MedicineToday 2015; 16(1): 12-18

PEER REVIEWED FEATURE
2 CPD POINTS

The clinical challenge of early Parkinson's disease

SIMON J.G. LEWIS MB BCh, BSc, MRCP, FRACP, MD

Early Parkinson's disease may be challenging to diagnose because of its potentially subtle symptoms, such as REM sleep behaviour disorder, and similarity to differential diagnoses including dystonic tremor and 'Parkinson-plus' conditions. Nevertheless, early diagnosis allows symptomatic relief and prognostication, which is crucial for many patients.

Key points

- The prevalence of Parkinson's disease (PD) is expected to rise by 80% over the next 20 years.
- PD is complex, with marked heterogeneity, making diagnosis and management difficult even for specialists experienced in movement disorders.
- Nonmotor symptoms such as affective disorder, anosmia, constipation and rapid eye movement sleep behaviour disorder can predate the development of motor symptoms by several years.
- Recent evidence suggests that early treatment of patients with PD does not accelerate disease.
- Evidence supports the use of levodopa, dopamine agonists and monoamine oxidase inhibitors.

Diagnosing Parkinson's disease (PD) in patients who present with a textbook pattern of history and examination findings can be straightforward in clinical practice. However, patients seldom present with this degree of differentiation, and many will have to navigate a number of different specialists before the diagnosis is eventually confirmed. This reflects a combination of factors that make the diagnosis of PD clinically challenging, including the potentially subtle symptoms in the early stages; confounding by common changes of ageing, such as arthritis and altered bowel habit; the wide range of differential diagnoses; and lack of a specific diagnostic test for use in routine practice that would clarify the diagnosis.

The question that arises is whether an early diagnosis of PD is all that crucial? In a progressive condition such as PD, with no curative or even effective neuroprotective agent, does knowing you have early disease matter? Despite this apparently depressing outlook, surely none of us would feel comfortable with delaying symptomatic relief to our patients. In addition, patients can be relieved to have an explanation for their symptoms, and an accurate diagnosis allows prognostication, which for many is crucially important. With our ageing population, the prevalence of PD is expected to rise by 80% over the next 20 years, and as such, we must all strive towards improving the clinical management of this common condition.[1]

DIAGNOSIS OF PARKINSON'S DISEASE

With a PD prevalence of 1 to 2% in people aged over 60 years, it is clear that ageing represents the most significant risk factor for developing PD. However, as many as 5% of all cases in Australia are diagnosed in people under the age of 40 years.[1] Therefore, PD needs to be considered in the differential diagnosis across a very broad spectrum of patients.

Although PD is characterised as the archetypal hypokinetic movement disorder, with bradykinesia, cogwheel rigidity and resting tremor, many patients with PD do not show all of these signs. Furthermore, there is a growing appreciation that many of the clinical features of PD are nonmotor, and that nonmotor complaints such as affective disorder, rapid eye movement sleep behaviour disorder (RBD) and loss of olfaction can predate the development of motor symptoms by several years, making it

Associate Professor Lewis is a Consultant Neurologist at Royal Prince Alfred Hospital, Sydney; and Associate Professor in Cognitive Neuroscience at the University of Sydney, Sydney, NSW.

important to seek them specifically.

To date, there is no diagnostic test or biomarker that can be used in routine practice to diagnose PD. This problem is further compounded by the significant list of 'Parkinson-plus' conditions that mimic PD and themselves do not have diagnostic tests to aid their exclusion. These include:

- Lewy body dementia
- multiple system atrophy
- progressive supranuclear palsy
- corticobasal degeneration
- vascular parkinsonism.

Thus we rely on a clinical diagnosis of PD, which in turn depends on the experience and confidence of the clinician. However, recent Australian research has found that GPs lack confidence in the diagnosis and management of PD, and even in specialist movement disorders centres misdiagnosis rates can be around 25%.[2,3]

TIPS FOR DIAGNOSING PARKINSON'S DISEASE

As with all diagnoses, there is a diminishing rate of return across history taking, examination and investigation. Although specialists may claim to have diagnosed PD by the time a patient has walked in from the waiting room, the history still holds many of the most important clues in confirming this suspicion. Some of the differential diagnoses of PD and their features are shown in the Table. Early and late symptoms of PD are shown in Box 1.

