

# Parkinson's disease: clinical features and diagnosis

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## ABSTRACT

**Objective:** Parkinson's disease (PD) is a progressive neurological disorder characterised by a large number of motor and non-motor features that can impact on function to a variable degree. This review describes the clinical characteristics of PD with emphasis on those features that differentiate the disease from other parkinsonian disorders.

**Methods:** A MedLine search was performed to identify studies that assess the clinical characteristics of PD. Search terms included "Parkinson's disease", "diagnosis" and "signs and symptoms".

**Results:** Because there is no definitive test for the diagnosis of PD, the disease must be diagnosed based on clinical criteria. Rest tremor, bradykinesia, rigidity and loss of postural reflexes are generally considered the cardinal signs of PD. The presence and specific presentation of these features are used to differentiate PD from related parkinsonian disorders. Other clinical features include secondary motor symptoms (eg, hypomimia, dysarthria, dysphagia, sialorrhoea, micrographia, shuffling gait, festination, freezing, dystonia, glabellar reflexes), non-motor symptoms (eg, autonomic dysfunction, cognitive/neurobehavioral abnormalities, sleep disorders and sensory abnormalities such as anosmia, paresthesias and pain). Absence of rest tremor, early occurrence of gait difficulty, postural instability, dementia, hallucinations, and the presence of dysautonomia, ophthalmoparesis, ataxia and other atypical features, coupled with poor or no response to levodopa, suggest diagnoses other than PD.

**Conclusions:** A thorough understanding of the broad spectrum of clinical manifestations of PD is essential to the proper diagnosis of the disease. Genetic mutations or variants, neuroimaging abnormalities and other tests are potential biomarkers that may improve diagnosis and allow the identification of persons at risk.

In his 1817 "An essay on the shaking palsy", James Parkinson first described the clinical syndrome that was later to bear his name.<sup>1</sup> He identified six cases, three of whom he personally examined; three he observed on the streets of London. Previously referred to as "paralysis agitans", Charcot later in the 19th century gave credit to Parkinson by referring to the disease as "maladie de Parkinson" or Parkinson's disease (PD). Charcot also recognised non-tremulous forms of PD and correctly pointed out that slowness of movement should be distinguished from weakness or "lessened muscular power", a term originally used by Parkinson.<sup>2</sup> More than 100 years passed (1919) after the original description by Parkinson before it was recognised that patients with PD lose cells in the substantia nigra, and 140 years passed (1957) before dopamine was discovered as a putative neurotransmitter by Carlsson and colleagues in Lund, Sweden.<sup>3</sup> The discovery by Ehringer and Hornykiewicz in

1960<sup>3,4</sup> that dopamine concentrations are markedly decreased in the striatum of patients with PD paved the way for the first trials of levodopa in PD patients the following year<sup>5</sup> and subsequent award of the Nobel Prize in Medicine to Carlsson in 2000. The ability of injected levodopa to improve akinesia in patients with PD was first demonstrated in 1961 and was followed by the development of oral levodopa later in the decade.<sup>6,7</sup> More recently, genetic mutations, abnormal handling of misfolded proteins by the ubiquitin-proteasome and the autophagy-lysosomal systems, increased oxidative stress, mitochondrial dysfunction, inflammation and other pathogenic mechanisms have been identified as contributing factors in the death of dopaminergic and non-dopaminergic cells in the brains of patients with PD.<sup>8,9</sup> It is beyond the scope of this review to discuss the various pathogenic mechanisms, management or treatment related complications that have been the subjects of recent reviews and volumes.<sup>10,11</sup> This article focuses on the clinical features of PD and the differentiation of the disease from other parkinsonian disorders.

## CLINICAL FEATURES

There are four cardinal features of PD that can be grouped under the acronym TRAP: Tremor at rest, Rigidity, Akinesia (or bradykinesia) and Postural instability. In addition, flexed posture and freezing (motor blocks) have been included among classic features of parkinsonism, with PD as the most common form. Because of the diverse profiles and lifestyles of those affected by PD, motor and non-motor impairments should be evaluated in the context of each patient's needs and goals.<sup>12</sup>

A number of rating scales are used for the evaluation of motor impairment and disability in patients with PD, but most of these scales have not been fully evaluated for validity and reliability.<sup>13,14</sup> The Hoehn and Yahr scale is commonly used to compare groups of patients and to provide gross assessment of disease progression, ranging from stage 0 (no signs of disease) to stage 5 (wheelchair bound or bedridden unless assisted). The Unified Parkinson's Disease Rating scale (UPDRS) is the most well established scale for assessing disability and impairment.<sup>13,15</sup> Studies making use of UPDRS to track the progression of PD suggest that the course of PD is not linear and that the rate of deterioration is variable and more rapid in the early phase of the disease and in patients with the postural instability gait difficulty (PIGD) of PD.<sup>16-18</sup> We prospectively followed-up 297 patients (181 men, 116 women) with clinically diagnosed PD for at least 3 years and, based on data from 1731 visits during an average of 6.36 years (range 3-17), we concluded that the annual rate of decline in the

