
- Increase fruit and vegetable intake.
- Exercise
- Avoid constipating medications (anticholinergics, TCADs, oxybutynin).
- Stool softener (e.g. docusate)
- Osmotic laxative (e.g. Movicol).

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Orthostatic hypotension

Patients complain of lightheadedness, dizziness or 'fogginess'. Treatment entails:

- Discontinue offending medications including anti-hypertensive drugs, selegiline and dopamine agonists.
- Increase daytime fluid intake,
- Liberalise salt intake,
- Compression stockings
- Small regular meals.
- Fludrocortisone (0.1-0.4 mg/day)
- Midodrine (2.5-5 mg q 4 hourly until late afternoon).

Depression and anxiety

Depression affects at least 30% of PD patients. Psychomotor symptoms may be difficult to differentiate from bradykinesia. It remains unclear to what extent depression represents a part of the symptom complex of PD or whether it is a reactive disorder in the setting of a debilitating disease. Patients often complain of anxiety during off-periods which are rapidly reversed when they turn on, suggesting a direct of dopamine on mood. Whatever the cause, depression should be treated aggressively.

Psychosis

The development of psychotic symptoms in a patient with PD presents a major management problem. The most common cause is medication related. Patients typically present initially with mild, non-threatening visual hallucinations which over time become associated with paranoid features and a gradual loss of insight. In these cases all medications with the exception of sinemet should be withdrawn (anticholinergics need to be slowly tapered), and levodopa reduced to the lowest acceptable dose. Night-time dosing should be minimised, preferably using controlled release preparations. If an antipsychotic is required, quetiapine (Seroquel) is associated with the fewest extrapyramidal side-effects; half of a 25 mg tablet at night may be a sufficient dose initially. Risperidone and olanzepine should be avoided if at all possible on account of worsening the motor symptoms. Clozapine is the only proven medication for treatment of psychotic symptoms in PD, but requires regular blood monitoring on account of the risk of agranulocytosis; nonetheless, in refractory cases, this agent can be most effective and prevent unnecessary nursing home placement.

Cognitive decline and dementia

It is important to remember that cognitive disturbance in PD may not be related to the disease itself, but arise from infection, organ failure, medications, subdural haematoma, depression, Lewy body dementia or coincident Alzheimer's disease. As many as 60%-80% of PD patients will develop dementia. Every effort needs to be made to eliminate potentially reversible causes by appropriate use of CT scanning, vitamin B12 estimation and general medical assessment. A proportion of patients with parkinsonism who develop dementia or psychotic symptoms within a year of diagnosis will turn out to have Lewy body dementia. In these patients, acetylcholinesterse inhibitors, such as donepezil (Aricept) or rivastigmine (Exelon) may be helpful, although they are associated with increase drooling and urinary incontinence in some patients.