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The Diagnosis and Management of Parkinson's Disease

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Abstract

Parkinson's disease is the second commonest neurodegenerative disorder, after Alzheimer's, and represents a major cause of neurological morbidity globally. The diagnosis is made clinically and management is currently restricted to symptomatic treatments, with levodopa continuing to form the cornerstone of pharmacological therapy. Deep brain stimulation of specific basal ganglia targets can offer significant symptomatic benefits in selected patient groups. To date, no established disease-modifying agents that can halt or reverse the underlying neurodegenerative process are available in clinical practice. The aim of this article is to provide an overview, and an update, on the diagnosis and management of Parkinson's disease.

Keywords: Parkinson's disease, bradykinesia, rigidity, tremor, dyskinesia, levodopa, dopamine receptor agonists, deep brain stimulation.

Introduction

Idiopathic Parkinson's Disease (PD) is the second commonest neurodegenerative disease, after Alzheimer's, with an estimated lifetime risk of nearly 3-7% [1,2]. From 1990 to 2016, the worldwide burden of PD has increased from an estimated 2.5 to 6.1 million patients [3,4]. With age representing the biggest risk factor for the disease, and in the context of an exponentially ageing population, the prevalence of PD is predicted to continue to rise [4].

The pathological hallmark of PD is characterized by the accumulation of misfolded aggregates of alpha-synuclein-containing Lewy bodies throughout the brain, and degeneration of neurons in the substantia nigra pars compacta (SNpc) [5]. This leads to a state of dopaminergic deficiency, most profoundly in the striatum, which eventually culminates in the cardinal motor symptoms that exemplify the disease. However, there has been an increasing awareness and interest in the non-motor manifestations of the disease as well, such as anosmia, constipation, Rapid Eye-Movement (REM) sleep behavior disorder (RBD) and neurocognitive dysfunction, some of which may predate the motor features by up to several decades [6,7]. Indeed, this is in line with neuropathological studies, which have shown that the deposition of Lewy Bodies begins in lower brainstem structures and olfactory bulbs, before affecting the midbrain [8].

Herein I provide a pragmatic overview of the diagnosis and management of PD in clinical practice, albeit with a particular emphasis on motor symptomatology. For useful reviews on non-motor symptoms in PD, see references [6,7,9,10].

Diagnosis

The diagnosis of PD is clinical and can be made using the UK Parkinson's Disease Society (UKPDS) Brain Bank Criteria [11]. The core

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clinical features of PD are bradykinesia (without which a diagnosis cannot be made) and a combination of muscular rigidity, tremor and/or postural instability not explained by visual, cerebellar, proprioceptive or vestibular failure. Bradykinesia can be elicited at the bedside by asking the patient to perform repetitive motor tasks (such as finger-thumb opposition) as fast and as large as possible – progressive decrement in amplitude is confirmatory of bradykinesia. Rigidity, which represents the velocity-independent increase in muscle tone (distinguished from spasticity, which is velocity-dependent), can be assessed by passive flexion/extension and pronation/supination of the elbow and forearm, respectively. Cogwheeling, which describes the 'ratchety' motion elicited on circumduction of the wrist, represents rigidity interrupted by periodic tremor and is ubiquitous in PD.

The tremor of PD is typically unilateral in onset, a 'pill-rolling' quality (with the thumb in flexion) and 4-6Hz in frequency [12]. Tremor amplitude is often enhanced at rest, during walking, distraction, concentration on a cognitive or motor task (with the contralateral limb), and during times of stress [13]. Due to tremor variability in PD, it can sometimes be difficult to differentiate from a functional (psychogenic) tremor, particularly in early, or tremor-predominant, disease. The following tests may help distinguish the two:

1) Performing ballistic movements of the contralateral unaffected limb, which leads to temporary tremor arrest in functional tremor but not in PD [14].