total UPDRS scores was 1.34 points when assessed during ON and 1.58 points when assessed during OFF. Patients who were older and had the PIGD form of PD at onset experienced more rapid disease progression than did those who were younger at onset and had the tremor dominant form of PD. Furthermore, the older group experienced significantly more progression in mentation, freezing and parts I and II UPDRS subscores. Handwriting was the only component of the UPDRS that did not significantly deteriorate during the observation period. On the other hand, many studies have shown that younger patients are at a higher risk for levodopa induced dyskinesias than older patients.<sup>19</sup> In a prospective study of 145 clinic based patients followed-up for 1 year and of 124 community based patients followed-up for 4 years, the annual mean rate of deterioration in motor and disability scores ranged from 2.4% to 7.4%.<sup>20</sup> The current UPDRS is undergoing revisions so that the revised scale will be more sensitive to detect small changes and it will integrate non-motor elements of PD.<sup>15</sup> Other types of rating scales include those that assess psychiatric manifestations (eg, depression)<sup>21</sup> and quality of life.<sup>14 21</sup> The most frequent clinical features associated with PD are listed in table 1 and are discussed in the following sections.

### Bradykinesia

Bradykinesia refers to slowness of movement and is the most characteristic clinical feature of PD, although it may also be seen in other disorders, including depression. Bradykinesia is a hallmark of basal ganglia disorders, and it encompasses difficulties with planning, initiating and executing movement and with performing sequential and simultaneous tasks.<sup>22</sup> The initial manifestation is often slowness in performing activities of daily living and slow movement and reaction times.<sup>23 24</sup> This may include difficulties with tasks requiring fine motor control (eg, buttoning, using utensils). Other manifestations of bradykinesia include loss of spontaneous movements and gesturing, drooling because of impaired swallowing,<sup>25</sup> monotonic and hypophonic dysarthria, loss of facial expression (hypomimia) and decreased blinking, and reduced arm swing while walking. Given that bradykinesia is one of the most easily recognisable symptoms of PD, it may become apparent before any formal neurological examination. Assessment of bradykinesia usually includes having patients perform rapid, repetitive, alternating movements of the hand (finger taps, hand grips, hand pronation–supination) and heel taps and observing not only slowness but also decrementing amplitude.

In common with other parkinsonian symptoms, bradykinesia is dependent on the emotional state of the patient. For example, immobile patients who become excited may be able to make quick movements such as catching a ball (or may be able to suddenly run if someone screams “fire”). This phenomenon (kinesia paradoxa) suggests that patients with PD have intact

motor programmes but have difficulties accessing them without an external trigger, such as a loud noise, marching music or a visual cue requiring them to step over an obstacle.

Although the pathophysiology of bradykinesia has not been well delineated, it is the cardinal PD feature that appears to correlate best with degree of dopamine deficiency.<sup>26</sup> This is supported by the observation of decreased neuronal density in the substantia nigra in elderly patients with parkinsonism regardless of PD diagnosis.<sup>27</sup> In addition, positron emission tomography in patients with PD has demonstrated that the decreased <sup>18</sup>F-fluorodopa uptake in the striatum and accumbens–caudate complex is proportional to the degree of bradykinesia.<sup>28</sup>

It is hypothesised that bradykinesia is the result of a disruption in normal motor cortex activity mediated by reduced dopaminergic function. In a study assessing recordings from single cortical neurons in rats with haloperidol induced bradykinesia, a decrease in firing rates correlated with bradykinesia.<sup>29</sup> Functional neuroimaging studies also suggest impairment in the recruitment of cortical and subcortical systems that regulate kinematic parameters of movement (eg, velocity).<sup>30</sup> Conversely, recruitment of various premotor areas, such as those responsible for visuomotor control, is increased.<sup>30</sup> Anatomically, the deficit appears to be localised in the putamen and globus pallidus,<sup>28</sup> resulting in a reduction in the muscle force produced at the initiation of movement. Analysis of electromyographic recordings showed that patients with bradykinesia are unable to energise the appropriate muscles to provide enough force to initiate and maintain large fast movements.<sup>31</sup> Because patients with PD have decreased electromyographic activity,<sup>22</sup> they need a series of multiple agonist bursts to accomplish larger movements.

### Tremor

Rest tremor is the most common and easily recognised symptom of PD. Tremors are unilateral, occur at a frequency between 4 and 6 Hz, and almost always are prominent in the distal part of an extremity. Hand tremors are described as supination–pronation (“pill-rolling”) tremors that spread from one hand to the other. Rest tremor in patients with PD can also involve the lips, chin, jaw and legs but, unlike essential tremor, rarely involves the neck/head or voice. Thus a patient who presents with head tremor most likely has essential tremor, cervical dystonia, or both, rather than PD. Characteristically, rest tremor disappears with action and during sleep. Some patients also report an “internal” shaking that is not associated with a visible tremor.<sup>32</sup> The tremor of PD is differentiated from that of essential tremor by a number of features (table 2).

