

REVIEW

The clinical symptoms of Parkinson's disease

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In this review, the clinical features of Parkinson's disease, both motor and non-motor, are described in the context of the progression of the disease. Also briefly discussed are the major treatment strategies and their complications.

Keywords: clinical symptoms, dopamine, Parkinson's disease, therapy.

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Parkinson's disease (PD) is a progressive multi-system neurodegenerative disease affecting people mainly in later years of life. It is the second most common neurodegenerative disease worldwide with incidence and prevalence on the rise along with changing population demographics (Pringsheim *et al.* 2014). The prevalence of PD in industrialised countries is generally estimated at 0.3% of the entire population and about 1% in people over 60 years of age (De Lau and Breteler 2006). The prevalence increases with advancing age both for men and women with no decreases at higher ages (De Rijk *et al.* 1997). In Europe, the prevalence at ages 85–89 has been reported as 3.5% (Clarke and Moore 2007).

The disease has distinctive neuropathological brain changes. There is formation of abnormal proteinaceous spherical bodies called Lewy bodies (Fig. 1), and a spindle- or thread-like and, in part, branching Lewy neurites in the somata of the involved nerve cells, beginning at defined induction sites and advancing in a topographically predictable sequence within the nervous system (Braak *et al.* 2004). Braak *et al.* (2003) have mapped PD into six neuropathological disease stages. In the pre-symptomatic stages of the disease (stages 1–2), the inclusion bodies are confined to the medulla oblongata/pontine tegmentum and olfactory bulb/anterior olfactory nucleus. With progression of the disease, substantia nigra and other nuclei of the midbrain and forebrain become affected (stages 3–4). It has been suggested that patients develop clinical symptoms of the disease at this stage. In the end stage (stage 5–6), the process enters the neocortex with a wide variety of clinical manifestations (Braak *et al.* 2004). The degeneration of dopaminergic nigrostriatal neurons with Lewy bodies is regarded as the primary neuropathological correlate of motor

impairment in Parkinson's disease, but glutamatergic, cholinergic, GABA-ergic, tryptaminergic, noradrenergic and adrenergic nerve cells may show similar damage in their cytoskeleton (Braak and Braak 2000). The clinical symptoms of PD are usually defined by the motor disturbances, but there may be disturbances in several other functions of the nervous system. The symptoms are generally categorized into motor and non-motor symptoms, and some of the symptoms may be provoked or aggravated by the dopaminergic treatment (see below).

Treatment of Parkinson's disease

The aetiology of PD is probably multifactorial and there is no available treatment that will halt or stop progression of the disease. Treatment with dopaminergic drugs is symptomatic and aims at correcting the motor disturbances. Levodopa, a prodrug to dopamine, is standard and the most common initial therapy for patients. Early on, response is usually good. With disease progression and less capacity of the system to store dopamine, the majority of patients experience shorter duration of response to individual doses (wearing-off symptoms), alternative phases with good and poor response to medication (on-off symptoms), involuntary movements of the head, trunk or limbs (dyskinesias) and other motor complications. Other dopaminergic medications are used to manage these fluctuations. They include monoamine oxidase

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Abbreviation used: PD, Parkinson's disease.

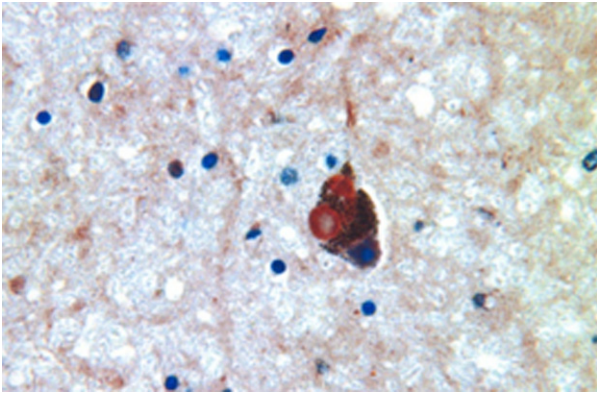


Fig. 1 Lewy bodies in a degenerating neuron. Synuclein staining. Blondal and Sveinbjornsdottir, unpublished.

type B inhibitors, catechol-*O*-methyltransferase inhibitors, the NMDA receptor antagonist amantadine and dopamine receptor agonists (Jankovic and Stacy 2007). Surgical therapy, usually with deep brain electrical stimulation, is available for a selected proportion of patients when medical therapy fails to control the motor symptoms.