2) Testing entrainment by asking the patient to perform a motor task with the unaffected (or less affected) limb, such as finger tapping, at a frequency that differs from the tremor. If the tremulous hand adopts the new frequency, changes significantly or the patient has excessive difficulty performing the task, this would suggest a functional tremor [15].

Essential tremor (ET) may sometimes mimic a tremor of PD, but can be distinguished by certain findings (Box 1) [16]. These are not infallible and in a significant proportion of cases, there may be overlap in tremor characteristics, occasionally making clinical differentiation difficult [17]. Although the associated signs of bradykinesia and rigidity point strongly towards PD, in circumstances where tremor is the dominant clinical finding, a dopamine transporter (DaT) scan may assist in diagnostic formulation (discussed later).

The classic signs of a festinating, shuffling gait with stooped posture, camptocormia, reduced arm swing and freezing, are findings of relatively advanced disease. The features of early PD, however, are usually subtler and should actively be sought for in order to prevent any delay in diagnosis. Patients may report a stiff shoulder that aches (mistakenly diagnosed as a 'frozen shoulder') or a limb that feels stiffer and not quite right, they may have hypomimia masquerading as a depressive demeanour or they may even blame a slowing down of the limbs on supposedly 'faulty equipment' [18]. The nature of the presenting PD phenotype and gender are key determinants of duration of symptom onset to presentation to the primary care physician; presentation with gait disturbance, along with male sex, are associated with delayed diagnoses, compared with tremor [19].

Box 1

- ET is usually bilateral and symmetrical (PD is more often unilateral in onset).
- ET is mainly an action and postural tremor (PD tremor is more pronounced at rest, but patients can have a postural re-emergent tremor after a latency of several seconds).
- ET has a higher frequency of 4-12 Hz and more commonly affects the head and voice, compared with PD.
- ET has a stronger family history (>50%) and is classically alleviated with alcohol.
- Bradykinesia, rigidity and postural instability are not seen in patients with ET.

Non-motor features such as anosmia, RBD (vivid dreams and thrashing about violently in sleep), constipation, fatigue and neuropsychiatric disturbances such as depression, anxiety and cognitive dysfunction (bradyphrenia, poverty of thought) may precede overt motor manifestations by many years [6]. However, with the slight exception of RBD, the non-motor symptoms alone are incredibly non-specific, and common amongst the general population, such that in the absence of motor symptoms, a clinical diagnosis of PD cannot be made with current established diagnostic criteria.

Box 2: Clinical mimics of PD

- **Drug-induced parkinsonism:** may be caused by anti-dopaminergics such as metoclopramide or anti-psychotics (particularly first-generation agents such as haloperidol, prochlorperazine and chlorpromazine but also atypical agents like risperidone and olanzapine) or other drugs including valproate and calcium channel blockers (flunarizine, cinnarizine) [20].
- **Toxins:** 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) poisoning in intravenous drug users, Meow Meow, Manganese, methanol, ethylene glycol and carbon monoxide poisoning can lead to basal ganglia dysfunction and/or degeneration with Parkinsonism [21-23].
- **Vascular parkinsonism:** These patients would be expected to have a history of strokes and a heavy burden of small vessel disease with or without lacunar infarcts on neuroimaging. There may be a stepwise deterioration, with preferential involvement of the lower limbs resulting in an apraxic gait and shortened stride (Marche à petits pas) [24].
- **Dementia with Lewy Bodies (DLB):** Dementia and Parkinsonism occurring within 1 year of each other (in contrast to PD with dementia), alongside complex visual hallucinations and fluctuating cognition [25].
- **Normal Pressure Hydrocephalus (NPH):** triad of gait apraxia (with a shuffling/'magnetic' quality), urinary incontinence and cognitive decline (initially a subcortical, dysexecutive syndrome with bradyphrenia, attention deficits, mental inflexibility and apathy, which overlaps

with the cognitive profile in PD). Neuroimaging and a therapeutic response to a high volume cerebrospinal fluid (CSF) tap support the diagnosis. Patients with advanced dementia are predicted to respond poorly to CSF shunting procedures as they often have concomitant Alzheimer's pathology with severe hippocampal atrophy [26].