Tremor

Tremor is probably the easiest symptom of PD for patients to identify, whereas walking more slowly may be dismissed as arthritis or simply ageing. Nevertheless, many patients have not considered their tremor in detail, and thus history taking should include specific enquiries. Classically, we are seeking a history of tremor at rest, but it is important to note that many patients with PD have tremor when using their hands and in posture. Similarly, although lateralisation of tremor is helpful in supporting a diagnosis of PD, this can also be seen in benign essential tremor and in dystonic tremor.

In the past, dystonic tremor has been relatively underappreciated as a differential diagnosis of PD. However, interest in this

© STEVE OH

presentation has increased over the past decade, prompted by results of a number of medication trials targeting patients with newly diagnosed PD.[4-6] These trials reported that 4 to 15% of the patients recruited did not in fact show the loss of dopamine on functional neuroimaging that would be expected in PD, categorised as 'scans without evidence for dopaminergic deficit' (SWEDD). Patients with SWEDD did not deteriorate clinically over time and are likely to have misdiagnosed cases of dystonic tremor. Indeed, it is possible that these patients represent the historically described subgroup with benign tremulous PD, who have little bradykinesia, rigidity or disease progression. Therefore, when assessing tremor, one must pay attention to the presence of other dystonic features in the patient (and other family members), such as writer's cramp and torticollis.

Nonmotor symptoms

As stated above, it is important to probe for nonmotor features as they are very much part of PD. Some nonmotor features, including major

TABLE. SOME DIFFERENTIAL DIAGNOSES OF PARKINSON'S DISEASE

Parkinsonian condition	Common features
Drug-induced parkinsonism	• Associated with treatment with antiemetics, antipsychotics, antidepressants, antiepileptics
Lewy body dementia	• Cognitive decline and hallucinations within first 12 months • Fluctuation in motor and cognitive symptoms throughout the day
Multiple system atrophy	• Parkinsonism with autonomic dysfunction and/or cerebellar signs
Progressive supranuclear palsy	• Parkinsonism with slowed and restricted saccades • Early falls, often backwards
Corticobasal degeneration	• Parkinsonism with dysfunctional (alien) limb and dystonia
Dystonic tremor	• Associated dystonic features (e.g. writer's cramp, torticollis) • Extended posture of the thumb in resting tremor, whereas the thumb is commonly flexed in Parkinson's disease • Usually no progressive functional decline
Vascular parkinsonism	• Stepwise decline with stroke episodes

1. SYMPTOMS AND SIGNS OF PARKINSON'S DISEASE

Early symptoms and signs

Motor
- Tremor
- Bradykinesia
- Muscle rigidity or stiffness

Nonmotor
- Late-onset affective disorder (e.g. depression or anxiety)
- Anosmia
- Constipation
- Rapid eye movement sleep behaviour disorder (RBD)

Later symptoms and signs

Motor
- Wearing-off phenomenon
- Dyskinesia
- Freezing of gait

Nonmotor
- Major cognitive impairment
- Visual hallucinations
- Psychosis
- Postural hypotension
- Urinary incontinence

cognitive impairment, visual hallucinations, psychosis, postural hypotension and urinary incontinence, are commonly seen in patients with advanced PD. Their identification at the time of initial presentation should raise the suspicion of alternative diagnoses, including Lewy body dementia and multiple system atrophy (see the Table).

In contrast, features such as the first onset of affective disorder (e.g. depression and anxiety) in later life, anosmia, constipation and RBD are all known to predate the formal diagnosis of PD. The potential emergence of PD over the coming years should be considered in patients who present with these premotor features without another clear explanation.