The motor symptoms of Parkinson's disease

It is estimated that up to 80% of dopaminergic cells in the nigro-striatal system are lost before the cardinal motor features of PD start to appear (Chung *et al.* 2001). The disease is usually diagnosed by the first motor symptoms. The diagnosis is based on defined criteria from the UK PD Brain bank (Table 1, Hughes *et al.* 1992). Slowness of initiation of voluntary movements with progressive reduction in speed and amplitude of repetitive actions (bradykinesia) with one additional symptom, i.e., muscular rigidity, resting tremor or postural instability, are a prerequisite for the diagnosis (Hughes *et al.* 1992). Step 2 in the diagnosis is to exclude symptoms that might indicate other aetiologies such as parkinsonian syndromes that have their own neuropathological changes, and Step 3 to ascertain at least three supportive criteria for PD, such as unilateral onset of symptoms, persistent asymmetry of clinical symptoms, good response to levodopa treatment and induction of dyskinesias by the dopaminergic treatment. In most cases, symptoms start in one side of the body with contralateral symptoms appearing within a few years. The body posture becomes stooped, there is axial and limb rigidity with or without cogwheel phenomenon, tendency for a shuffling gait and lack of arm swing while walking. The bradykinesia may lead to expressionless face (hypomimia) and the amplitudes of hand writing become smaller (micrographia). Around 80% have limb tremor, most commonly a resting pill-rolling type of tremor of the hands. Pill rolling relates to the tendency of the thumb and the index finger to get into contact and perform a

Table 1 UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria

Step 1: Diagnosis of Parkinsonian syndrome
Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive action)
And at least one of the following
Muscular rigidity
4–6 Hz rest tremor
Postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction
Step 2: Exclusion criteria for Parkinson's disease
History of repeated strokes with stepwise progression of parkinsonian features
History of repeated head injury
History of definite encephalitis
Oculogyric crises
Neuroleptic treatment at onset of symptoms
More than one affected relative
Sustained remission
Strictly unilateral features after 3 years
Supra-nuclear gaze palsy
Cerebellar signs
Early severe autonomic involvement
Early severe dementia with disturbances of memory, language and praxis
Babinski sign
Presence of cerebral tumour or communicating hydrocephalus on CT scan
Negative response to large doses of levodopa (if malabsorption excluded)
MPTP exposure
Step 3: supportive prospective positive criteria for Parkinson's disease (three or more required for diagnosis of definite Parkinson's disease)
Unilateral onset
Rest tremor present
Progressive disorder
Persistent asymmetry affecting side of onset more
Excellent response (70–100%) to levodopa
Severe levodopa-induced chorea
Levodopa response for 5 years or more
Clinical course of 10 years or more

Source: Hughes *et al.* (1992).

circular movement (Jankovic 2008). Occasionally, the tremor involves the legs and other tremor types may occur (Reichmann 2010). Other gait disturbances than shuffling include blocking, hesitancy and gait festination where steps become progressively smaller and more rapid which may lead to loss of balance and falls. A quarter to 60% of patients experience freezing of movements usually after several years from onset (Virmani *et al.* 2015).

Postural stability may be affected either early or later in the disease process and this may lead to falls and injuries. Early falls are atypical for those who are younger at onset but age is an independent risk factor for falls in PD (Williams *et al.*

2006) and, in the elderly, the disease is sometimes first diagnosed in hospitals after a fall. A study by Wood *et al.* (2002) showed that falls occurred in 68% of 109 patients with PD with a mean age of 75 years and mean disease duration of 3 years. Another study reported falls in 62% of patients with PD (Stolze *et al.* 2004). Predictors of falls other than older age include duration of disease, dementia, symmetrical onset, postural and autonomic instability (Wood *et al.* 2002; Williams *et al.* 2006).

Oral motor disorders are common. Speech disturbances such as very quiet and hurried speech occur in more than half of the patients (Perez-Lloret *et al.* 2012), swallowing problems have been reported in 40–80% (Kalf *et al.* 2011) and a quarter of the patients report dribbling of saliva (Kalf *et al.* 2012).

Dystonia is another motor symptom in PD. Dystonia describes a sustained muscular contraction frequently accompanied by abnormal movements, postures or both. This may rarely be a prediagnostic symptom in PD (Tolosa and Compta 2006), but dystonic symptoms are mostly related to treatment, both medical and surgical (Jankovic and Tintner 2001). The typical prediagnostic dystonias include unilateral equinovarus foot position, upper arm–forearm or forearm–hand flexion, writer's cramp, oro-mandibular dystonia, torticollis or different combinations of these symptoms (Tolosa and Compta 2006). In the majority of cases, the PD symptoms appear within 10 years from onset of the dystonia. In young onset familial PD, dystonia typically involves the foot with cramp-like discomfort or inversion of the affected foot (Tolosa and Compta 2006).