Some patients with PD have a history of postural tremor, phenomenologically identical to essential tremor, for many years or decades before the onset of parkinsonian tremor or

**Table 1** Parkinson's disease symptoms

Motor symptoms	Non-motor symptoms
Tremor, bradykinesia, rigidity, postural instability	Cognitive impairment, bradyphrenia, tip-of-the-tongue (word finding) phenomenon
Hypomimia, dysarthria, dysphagia, sialorrhoea	Depression, apathy, anhedonia, fatigue, other behavioural and psychiatric problems
Decreased arm swing, shuffling gait, festination difficulty arising from chair, turning in bed	Sensory symptoms: anosmia, ageusia, pain (shoulder, back), paresthesias
Micrographia, cutting food, feeding, hygiene, slow activities of daily living	Dysautonomia (orthostatic hypotension, constipation, urinary and sexual dysfunction, abnormal sweating, seborrhoea), weight loss
Glabella reflex, blepharospasm, dystonia, striatal deformity, scoliosis, camptocormia	Sleep disorders (REM behaviour disorder, vivid dreams, daytime drowsiness, sleep fragmentation, restless legs syndrome)

**Table 2** Features differentiating Parkinson's disease from essential tremor

Feature	Parkinson's disease	Essential tremor
Age at onset (y)	55–75	10–80
Family history	+/-	++
Tremor frequency (Hz)	4–6	5–10
Tremor characteristics	Supination–pronation	Flexion–extension
Influencing factors		
Rest	Increases	Decreases
Action	Decreases	Increases
Mental concentration	Decreases	Increases
Writing	Decreases (micrographia)	Increases (tremulous)
Walking	Increases	Decreases
Alcohol	—	Decreases
Postural tremor	Re-emergent	Without latency
Kinetic tremor	+/-	Yes
Limb tremor	Asymmetric	Symmetric
Distribution other than limbs	Face, jaw, lips, chin	Head, voice
Neuroimaging—dopaminergic system	Marked dopaminergic deficit	Mild dopaminergic deficit
Mid-brain sonography	Marked hyper-echogenicity	Mild hyper-echogenicity
Neuropathology	Nigrostriatal degeneration, Lewy bodies	Mild cerebellar degeneration, Lewy bodies in the substantia nigra, brainstem and cerebellum some cases
Treatment	Anticholinergics, amantadine, dopaminergic drugs, deep brain stimulation	Alcohol, beta-blockers, primidone, topiramate, gabapentin, botulinum toxin, deep brain stimulation

other PD related features. We and others have provided a growing body of evidence that indicates that essential tremor is a risk factor for PD.<sup>33</sup>

In addition to rest tremor, many patients with PD also have postural tremor that is more prominent and disabling than rest tremor and may be the first manifestation of the disease.<sup>34–35</sup> Parkinson's related postural tremor ("re-emergent tremor") is differentiated from essential tremor in that the appearance of tremor is often delayed after the patient assumes an outstretched horizontal position.<sup>34</sup> Because re-emergent tremor occurs at the same frequency as classical rest tremor and is responsive to dopaminergic therapy, it is likely that it represents a variant of the more typical rest tremor. There are several clues to the diagnosis of existent essential tremor when it coexists with PD, including longstanding history of action tremor, family history of tremor, head and voice tremor, and no latency when arms are outstretched in a horizontal position in front of the body, although some patients may also have a re-emergent tremor related to their PD, tremulous handwriting and spiral, and improvement of the tremor with alcohol and beta-blockers.

The occurrence of rest tremor is variable among patients and during the course of the disease. In one study, Hughes and colleagues<sup>36</sup> reported that 69% of patients with PD had rest tremor at disease onset and that 75% had tremor during the course of their disease. Tremor was lost in 9% of patients late in the disease. Others have reported that a small proportion of patients (11%) never have tremor,<sup>37</sup> although a prospective study in patients with autopsy proven disease found that 100% of patients had tremor at some point.<sup>38</sup> Clinical–pathological studies have demonstrated that patients with PD and prominent tremor have degeneration of a subgroup of midbrain (A8) neurons, whereas this area is spared in PD patients without tremor.

### Rigidity

Rigidity is characterised by increased resistance, usually accompanied by the "cogwheel" phenomenon, particularly when associated with an underlying tremor, present throughout

the range of passive movement of a limb (flexion, extension or rotation about a joint). It may occur proximally (eg, neck, shoulders, hips) and distally (eg, wrists, ankles). Reinforcing manoeuvres (eg, voluntary movements of the contralateral limb), known as the Froment's manoeuvre,<sup>39</sup> usually increase rigidity and are particularly useful in detecting mild cases of rigidity.