- **Progressive supranuclear palsy (PSP):** initially slowing of volitional vertical saccades, followed by vertical gaze paresis (but with preserved vestibulo-ocular reflex), then eventually supranuclear horizontal gaze paresis late in the disease. Patients have a symmetrical bradykinesia with significant axial rigidity, may demonstrate frontalis overactivity, emotional lability and have a particular tendency to fall backwards. Profoundly reduced verbal fluency is a sensitive marker of differentiating PSP from PD [27]. Sagittal MRI of the brainstem may reveal the 'humming bird' sign [28].
- **Corticobasal degeneration (CBD):** asymmetric presentation with bradykinesia, rigidity, dystonia, alien-limb phenomena, dyspraxia, cortical sensory loss (astereognosis, agraphaesthesia) and/or myoclonus [29].
- **Multi-system atrophy (MSA):** associated with early severe autonomic failure and cerebellar syndrome. Parkinsonism is a core feature of the MSA-P variant, but cerebellar dysfunction is more prominent in MSA-C. A very specific neuroimaging finding is the 'hot-cross bun' sign on axial MRI brainstem sections, which occurs due to degeneration of pontine neurons and myelinated transverse pontocerebellar fibres, but with sparing of the corticospinal tracts [30,31]
- **Sporadic Creutzfeldt-Jakob disease (sCJD):** can manifest as a corticobasal syndrome as one of many possible presentations. The key distinguishing feature of prion disease is its sheer rapid clinical progression (normal function to death in less than 1 year in 90% of patients) [32,33]. Supportive diagnostic features include cortical ribboning and hyper-intense basal ganglia on MRI. CSF RT-QuIC analysis helps confirm the diagnosis with up to 92% sensitivity and 100% specificity [34].
- **Genetic:** Wilson's disease is an autosomal recessive condition with a mutation in the ATP7B gene leading to copper accumulation and hepato-lenticular degeneration. Associated with dystonia, 'wing-beating' tremor, chorea, neuropsychiatric disturbance and liver dysfunction. Slit-lamp examination demonstrates Kayser-Fleischer rings in up to 95% of patients [35,36]. Low serum caeruloplasmin, low serum and high urinary copper help affirm the diagnosis. Patients with neurodegeneration with brain iron accumulation (NBIA) syndromes, Huntington's, Fragile X-associated tremor/ ataxia syndrome (FXTAS) and the autosomal dominant spinocerebellar ataxias (SCAs) may also develop extrapyramidal features of Parkinsonism.

Before making a diagnosis of PD, it is important to search for any features that would suggest a Parkinsonian mimic (Box 2). Unlike its mimics, however, PD patients typically display an excellent response to levodopa early in the disease course and response is usually maintained for at least 5 years. Other supportive clinical features of PD include gradual progression over at least 10 years and persistent asymmetry disproportionately affecting the side of onset [11].

Sometimes the clinical diagnosis of PD is difficult and a dopamine transporter (DaT) scan, which received FDA approval in the United States in 2011, may help. This technique involves intravenous administration of a radioligand (Ioflupane [123I]), and imaging using Single Photon Emission Computed Tomography (SPECT), to visualise tracer uptake in nigrostriatal dopaminergic nerve terminals. Reduced tracer uptake signifies degeneration of these dopaminergic neurons, which may be supportive of a diagnosis of PD. However, the results must be interpreted within the right clinical context. For example, DaT scans can be helpful when trying to differentiate PD from essential tremor or drug-induced parkinsonism - the scan would be normal in the latter 2 cases, unlike in PD. However, abnormal DaT scans in cases of supposed drug-induced parkinsonism would suggest unmasking of pre-clinical PD. Reduced radioligand uptake also occurs in other neurodegenerative conditions including PSP, CBD, MSA and DLB - PD cannot, therefore, be differentiated from these conditions by DaT scans alone.