In medically treated PD, dystonia, along with dyskinesias, constitutes one of the main motor complications related to chronic therapy, usually occurring as an off-period phenomenon, but can present as peak dose dystonia or diphasic dystonia (Tolosa and Compta 2006). In reports by Poewe and colleagues, the most frequent site for off dystonia is the foot, whereas in peak dose dystonia neck and face are more commonly involved (Poewe and Lees 1987; Poewe *et al.* 1988).

Postural deformities are a frequent complication of Parkinson's disease. These deformities include abnormally flexed body posture with flexion originating in the thoracic or lumbar spine (camptocormia), forward flexion of the head and neck (antecollis) and scoliosis of the spine, i.e., a lateral curve of the spine usually combined with rotation of the vertebrae (Doherty *et al.* 2011). The pathophysiology of these deformities may be multifactorial and probably includes rigidity, axial dystonia, myopathy and centrally impaired proprioception.

The non-motor symptoms of Parkinson's disease

Before motor symptoms appear and the diagnosis is made, patients may have a variety of pre-motor symptoms. These

may start as early as 10 or more years before the diagnosis (Schrag *et al.* 2015) and presentation with non-motor symptoms may delay the diagnosis (O'Sullivan *et al.* 2008). One study of 109 recently diagnosed patients who had not yet started treatment showed that symptoms such as a lack of emotional involvement and interest (apathy), excessive daytime sleepiness, sleep problems and constipation may occur in up to 60–70% of patients prior to the diagnosis and these symptoms were more common than in normal controls. Other pre-motor symptoms included inability to experience pleasure from activities usually found enjoyable (anhedonia) memory complaints, loss of smell and taste, mood disturbances, excessive sweating, fatigue and pain. Constipation, dream-enacting behaviour (REM behaviour sleep disorder), frequent nightmares, daytime drowsiness and postprandial fullness were often reported to occur more than 10 years before onset of motor symptoms (Pont-Sunyer *et al.* 2015). Depression and anxiety may also occur long before the diagnosis is made (Chen *et al.* 2013). The pre-motor symptoms vary from patient to patient, but they continue while other motor or non-motor symptoms of PD may appear in the clinical course. With advancing disease, the non-motor symptoms generally become more troublesome for the patients than the motor symptoms.

The non-motor symptoms are categorized here into disturbances in autonomic function, sleep disturbances, cognitive and psychiatric disturbances and sensory symptoms.

Disturbances in autonomic function

Autonomic dysfunction may present prior to the diagnosis or become apparent with disease progression or be induced by medication (Koike and Takahashi 1997). All areas of autonomic function may be affected and this has been reported to affect daily life of over 50% of patients (Jost 2003). The autonomic dysfunction is considered because of involvement of both the central and peripheral postganglionic autonomic nervous system (Jost 2003). Orthostatic hypotension affects 30–40% of patients. This is defined as a fall in systolic blood pressure of > 20 mm Hg or in diastolic blood pressure > 10 mm Hg on either standing or head-up tilt to at least 60 degrees within 3 min (Lahrmann *et al.* 2006). On assuming the upright posture, hypotension-induced hypoperfusion of the brain can result in dizziness, visual disturbances and impaired cognition that may precede loss of consciousness. In PD, the blood pressure drop may last several minutes (Jost 2003). Duration of PD may be unrelated to the occurrence of orthostatic hypotension (Jost and Augustis 2015). In elderly PD patients, this may mainly occur after food intake (Iodice *et al.* 2011).

Gastrointestinal symptoms are common. There is slowing of mobility of the gastrointestinal tract with symptoms such as postprandial fullness and gastric retention, but slow-transit

constipation is by far the most common, occurring in 70–80% (Jost and Eckardt 2003; Jost 2010). Patients may also experience difficulties in rectal evacuation because of rectal sphincter dysfunction (Mathers *et al.* 1989).

Urinary control disturbances include urinary frequency, urgency and incontinence (Jost 2003). Frequent nocturia is reported by 60% of patients and is caused by detrusor overactivity (Yeo *et al.* 2012). Erectile dysfunction is common in males (Sakakibara *et al.* 2011).