Rigidity may be associated with pain, and painful shoulder is one of the most frequent initial manifestations of PD although it is commonly misdiagnosed as arthritis, bursitis or rotator cuff injury.<sup>40–41</sup> A prospective study of 6038 persons (mean age 68.5 years) with no evidence of dementia or parkinsonism at baseline found that the presence of stiffness, tremor and imbalance were each associated with increased risk for PD (hazard ratios 2.11, 2.09 and 3.47, respectively).<sup>42</sup> Among this cohort, 56 new cases of PD were identified over a mean follow-up of 5.8 years.

### Postural deformities

In addition, rigidity of the neck and trunk (axial rigidity) may occur, resulting in abnormal axial postures (eg, anterocollis, scoliosis). Postural deformities resulting in flexed neck and trunk posture and flexed elbows and knees are often associated with rigidity. However, flexed posture generally occurs late in the disease. Striatal limb deformities (eg, striatal hand, striatal toe) may also develop in some patients. Striatal hand is characterised by ulnar deviation of the hands, flexion of the metacarpophalangeal joints and extension of the proximal and flexion of the distal interphalangeal joints (fig 1A); striatal foot is characterised by extension or flexion (fig 1B) of the toes.<sup>43–44</sup> In one study, striatal toe (extension of the big toe) was reported in 21% of patients with clinically diagnosed PD.<sup>45</sup> Patients with striatal deformities tend to be younger and to experience earlier onset of initial parkinsonian symptoms.<sup>44</sup>

Other skeletal abnormalities include extreme neck flexion ("dropped head" or "bent spine"), truncal flexion (camptocormia) and scoliosis.<sup>44–46–48</sup> Camptocormia is characterised by extreme flexion of the thoracolumbar spine. The condition is

exacerbated by walking and is relieved by sitting, lying in the supine position or by volitionally extending the trunk when the patient leans against a wall or a high walker or a table (fig 2A–C).<sup>48</sup> In addition to PD, other causes of camptocormia include dystonia and extensor truncal myopathy.<sup>49–50</sup> Another truncal deformity is the Pisa syndrome, which is characterised by a tilting of the trunk, particularly when sitting or standing.<sup>51</sup>

### Postural instability

Postural instability due to loss of postural reflexes is generally a manifestation of the late stages of PD and usually occurs after the onset of other clinical features. The pull test, in which the patient is quickly pulled backward or forward by the shoulders, is used to assess the degree of retropulsion or propulsion, respectively. Taking more than two steps backwards or the absence of any postural response indicates an abnormal postural response. Postural instability (along with freezing of gait) is the most common cause of falls and contributes significantly to the risk of hip fractures.<sup>52</sup> The long latency to the onset of falls differentiates PD from other neurodegenerative disorders, such as progressive supranuclear palsy (PSP) and multiple systems atrophy (MSA).<sup>53</sup> In one study, the average time from onset of symptoms to the first fall was 108 months in patients with PD compared with 16.8 and 42 months, respectively, in patients with PSP and MSA.<sup>52</sup>

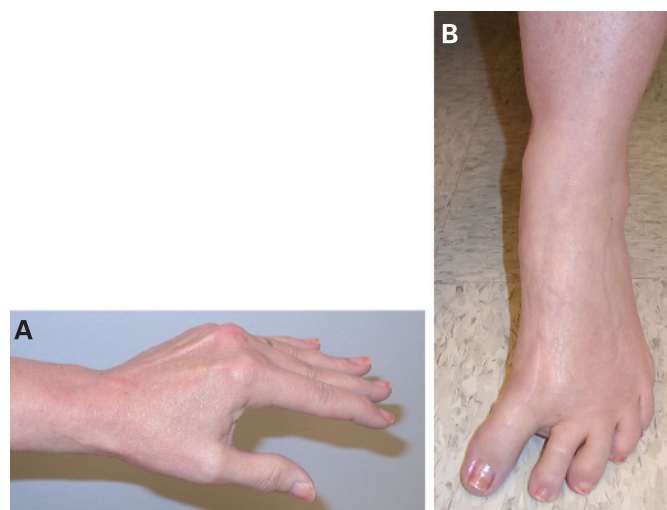
Several other factors also influence the occurrence of postural instability in patients with PD. These include other parkinsonian symptoms, orthostatic hypotension, age related sensory changes and the ability to integrate visual, vestibular and proprioceptive sensory input (kinesthesia).<sup>54–55</sup> The fear of falling can further impair balance control in patients with PD.<sup>56</sup> In one study, 38% of those evaluated experienced falls, and 13% fell more than once a week.<sup>57</sup> As expected, the frequency of falls correlated with the severity of disease.<sup>57</sup> Treatment (dopaminergic therapy, pallidotomy, deep brain stimulation) can improve some axial signs<sup>58</sup> but usually does not robustly improve postural instability, measured by platform tilt and visual tilt.<sup>59</sup> Targeting other nuclei for deep brain stimulation in addition to the subthalamic nucleus and globus pallidus, such as the zona incerta and pedunculopontine nucleus, is being

explored as a potential surgical treatment of gait difficulties and postural stability.<sup>60</sup>