In particular, it has been reported that the development of RBD in a patient aged over 50 years is associated with an 80% transition to synucleinopathy (PD, Lewy body dementia or, less frequently, multiple system atrophy) over the subsequent 15 years.[7,8] The characteristic description of dream enactment or injurious behaviour overnight associated with RBD is relatively specific, unlike mood disturbance, anosmia and constipation, and should be a red flag for GPs, triggering further specialist assessment.[9]

INVESTIGATIONS AND REFERRAL

In general practice, there is probably little role for many specialist investigations, although a CT head scan can help to exclude rare meningiomas and other space-occupying lesions that can present with parkinsonism. Blood, urine and MRI investigations are usually restricted to specialist practice for the exclusion of rare metabolic and inherited conditions (e.g. Wilson's disease). Given the complexity of the diagnosis of PD and subsequent treatment decisions, there is a very simple rule for referring patients to a specialist: if you consider PD is a possibility then refer to a neurologist without delay.

TREATMENT OF NEWLY DIAGNOSED PARKINSON'S DISEASE

Does early treatment accelerate disease?

All current treatments for PD are directed towards ameliorating symptoms. It is important to recognise that, despite treatment, there is a relentless progression of predominantly dopaminergic cell death in PD. This process has led to common misconceptions among patients about the safety of medications for PD, but fortunately recent data allow us to reassure them about the benefit and low risk of early treatment.

A common patient concern is that medications for PD will accelerate their disease. Research demonstrating that initial dopamine agonist monotherapies such as pramipexole were associated with a

delay in the development of motor fluctuations (wearing off and dyskinesia) led many to ask whether levodopa could in fact be harmful.[4,10] Reassuringly, the Earlier versus Later Levodopa Therapy in Parkinson Disease (ELLDOPA) trial of the effect of this medication did not find any toxic effect of levodopa.[5] Furthermore, patients treated initially with levodopa, a dopamine agonist or a monoamine oxidase inhibitor showed no difference in their rates of motor fluctuations at 14-year follow up.[11]

Most recently, the role of levodopa in the development of motor fluctuations has been illuminated by studies evaluating the emergence of dyskinesias in an African (Ghana) population of patients with PD who received no treatment in the first few years of their disease.[12] This study showed that untreated patients with an average disease duration of six years developed motor fluctuations just a few months after receiving levodopa treatment. This finding underscores that the development of these motor complications is dictated not by the duration of exposure to levodopa but by the cell loss associated with disease progression.

How should early Parkinson's disease be treated?

As none of the available treatments for PD accelerates disease and all give better responses when there are more remaining dopaminergic neurons, the argument for early treatment of patients with PD seems overwhelming.

Initial monotherapy in PD can be challenging, with a number of pros and cons contributing to the complex decision-making process. There is good evidence to support the use of all available medication classes. In younger patients and some in particular occupations, therapies that can be administered once daily or as a patch may be favoured. In older patients, priority would be given to medications with less potential for side effects. Finally, a known history of problems such as gambling addiction would also influence treatment choice. Medications commonly used to treat patients with early PD are listed in Box 2.

Levodopa has on balance been shown to be the most effective treatment for PD, but at least three doses per day are usually required for its best effect. This agent is always combined with a peripheral decarboxylase inhibitor such as benserazide or carbidopa to aid absorption and can also be combined with a catechol-*O*-methyltransferase inhibitor such as entacapone in patients with more advanced disease.

The dopamine agonists cabergoline, pramipexole and rotigotine are available in once-daily administration form, which can be more convenient especially in younger patients. However, there is

2. DRUGS COMMONLY USED IN PATIENTS WITH EARLY PARKINSON'S DISEASE

Levodopa combinations*
Levodopa–benserazide
Levodopa–carbidopa

Dopamine agonists†
Cabergoline
Pramipexole
Rotigotine

Monoamine oxidase inhibitors
Rasagiline
Selegiline

Anticholinergics (restricted to treatment of tremor)
Benzhexol
Benztropine
Biperiden

* The catechol-*O*-methyltransferase inhibitor entacapone may be combined with levodopa preparations in late-stage Parkinson's disease.
† The ergot derivatives bromocriptine and pergolide are rarely used to treat patients with Parkinson's disease because of the risk of cardiac fibrosis.