There may also be autonomic dermatological symptoms such as excessive sweating (hyperhidrosis). This may be associated with dyskinesias or low blood concentrations of the dopaminergic drugs but does not appear to correlate with duration of the disease (Hirayama 2006). Salivary secretion appears to be reduced in PD despite frequent problem with dribbling of saliva in advanced disease (Cersosimo *et al.* 2009). Seborrhoeic keratosis is a dermatological facial and scalp disorder that has been reported in 18.6% of patients (Fischer *et al.* 2001). There is increased fat in the central face often associated with scaling of the skin of the forehead. The cause of this is unclear.

Sleep disturbances

The neuropathology of PD is known to affect anatomical structures and central neurotransmitters that are involved in the modulation of the physiological sleep cycle. Polysomnographic findings have shown changes in the architecture of sleep waves compared with healthy controls, but the medical treatment for different symptoms related to PD may also disrupt night-time sleep (Larsen and Tandberg 2001; Monderer and Thorpy 2009). A variety of sleep disorders may appear with approximately two third of patients affected (Mehta *et al.* 2008).

Fractionated sleep is most common (Porter *et al.* 2008). Sleep studies have shown that patients have more shallow sleep and tendency to frequent awakenings in the night (Yong *et al.* 2011). Other PD symptoms such as difficulties with turning around in bed, frequent nocturia, nocturnal tremor and depression may also lead to fractionated sleep (Lees *et al.* 1988).

Excessive daytime sleepiness has been estimated to occur in up to 50% (Monderer and Thorpy 2009) and may be partly induced by the dopaminergic drugs (Knie *et al.* 2011). Sleep syndromes are also more common in PD than in controls. They include REM behaviour sleep disorder where patients act out their dreams, thrash and kick around in the night while dreaming. The frequency in clinically manifested PD has been reported as 27–32% (Monderer and Thorpy 2009), but symptoms may appear years or decades before the motor symptoms appear (Hickey *et al.* 2007). The syndrome of restless legs with or without periodic leg movements of sleep is more common among patients than controls (Monderer and Thorpy 2008). Restless legs syndrome is an urge to

move the legs while sitting or lying down that is relieved by walking about, while periodic leg movements of sleep consist of rhythmic jerking of lower limbs during sleep, usually observed by the partner.

Although obstructive sleep apnoea, where breathing stops intermittently during sleep, is well known in PD (Monderer and Thorpy 2008), not all studies have shown increased prevalence among patients (Zeng *et al.* 2013). Sudden sleep attacks occurring without normal drowsiness as induction to sleep have been reported in patients on dopaminergic treatment. It seems that nearly all available dopaminergic drugs may induce sleep attacks (Larsen and Tandberg 2001) and the dopaminergic treatment load may be implicated (Brotsky *et al.* 2003).

Neuropsychiatric symptoms and dementia

Visual hallucinations and illusions are common in PD and reportedly occur in a third to 40% of patients (Onofrij *et al.* 2007). Although virtually all anti-parkinsonian medications have been reported to induce hallucinations and psychosis, visual hallucinations have also been reported to occur prior to drug treatment (Pagonabarraga *et al.* 2016). Neuropathological changes in the amygdala and hippocampus caused by the disease process seem to be implicated in the aetiology (Williams-Gray *et al.* 2006). Frequently, images of people, small animals or objects are conceived or the hallucinations may have multiple content. The images may be familiar or not. They last from seconds to minutes, and may recur over the day (Holroyd *et al.* 2001). Usually, non-demented patients retain insight and the hallucinations are usually not threatening. Less commonly, the hallucinations are olfactory (McAuley and Gregory 2012), auditory (Inzelberg *et al.* 1998) and tactile (Fenelon *et al.* 2002). One study showed that visual component was lacking in 10% of cases (Papapetropoulos and Heather Katzen 2008). Minor visual phenomena such as sense of presence and visual illusions affect 17–72% of patients and delusions about 5% (Fenelon and Alves 2010). Higher load of dopaminergic treatment may be related to the hallucinations, but disease severity, cognitive impairment, depression, older age and worse visual acuity may also be important (Holroyd *et al.* 2001; Fenelon and Alves 2010).

With advancing disease patients may develop paranoid illusions often with persecutory ideas or suspicions towards the spouse (Williams-Gray *et al.* 2006). If psychosis occurs it is usually late in the disease process in patients on high doses of drugs or may be associated with old age, cognitive impairment and history of depression (Thanvi *et al.* 2005).

The dopaminergic treatment may also induce behavioural abnormalities such as euphoria/hypomania, poor organisational skills, hypersexuality, abnormal hoarding or punting and risk taking behaviour (O'Sullivan *et al.* 2009). Risk taking behaviour may be reflected in gambling, driving at speed or excessive spending. These symptoms that together

have been called dopamine dysregulation syndrome or impulse control disorders are increasingly recognized (Evans and Lees 2004). They appear to be related to the dopaminergic treatment load and possibly more to dopamine receptor agonist drugs than others (O'Sullivan *et al.* 2009; Ceravolo *et al.* 2010). Dopamine dysregulation syndrome is most common in men with relatively young onset disease (Ceravolo *et al.* 2010).