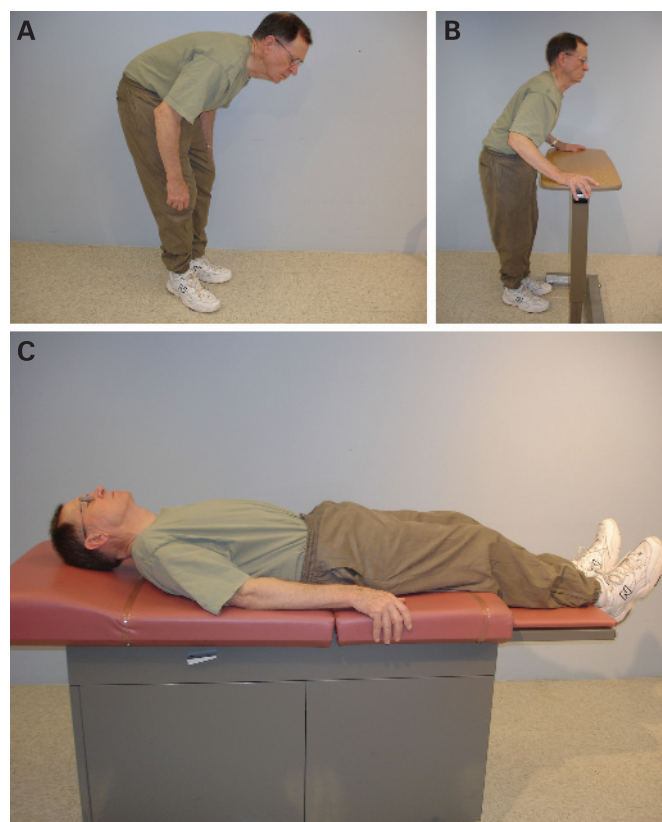
### Freezing

Freezing, also referred to as motor blocks, is a form of akinesia (loss of movement) and is one of the most disabling symptoms of PD.<sup>61</sup> Although freezing is a characteristic feature of PD, it does not occur universally.<sup>62</sup> Based on responses by 6620 patients to a questionnaire sent to 12 000 members of the German Parkinson Association, 47% of patients reported freezing; it occurs more frequently in men than in women and less frequently in patients whose main symptom is tremor.<sup>63</sup> Freezing most commonly affects the legs during walking, but the arms and eyelids can also be involved.<sup>64</sup> It typically manifests as a sudden and transient (usually <10 s) inability to move. This may include hesitation when beginning to walk (start hesitation) or a sudden inability to move the feet during specific situations (eg, turning or walking through a narrow passage, crossing busy streets, approaching a destination). Freezing is associated with substantial social and clinical consequences for patients. In particular, it is a common cause of falls.<sup>62</sup>

Five subtypes of freezing have been described: start hesitation, turn hesitation, hesitation in tight quarters, destination hesitation and open space hesitation.<sup>65</sup> Episodes are more severe in the OFF state and are mitigated by levodopa therapy. In addition, patients often develop tricks to overcome freezing attacks. This includes marching to command, stepping over



**Figure 1** Striatal hand (A) and foot (B) deformity in a patient with typical Parkinson's disease. Patient consent has been received to publish this figure.



**Figure 2** Camptocormia in a patient with Parkinson's disease manifested by flexion of the trunk (A) which the patient can correct by pushing himself into extension posture (B) or by lying in a supine position (C). Patient consent has been received to publish this figure.

objects (eg, a walking stick, cracks in the floor), walking to music or a beat, and shifting body weight.<sup>66-68</sup>

Risk factors for the development of freezing include the presence of rigidity, bradykinesia, postural instability and longer disease duration.<sup>61</sup> In contrast, tremor at disease onset is associated with a decreased risk of freezing. As freezing typically occurs later in the course of the disease or is not the predominant symptom, alternative diagnoses should be considered when these presentations occur. Freezing, particularly when it occurs during the ON period, does not usually respond to dopaminergic therapy, but patients treated with selegiline have been found to be at lower risk.<sup>69</sup> Botulinum toxin injections, although effective for a variety of parkinsonian symptoms such as tremors, dystonia and sialorrhoea, have not been found consistently effective in the treatment of freezing.<sup>70</sup>