Treatment of PD

A focus of this article will be on the treatment of motor symptoms in PD. The management of non-motor symptoms is outside the scope of this review but clearly merits its own special attention when managing the patient with PD as these symptoms can be just as disabling [6,7,9,10].

Levodopa: Levodopa is the most effective and widely used symptomatic pharmacologic treatment for PD. Levodopa-responsive symptoms in PD include bradykinesia, rigidity and tremor. Postural instability and non-motor symptoms are less responsive. Commonly prescribed oral preparations combine levodopa with peripheral DOPA decarboxylase inhibitors such as carbidopa (carbidopa/levodopa: Sinemet) or benserazide (benserazide/levodopa: Madopar), which increase the availability of levodopa in the central nervous system (CNS). Oral levodopa is often commenced at a low dose and slowly up-titrated in order to reduce the risk of adverse drug reactions, particularly in the elderly (such as nausea, hallucinations and postural hypotension). A typical starting regimen would be to commence Sinemet/Madopar 62.5mg (12.5mg DOPA decarboxylase inhibitor/50mg levodopa) once a day and to up-titrate as tolerated in 62.5mg increments every 5-7 days to an initial maintenance of 62.5mg three times per day. It is important to note that it can take several weeks for plasma levodopa to equilibrate in the brain so that any symptomatic effects after further up- or down-titration of levodopa may be delayed by a similar period [37]. Most PD patients show a good, smooth response in early disease to levodopa doses of 300-600mg

per day, during the so-called 'honeymoon period,' although increasing rates of dyskinesia are seen at higher doses [38]. Before it can be concluded that the patient is not responsive to levodopa, doses should be up-titrated as tolerated to a maximum dose of 1-1.5g/day [39].

With disease progression, patients experience wearing-off effects and end of dose deterioration, whereby PD symptoms of bradykinesia, rigidity and tremor emerge prior to the next dose of levodopa, necessitating more frequent and/or higher future dosing. The therapeutic window gradually narrows with time so that it becomes increasingly challenging to treat extrapyramidal symptoms without experiencing unwanted dyskinesia.

Dyskinesia can occur during periods of maximum levodopa plasma concentrations (peak-dose dyskinesia) or less frequently during the rise and fall of levodopa levels (diphasic dyskinesia). The pathophysiology is complex. A potential mechanism underpinning this is pulsatile striatal dopaminergic activity, whereby intracerebral dopamine levels closely correlate with plasma concentrations as a consequence of depleted endogenous dopamine stores, with loss of buffering effects, in advanced PD [40,41]. Peripheral-acting Catechol-O-methyltransferase (COMT) inhibitors, such as entacapone, help prolong the half-life of levodopa and can be used to reduce wearing-off effects and motor fluctuations [42]. Some are limited by their toxicity (namely tolcapone resulting in liver damage), but more recently opicapone, which can be administered once daily, has shown promise, and non-inferior efficacy compared with the conventionally prescribed entacapone, in reducing "off" time [43].

Carbidopa-levodopa gel can be given as a continuous infusion via the duodenum (Duodopa) in advanced levodopa-responsive PD when other medical treatments have failed. Multiple RCTs have shown that duodopa can reduce "off" time, increase "on" time without associated troublesome dyskinesias, and can improve quality of life, when compared with equivalent oral medical treatments [44].