3. PATIENT RESOURCES ON PARKINSON'S DISEASE

- Parkinson's Australia (www.parkinsons.org.au)
- Brain Foundation (http://brainfoundation.org.au)
- The Michael J. Fox Foundation for Parkinsons Research – USA (www.michaeljfox.org)
- Parkinson Foundation of the National Capital Area – USA (www.parkinsonfoundation.org)
- Parkinson's UK (www.parkinsons.org.uk)
- European Parkinson's Disease Association (www.epda.eu.com)

4. PRACTICE POINTS FOR GPS

- Motor and nonmotor symptoms need to be sought and assessed in patients whose presentation suggests Parkinson's disease (PD), including tremor, bradykinesia, rigidity, mood disturbance, anosmia, constipation and rapid eye movement sleep behaviour disorder (RBD).
- RBD is a red flag symptom suggesting the need for specialist assessment. Major cognitive impairment, visual hallucinations, psychosis, postural hypotension and incontinence at the time of presentation raise the suspicion of alternative diagnoses to PD.
- Early treatment of PD symptoms does not worsen prognosis.
- Initial treatment choice should be tailored to the individual; levodopa is the most effective treatment, but dopamine agonists and monoamine oxidase inhibitors have the advantage of once daily dosing and may be more suitable in patients with younger onset PD.
- It is possible to advise patients on many of their concerns, even at diagnosis, including why did I get PD and what is the outlook?

evidence to suggest that this class of medication is more sedating than other classes of PD treatments. In addition, dopamine agonists appear to carry a significantly greater risk than levodopa for the development of impulse control disorders such as pathological gambling, hypersexuality and compulsive shopping.[13] Patients and their carers should be warned about this, as well as the more general side effects of sedation and nausea.

Monoamine oxidase inhibitors (e.g. rasagiline and selegiline) can also be used once daily and appear to have a low risk of adverse events. Although caution is advised regarding the combination of rasagiline with common antidepressants (selective serotonin reuptake inhibitors [SSRIs] and serotonin–noradrenaline reuptake inhibitors [SNRIs]) and with dietary tyramine, the risk of adverse effects is considered low.[14]

The ergot derivatives bromocriptine and pergolide are also dopamine agonists but are rarely prescribed nowadays because of the risk of triggering cardiac fibrosis. The anticholinergics benzhexol, benztropine and biperiden are indicated only for treatment of tremor; the diagnosis of PD would have to be questioned in patients who continue to respond well to anticholinergics on their own over several years, without requiring the addition of dopaminergics.

WHAT SHOULD I TELL MY PATIENTS WHEN THEY ASK ...?

When patients are initially diagnosed with PD, they are often quietly accepting, presumably because they have considered this diagnosis themselves before presentation. It is usually after they leave their specialist's office that the questions begin. It is then GPs who find themselves in the front line and must be ready to provide answers to their numerous concerns.

How did I get Parkinson's disease?

Patients often want to know how they got PD. Although there are some data to suggest that there are likely genetic and environmental factors, these do not explain the overwhelming majority of cases. In most patients the aetiology of PD remains unknown.

A number of genes have been reported as causing PD but these are often limited to known kindreds with young onset of PD (under 30 years) and a very strong family history (many members across generations). The currently identified sporadic genes in the Australian population would account for fewer than 2% of cases of idiopathic PD. Thus most patients can be reassured that there is a low risk of passing on PD to their children.

Factors such as heavy exposure to pesticides and head trauma have been flagged as possible causes of PD, but their likely contribution to the bulk of cases is considered very low. Epidemiological studies

have also suggested that there might be some protective factors that reduce the risk of developing PD, such as smoking, caffeine intake and specific diets (e.g. the Mediterranean diet), but again these are likely to play only a small role. Thus patients with PD should be advised to avoid any dramatic change in their lifestyle after diagnosis.

What is my future?

Most frequently, patients will want to know their future, and this is very difficult to predict early in the course of the disease. However, the rate of progression of PD tends not to vary greatly within individuals once it appears to be constant. Thus a patient who is clearly deteriorating rapidly over the first few years after diagnosis is likely to do much worse than a patient whose symptoms remain relatively stable and respond well to treatment. Although patients with PD have higher rates of nursing home admission, dementia and psychosis, there is a marked heterogeneity across cases, and generalisations are not helpful at the individual level.