### Other motor abnormalities

Patients with PD may exhibit a number of secondary motor symptoms that may impact on their functioning at home, at work and while driving.<sup>71</sup> Because of a breakdown of the frontal lobe inhibitory mechanisms, some patients display a re-emergence of primitive reflexes.<sup>72-73</sup> One study that included 41 patients with PD found that the primitive glabellar reflex was present in 80.5% of patients.<sup>74</sup> This symptom was a moderately sensitive (83.3%) indicator of a parkinsonian disorder but was not specific (47.5%) for PD. Patients with PD in this study also experienced an increased frequency (34.1%) of the palmomental reflex. This symptom was not sensitive (33.3%) but was more specific (90%) than the glabellar reflex. In addition, these primitive reflexes cannot differentiate among the three most common parkinsonian disorders (PD, PSP, MSA).<sup>74</sup> Similarly, the “applause sign”, initially thought to be specific for PSP, is frequently present in other parkinsonian disorders, particularly corticobasal degeneration.<sup>75</sup> In some cases, unintended movements accompany voluntary activity in homologous muscles on the opposite side of the body. These so-called mirror movements may be observed in early asymmetric PD.<sup>76</sup>

Bulbar dysfunction manifested by dysarthria, hypophonia, dysphagia and sialorrhoea, frequently observed in patients with PD, can be equally or even more disabling than the cardinal features. These symptoms are thought to be related to orofacial-laryngeal bradykinesia and rigidity.<sup>77</sup> Speech disorders in patients with PD are characterised by monotonous, soft and breathy speech with variable rate and frequent word finding difficulties, referred to as “tip-of-the-tongue phenomenon.”<sup>77-79</sup> Speech therapy, such as the Lee Silverman Voice Treatment,<sup>80</sup> that emphasises efforts to improve the volume and quality of the speech, may ameliorate the symptoms of dysarthria. Dysphagia is usually caused by an inability to initiate the swallowing reflex or by a prolongation of laryngeal or oesophageal movement. Dysphagia is often subclinical, particularly in the early course of the disease.<sup>81</sup> PD related drooling may result from a decrease in swallowing.<sup>25</sup>

A number of neuro-ophthalmological abnormalities may be seen in patients with PD. These include decreased blink rate, ocular surface irritation, altered tear film, visual hallucinations, blepharospasm and decreased convergence.<sup>82</sup> The degree of abnormality in ocular pursuit and saccades as well as antisaccades<sup>83</sup> is related to the degree of disease progression.<sup>84</sup> Dopaminergic therapy generally improves these changes, but one study found no difference in smooth ocular pursuit between ON and OFF periods in patients with PD.<sup>85</sup> Other neuro-ophthalmological abnormalities associated with PD

include apraxia of eyelid opening, limitation of upward gaze and oculogyric crises.<sup>86-87</sup>

Respiratory disturbances in patients with PD can be restrictive or obstructive.<sup>88</sup> These complications are associated with substantial morbidity and mortality; pneumonia is an independent predictor of mortality in nursing home patients with PD.<sup>89</sup> The obstructive pattern may be related to rigidity, cervical arthrosis or restricted range of motion in the neck, and the restrictive pattern may be related to chest wall rigidity.<sup>90</sup> Respiration may also be compromised by levodopa related respiratory dyskinesia in patients with PD.<sup>91</sup>

### Non-motor features

Non-motor symptoms are a common and under appreciated feature of PD.<sup>92</sup> These include autonomic dysfunction, cognitive/neurobehavioral disorders, and sensory and sleep abnormalities.

#### Autonomic dysfunction

Autonomic failure may be the presenting feature of PD, although it is more typically associated with MSA. Features include orthostatic hypotension, sweating dysfunction,<sup>93</sup> sphincter dysfunction and erectile dysfunction.<sup>94-95</sup> A community based study found that 47% (42/89) of PD patients met the diagnostic criteria for orthostatic hypotension.<sup>96</sup>

#### Cognitive and neurobehavioural abnormalities

Neuropsychiatric disturbances can be as disabling as motor symptoms. The Sydney Multicenter Study of PD found that 84% of patients evaluated showed cognitive decline and that 48% met the diagnostic criteria for dementia after 15 years of follow-up.<sup>97</sup> Another community based prospective study found that patients with PD are at almost sixfold increased risk for dementia.<sup>98</sup> PD related dementia is also associated with a number of other neuropsychiatric comorbidities. Among 537 such patients, depression (58%), apathy (54%), anxiety (49%) and hallucinations (44%) were frequently reported.<sup>99</sup> In a study of 114 patients with PD, 27.6% screened positive for depression during the average 14.6 months of follow-up; 40% were neither treated with antidepressants nor referred for further psychiatric evaluation.<sup>100</sup> In addition to cognitive and affective disorders, many patients with PD exhibit features of obsessive-compulsive and impulsive behaviour, such as craving (especially for sweets),<sup>101</sup> binge eating, compulsive foraging, hypersexuality, pathological gambling, compulsive shopping and punding, characterised by intense fascination with repetitive handling, examining, sorting and arranging of objects.<sup>102</sup> These behavioural symptoms, sometimes referred to as “hedonistic homeostatic dysregulation”, have been attributed to dopamine dysregulation syndrome associated with the use of dopaminergic drugs, particularly dopamine agonists, but the mechanism of these aberrant behaviours is not well understood.<sup>103</sup> Cognitive and behavioural dysfunction in PD is not well understood, and its discussion is beyond the scope of this article; the reader is referred to some recent reviews of this topic.<sup>104</sup>