Dopamine receptor agonists and other levodopa-sparing agents: Dopamine agonists, which directly activate striatal dopamine receptors, can be divided into ergot (e.g. bromocriptine, cabergoline, pergolide) and non-ergot-derived drugs (ropinirole, pramipexole, rotigotine, apomorphine). Due to long-term safety concerns, namely pulmonary, cardiac and retroperitoneal fibrosis, ergot-derived agonists are best avoided. Monoamine oxidase type B (MAO-B) inhibitors suppress the breakdown of dopamine and help prolong endogenous striatal dopaminergic stimulation. Dopamine agonists or MAO-B inhibitors are traditionally prescribed early in disease, and particularly in the younger (<60 years) PD cohort, in preference to levodopa as initial therapy. The rationale for this is to delay the onset of motor fluctuations and dyskinesia, which are most prominent with levodopa and especially in the younger age groups. A counter-argument to this practice has been highlighted by a landmark open-label randomised-controlled trial (RCT, n= 1620), which showed statistically better long-term benefits in mobility (measured using the PD questionnaire, PDQ-39) for patients commenced on levodopa, versus levodopa-sparing agents, and such benefits were maintained at 7 years follow up. However, the clinical effect sizes were actually modest (1.8 points higher in the levodopa group 95% CI 0.5-3.0) [45] and the younger onset age group (<60), who are at greater risk of dyskinesia, were under-represented [46].

Although motor complications are less with dopamine agonists compared with levodopa, the former treatments are associated with a greater risk of various non-motor side effects including somnolence, oedema, constipation, dizziness and hallucinations [47]. Moreover, dopamine agonists carry a far greater risk of impulse-control disorders (in up to 17% of patients) such as gambling, overeating, hypersexuality and compulsive spending [48]. They should therefore be avoided in patients with a history of addiction, compulsive behaviours or impulsive personality traits. These impulse control disorders arise as a consequence of a dopamine dysregulation syndrome (DDS), which may be seen in PD patients over-treated with levodopa and/or dopamine agonists. Punding is another manifestation of DDS and is characterised by repetitive, complex, purposeless, stereotyped activities, the natures of which are often pertinent to the individuals past or present occupation or hobby [49]. Symptoms of DDS are frequently not volunteered by patients due to lack of insight, denial or embarrassment, and so must be actively inquired for during consultations [50].

Other therapies in PD include anticholinergics (such as trihexyphenidyl), which may have a modest beneficial effect on tremor, and can improve sialorrhoea, but should be avoided in cognitively impaired patients as they can precipitate delirium [51]. Anticholinergics may also have ancillary benefits in treating urinary urgency and frequency in PD, but caution is advised in elderly men with comorbid prostatic hypertrophy due to risks of urinary retention.

Amantadine, an NMDA-receptor antagonist, can alleviate dyskinesia in PD and its clinical efficacy has been demonstrated in a meta-analysis of 11 RCTs (n=356) [52]. It may also reduce the risk of dyskinesia in drug naive PD patients as highlighted by a recent open-label pragmatic trial [53], although its use is limited by adverse effects that include hallucinations, confusion, livedo reticularis and ankle oedema. Botulinum toxin injections are efficacious in dystonia, sialorrhoea and tremor, which can be disabling symptoms in PD, but they're hampered by concomitant muscle weakness [54,55].

Deep brain stimulation (DBS): It is well established that DBS is significantly better than best medical therapy in improving "on" time (without troubling dyskinesias), motor function and quality of life in selected patients with PD [56,57]. The mechanism of action of DBS remains unclear but is likely to be pleiotropic [58]. It may involve a combination of disruption of information flow through the target site, attenuation of pathological oscillatory synchrony within local and network-wide basal ganglia circuitry, modulation of neurochemical balance and synaptic plasticity [58-61]. The most common target sites for DBS

are sub-thalamic nucleus (STN), globus pallidus interna (GPi) and, to a lesser degree, ventral intermediate nucleus of the thalamus (VIM). The target choice is dependent on the desired therapeutic outcomes. STN stimulation directly improves bradykinesia, rigidity and tremor, thereby reducing "off" time - it also allows for the greatest reduction in dopaminergic medication, when compared with other targets, which indirectly enables treatment of dyskinesia [62]. GPi stimulation has a direct anti-dyskinetic effect with equivalent motor benefits on other levodopa-responsive symptoms, compared with STN - GPi stimulation, however, may have a superior effect on mood and cognition [62-64]. VIM stimulation has significant long-term benefits for tremor, but due to lack of efficacy on other motor symptoms, its use is best perhaps restricted to tremor-predominant PD [62]. The effects of DBS in the aforementioned basal ganglia sites for levodopa-unresponsive symptoms, such as postural instability and freezing of gait during the "on" state, are limited. The symptomatic impact following stimulation of other target sites such as the pedunculopontine nucleus (PPN), however, has yielded some promising results but remains a subject of further research [65-67].