Patients should be advised to be proactive and encouraged to pursue exercise, physiotherapy, speech therapy and any form of cognitive training from the time of diagnosis. Additional information from patient support groups can be unpalatable for newly diagnosed patients, but these groups should be considered as a useful information resource (Box 3).

Given the progressive nature of PD, patients should consider future employment and health insurance needs without delay, so as to avoid challenging situations as their health deteriorates.

RESOURCES FOR GPS

In acknowledgement of the complexity of PD, the Movement Disorder Society of Australia has approved a free online educational resource that is accredited for continuing professional development points by the Australian College of Rural and Remote Medicine and the Royal Australian College of General Practitioners (www.rrmeo.com/parkaus). Some practice points for GPs are summarised in Box 4.

CONCLUSION

PD is relatively common in clinical practice, but each patient requires careful consideration and individualised management. Although the motor features of PD are often the major focus of our management, it is vital that nonmotor symptoms are actively sought and addressed. The challenge of PD will rise with the increasing number of older people in our population, and we all need to ensure that we have the skills to meet this demand. MT

REFERENCES

1. Access Economics. Living with Parkinson's disease – update. Canberra: Parkinson's Australia; 2011.
2. Abbott LM, Naismith SL, Lewis SJ. Parkinson's disease in general practice: assessing knowledge, confidence and the potential role of education. J Clin Neurosci 2011; 18: 1044-1047.
3. Hughes AJ, Daniel SE, Ben-Shlomo Y, Lees AJ. The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service. Brain 2002; 125(Pt 4): 861-870.
4. Whone AL, Remy P, Davis MR, et al. The REAL-PET study: slower progression in early Parkinson's disease treated with ropinirole compared with L-dopa. Abstracts of the American Academy of Neurology 54th Annual Meeting; 2002 Apr 13-20; Denver, Colorado. Abstract S11.006.
5. Fahn S, Oakes D, Shoulson I, et al. Levodopa and the progression of Parkinson's disease. N Engl J Med 2004; 351: 2498-2508.
6. Parkinson Study Group. Pramipexole vs levodopa as initial treatment for Parkinson disease: a randomized controlled trial. Parkinson Study Group. JAMA 2000; 284: 1931-1938.
7. Iranzo A, Tolosa E, Gelpi E, et al. Neurodegenerative disease status and post-mortem pathology in idiopathic rapid-eye-movement sleep behaviour disorder: an observational cohort study. Lancet Neurol 2013; 12: 443-453.
8. Schenck CH, Boeve BF, Mahowald MW. Delayed emergence of a parkinsonian disorder or dementia in 81% of older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder: a 16-year update on a previously reported series. Sleep Med 2013; 14: 744-748.
9. Coeytaux A, Wong K, Grunstein R, Lewis SJ. REM sleep behaviour disorder – more than just a parasomnia. Aust Fam Physician 2013; 42: 785-788.
10. Shoulson I. Pramipexole versus levodopa in early Parkinson's disease: the randomised controlled CALM-PD trial. Movement Disord 2000; 15 Suppl 3: S4-S5.
11. Katzenschlager R, Head J, Schrag A, et al. Fourteen-year final report of the randomized PDRG-UK trial comparing three initial treatments in PD. Neurology 2008; 71: 474-480.
12. Cilia R, Akpalu A, Sarfo FS, et al. The modern pre-levodopa era of Parkinson's disease: insights into motor complications from sub-Saharan Africa. Brain 2014; 137(Pt 10): 2731-2742.
13. Weintraub D, Koester J, Potenza MN, et al. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. Arch Neurol 2010; 67: 589-595.
14. Chen JJ, Swope DM, Dashtipour K. Comprehensive review of rasagiline, a second-generation monoamine oxidase inhibitor, for the treatment of Parkinson's disease. Clin Ther 2007; 29: 1825-1849.

COMPETING INTERESTS: Associate Professor Lewis sits on the Scientific Advisory Boards of Britannia Pharmaceuticals, Hospira, Lundbeck and UCB.