#### Sleep disorders

Although sleep disturbances (eg, excessive sleepiness, sleep attacks) were once largely attributed to the pharmacological therapy for PD,<sup>105</sup> some clinicians now believe that these features are an integral part of the disease.<sup>106</sup> This is supported by the observation that rapid eye movement sleep behaviour disorder, which occurs in approximately one-third of patients

### Box 1 UK Parkinson's Disease Society Brain Bank's clinical criteria for the diagnosis of probable Parkinson's disease

#### Step 1

Bradykinesia

At least one of the following criteria:

Rigidity

4–6 Hz rest tremor

Postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction

#### Step 2

Exclude other causes of parkinsonism

#### Step 3

At least three of the following supportive (prospective) criteria:

Unilateral onset

Rest tremor

Progressive disorder

Persistent asymmetry primarily affecting side of onset

Excellent response (70–100%) to levodopa

Severe levodopa induced chorea (dyskinesia)

Levodopa response for 5 years or more

Clinical course of 10 years or more

with PD, is a substantial risk factor for the development of PD.<sup>107–110</sup> Rapid eye movement sleep behaviour disorder, now considered a pre-parkinsonian state, is characterised by an increase in violent dream content<sup>110</sup> accompanied by talking,

yelling, swearing, grabbing, punching, kicking, jumping and other dramatic, violent and potentially injurious motor activity which may also involve the bed partner. Insomnia, particularly sleep fragmentation, is also frequent (>50% prevalence), but the occurrence is highly variable among patients.<sup>111 112</sup> The sleep abnormalities observed in patients with PD may possibly be related to a 50% loss of hypocretin (orexin) neurons.<sup>113 114</sup> Although excessive daytime sleepiness may contribute to fatigue, this common symptom is also seen independently of sleepiness.<sup>115</sup>

#### Sensory abnormalities

Sensory symptoms such as olfactory dysfunction, pain, paresthesia, akathisia, oral pain and genital pain are frequent but are often not recognised as parkinsonian symptoms.<sup>41 116–121</sup> One study found that olfactory dysfunction (hyposmia) may be an early marker of PD; it correlated with a 10% increased risk for the disease 2 years later compared with other asymptomatic relatives.<sup>122</sup> A study involving 62 pairs of twins discordant for PD found that smell identification was reduced in twins affected with PD than in those who were asymptomatic.<sup>123</sup> It has been postulated that olfactory dysfunction is related to either neuronal loss in the corticomедial amygdala<sup>124</sup> or to decreased dopaminergic neurons in the olfactory bulb.

### ASSESSMENT OF PATIENTS WITH PD

#### Diagnostic criteria

PD is diagnosed on clinical criteria; there is no definitive test for diagnosis. Historically, pathological confirmation of the hallmark Lewy body on autopsy has been considered the criterion standard for diagnosis.<sup>125</sup> In clinical practice, diagnosis is

### Box 2 National Institute of Neurological Disorders and Stroke (NINDS) diagnostic criteria for Parkinson's disease (PD)<sup>128</sup>

#### Group A features (characteristic of PD)

Resting tremor

Bradykinesia

Rigidity

Asymmetric onset

#### Group B features (suggestive of alternative diagnoses)

Features unusual early in the clinical course

Prominent postural instability in the first 3 years after symptom onset

Freezing phenomenon in the first 3 years

Hallucinations unrelated to medications in the first 3 years

Dementia preceding motor symptoms or in the first year

Supranuclear gaze palsy (other than restriction of upward gaze) or slowing of vertical saccades

Severe, symptomatic dysautonomia unrelated to medications

Documentation of condition known to produce parkinsonism and plausibly connected to the patient's symptoms (such as suitably located focal brain lesions or neuroleptic use within the past 6 months)

#### Criteria for definite PD

All criteria for probable Parkinson's are met and

Histopathological confirmation of the diagnosis is obtained at autopsy

#### Criteria for probable PD

At least three of the four features in group A are present and

None of the features in group B is present (note: symptom duration  $\geq 3$  years is necessary to meet this requirement) and

Substantial and sustained response to levodopa or a dopamine agonist has been documented

#### Criteria for possible PD

At least two of the four features in group A are present; at least one of these is tremor or bradykinesia and

Either none of the features in group B is present or symptoms have been present  $\leq 3$  years and none of the features in group B is present and

Either substantial and sustained response to levodopa or a dopamine agonist has been documented or the patient has not had an adequate trial of levodopa or a dopamine agonist

typically based on the presence of a combination of cardinal motor features, associated and exclusionary symptoms, and response to levodopa.<sup>126</sup> Although the diagnosis of PD is straightforward when patients have a classical presentation, differentiating PD from other forms of parkinsonism can be challenging early in the course of the disease, when signs and symptoms overlap with other syndromes.<sup>127</sup>