Cognitive deterioration and dementia is common in PD and may occur early or late (Williams-Gray *et al.* 2006, 2007). The earliest symptoms include problems with executive function, i.e., planning and organizing goal-directed behaviour, but visuospatial dysfunction, impaired speech fluency and memory impairment are also observed (Williams-Gray *et al.* 2006). Progression of the dementia shows a correlation with spread of the neuropathological changes to cortical brain structures (Irwin *et al.* 2012). Mild cognitive impairment has been reported to be twice as common in PD as in people not affected by the disease (Aarsland *et al.* 2009). Age itself rather than age at onset of PD has been associated with incident dementia in PD (Aarsland *et al.* 2007) and disease severity has been reported as the strongest predictor of dementia risk (Riedel *et al.* 2008). A 6-year longitudinal study of 141 PD patient with average disease duration of 5 years and a mean age of 69 years showed a cumulative risk of dementia increasing from 8.5% at 1 year to nearly 50% by year 6 (Pigott *et al.* 2015).

Depression and anxiety are other common symptoms in PD. A meta-analysis reported that one third of patients have clinically significant depression, while a major depressive disorder was reported in 17% (Reijnders *et al.* 2008). Depression and anxiety may relate to several factors, including advancing disease severity (Schrag *et al.* 2001). Anxiety and depression may disappear with dopaminergic treatment, but may be persistent or recur in the long clinical course of the disease.

Sensory symptoms

Sensory symptoms are common in PD. Reduced or lost sense of smell is found in at least 80% of patients and this often appears long before the motor symptoms (Doty *et al.* 1988). Vague abnormal sensations in body parts may be perceived and these sensations may fluctuate in relation to treatment (Bayulkemand and Lopez 2011). Pain is reported by 40–85% of patients (Broen *et al.* 2012). Limb pain may be the presenting symptom and misdiagnosed as a frozen shoulder or degenerative spine disease (Williams and Lees 2009). Limb pain is most common, but oral, thoracic, abdominal and genital pain may also occur (Waseem and Gwinn-Hardy 2001). Five different types of pain have been defined, i.e., musculoskeletal, radicular–neuropathic, dystonic, central neuropathic pain and pain-associated restlessness (akathisia) (Ford 2010).

Musculoskeletal pain is reported by almost half of the patients, but such pain is common in this age group and may not always be related to the PD. Dystonic, radicular and central neuropathic pain are less common (Broen *et al.* 2012).

The clinical course of PD

There is a great variability between patients in progression of symptoms (Poewe 2006). Early in the course of the disease, symptoms are usually unilateral and mild and the response to treatment is fair or excellent with no variability in motor function over the day. Although symptoms progress and motor symptoms appear in the contralateral side, drug response is usually reliable and patients are functioning well. This is often called the honeymoon period. With progression of the disease, treatment becomes heavier and drug response less reliable and the anti-parkinsonian drugs induce potentially disabling dyskinesias. Gait and balance disturbances and speech and swallowing difficulties may appear that are poorly responding to treatment. After prolonged disease duration of 10 or more years, a majority of patients will also have developed some non-motor symptoms for which there are currently limited available treatments. These include cognitive dysfunction, dementia and psychosis, autonomic failure, sleep–wake cycle dysregulation, depression, pain and sensory symptoms (Poewe 2006). The disease increasingly affects the quality of life and leads to dependency regarding activities of daily living. Patients with PD have greater and earlier need for nursing home placements (Parashos *et al.* 2002), higher rates of emergency hospital admissions, longer admissions and higher in-hospital mortality than comparable general population (Low *et al.* 2015). Relative risk of death compared with matched control populations has been reported 1.6–3.0 (Clarke and Moore 2007). Different studies show that the mean duration until death ranges from 6.9 to 14.3 years with increased age and the presence of dementia as the highest predictors of increased mortality (Macleod *et al.* 2014).

Final comments

The clinical treatment of PD with levodopa in the 1960s revolutionized the treatment of the motor complications of the disease. This revolution was portrayed in the film *Awakenings*. However, as I review, PD is a much more complex disease than just the motor manifestations. It remains a debilitating disorder for which no effective disease modification therapies have yet been identified.

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The authors have no conflict of interest to declare.

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