DBS is not without risks, which include neurosurgical complications of intracerebral haemorrhage, ischaemic stroke and hardware-related complications such as lead migration/fracture and infection [68]. Furthermore, non-motor symptoms such as neuropsychiatric disturbance and cognitive dysfunction can be exacerbated by DBS. Therefore, careful patient selection is of utmost importance when considering PD cases for this invasive procedure.

Although pharmacological and neurosurgical treatment of symptoms in PD have individually been discussed, the importance of managing this condition within the context of a multi-disciplinary setting cannot be over-emphasised. Patients with PD invariably require holistic care and input from multiple specialists during the course of their illness. This may involve input from a range of other professionals including specialist nurses, occupational therapists, physiotherapists, dieticians, psychiatrists, speech and language therapists and social workers. This highlights the multi-faceted and complex health-related needs of patients with PD.

Future therapies for PD: To date, no disease modifying therapies in PD are available in current clinical practice. There has been a great deal of interest in the therapeutic role of neurotrophic factors (such as BDNF, GDNF, neurturin, CDNF and VEGF-A), with encouraging results in pre-clinical models [69]. Although clinical trials testing disease modifying treatments in PD patients have generally yielded disappointing results [70], more recently, a randomised placebo-controlled trial, led by a group in Bristol (United Kingdom), investigating intra-putamenal delivery of GDNF, has yielded promising results [71]. Despite that GDNF-treatment did not result in significant improvements in the Unified Parkinson's Disease Rating Scale (UPDRS) scores at 40 weeks follow up (largely due to the substantial placebo effects), it did result in better putamenal fluorodopa uptake, compared with placebo, suggesting a successful neurobiological effect of GDNF delivery. Furthermore, in an open-label extension of the study at 80 weeks follow up, whereby all participants were treated with GDNF, there were significant motor improvements over baseline UPDRS scores. A major constraint in the interpretation of such clinical trials is the limited clinical readout of such outcome measures. The emphasis is often placed on UPDRS scores, but this only provides an isolated snapshot of function, and fails to take into consideration the continuous, longitudinal dynamics of disease activity. This may, therefore, underestimate any real life clinical improvements some patients may experience from potential therapies. Further robust multi-centre placebo-controlled RCTs, with more sophisticated clinical readouts of motor function, and longer-term follow-ups, are required before such therapies can be considered in future, routine clinical practice.

Neurofeedback is a non-invasive method of learnt self-regulation of selected brain regions or networks, using real-time functional MRI or electroencephalography (EEG), and has also sparked some interest as a potential therapeutic tool for psycho- and neuropathologies [72,73]. Its attraction lies in being able to directly modulate neural network rhythms, or localised brain activity, in an effort to restore physiological neural function, non-invasively. Although this technique is safe and has yielded some interesting results, the evidence for its role in the treatment of PD remains limited and requires further investigation [73-75].

Conclusion

PD remains a clinical diagnosis and management is currently restricted to control of symptoms, rather than modification of the underlying pathophysiological process. A key barrier for future disease modifying therapies is that with current diagnostic criteria, where the focus is on motor symptoms and signs, the diagnosis of PD can only be made once at least 60-70% of SNpc neurons have already degenerated [76-78]. This highlights the need for validated diagnostic biomarkers that herald the onset of PD at a much earlier stage in the course of disease than current criteria allow. The recent clinical trial on GDNF therapy by the Bristol group have yielded potentially promising results and call for further robust multi-centre clinical trials in neurotrophin-based therapeutics in PD.

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