Diagnostic criteria have been developed by the UK Parkinson's Disease Society Brain Bank (box 1) and the National Institute of Neurological Disorders and Stroke (NINDS) (box 2).<sup>128</sup>

However, the reliability and validity of these criteria have not been clearly established.<sup>129</sup> A study that included 100 patients who underwent biopsy after clinical diagnosis using the UK Parkinson's Disease Society Brain Bank criteria found that 76% of patients met the pathological criteria; when the diagnostic criteria were retrospectively applied, accuracy improved to 82%.<sup>130</sup> In a later study of the brains of patients examined by neurologists, diagnostic accuracy was considerably higher (91–92%).<sup>131</sup>

A study evaluating 800 patients from the DATATOP trial suggested that movement disorder specialists are skilful at diagnosing PD.<sup>132</sup> In this study, patients were followed-up from early pretreatment stages for a mean of 7.6 years. Based on autopsy data, imaging studies, response to levodopa and atypical clinical features, only 8.1% of patients did not meet the diagnostic criteria at the final diagnosis. Although this represents an improvement in diagnostic accuracy over earlier studies, it must be noted that not all diagnoses were confirmed on pathological examination.

Misdiagnosis of PD can arise for a number of reasons. In a community based study of patients taking antiparkinsonian medication (n = 402), the most common causes of misdiagnoses were essential tremor, Alzheimer's disease and vascular parkinsonism.<sup>127 133</sup> More than 25% of patients in this study did not respond to antiparkinsonian medication. In addition, many of the prominent features of PD (eg, rigidity, gait disturbance, bradykinesia) may also occur as a result of normal aging or from comorbid and multifactorial medical conditions (eg, diabetes, cancer).<sup>134 135</sup>

### Differential diagnosis

Parkinsonian disorders can be classified as four types: primary (idiopathic) parkinsonism, secondary (acquired, symptomatic) parkinsonism, hereditary parkinsonism and multiple system degeneration (parkinsonism plus syndromes). Several features, such as tremor, early gait abnormality (eg, freezing), postural instability, pyramidal tract findings and response to levodopa, can be used to differentiate PD from other parkinsonian disorders. Although differences in the density of post-synaptic dopamine receptors in patients with PD or other atypical parkinsonian disorders have been used to explain the poor response to levodopa therapy in the latter group, this may not be the only explanation. Recent positron emission tomography imaging studies have shown relative preservation of dopamine receptors in PSP,<sup>136</sup> suggesting downstream changes as a possible mechanism for the lack of response. Furthermore, patients with MSA often have excellent initial responses but frequently develop levodopa related orofacial dyskinesias and lose antiparkinsonian efficacy. Although improvement with levodopa is suggestive of PD, it does not definitively differentiate PD from other parkinsonian disorders.<sup>137</sup> One study found that only 77% of patients with pathologically proven PD had a "good" or "excellent" initial

response to levodopa.<sup>36</sup> Subcutaneous injection of apomorphine has been used to differentiate between PD and other parkinsonian disorders; however, this test is not superior to levodopa therapy and contributes little to diagnostic evaluation.<sup>138</sup>

Neuroimaging techniques may also be useful for differentiating PD from other parkinsonian disorders.<sup>139</sup> Potential imaging studies include high field strength (1.5 T) heavily T<sub>2</sub> weighted MRI,<sup>139</sup> [<sup>18</sup>F]-fluorodopa positron emission tomography,<sup>139</sup> [<sup>11</sup>C]-raclopride imaging of dopamine D<sub>2</sub> receptors<sup>140</sup> and single photon emission computed tomography of striatal dopamine reuptake sites.<sup>141</sup> One study suggested that brain parenchyma sonography may be highly specific for differentiating between PD and atypical parkinsonism<sup>142</sup>; however, it also showed abnormal hyperchogenicity not only in PD but in essential tremor.<sup>143</sup> Although these neuroimaging techniques are promising, further refinement in resolution and improvement in sensitivity are needed before their diagnostic potential is fully realised.

### CONCLUSIONS

PD is a progressive neurodegenerative disorder manifested by a broad spectrum of motor and non-motor features. The natural progression of PD is variable but is usually more rapid in patients with late onset and with the PIGD form of PD. In a comprehensive review of the literature, the standardised mortality ratio has been reported to range between 1 and 3.4.<sup>144</sup> Because there are no definitive diagnostic tests for it, clinicians require thorough knowledge of the clinical manifestations of PD to aid them in differentiating it from related disorders. Future research may uncover disease specific biomarkers allowing for its differentiation from other neurodegenerative disorders. Not only will such testing be useful for diagnosing the disease in affected persons, it will be useful for identifying family members or populations at risk, thus providing an opportunity to initiate neuroprotective therapy at an asymptomatic stage.

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