

Parkinson's Disease: An update on Pathophysiology, Epidemiology, Diagnosis and Management

Part 3 : Diagnosis , Symptoms, and Prognosis of Parkinson's Disease

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Abstract

Parkinson disease is a clinical diagnosis. For the condition, there are no laboratory biomarkers, and findings on routine magnetic resonance imaging and computed tomography scans are unremarkable. Medical diagnosis involves 2 of 3 cardinal signs: Resting tremor Bradykinesia and Rigidity. Parkinson's disease often has a multitude of non-motor symptoms; some may precede the diagnosis, while others may occur early or late after the diagnosis is made, depending on motor features. Careful attention to the history is needed in patients with Parkinsonism to exclude secondary causes such as medication, toxins, or trauma. Medicines that block receptors of striatal dopamine, such as metoclopramide and neuroleptics, can cause drug-induced parkinsonism. Parkinsonism can also be caused by other chemicals, such as MPTP (1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine) and manganese (at high exposure). Practical laboratory testing for PD is not available; the diagnosis is based on the clinical characteristics or excluding other causes of parkinsonism. However there are some promising developments in radiology.

Key words: Parkinson's disease, pathophysiology, epidemiology, management, diagnosis, symptoms, prognosis

Introduction

Parkinson's disease diagnosis tends to be focused on having signs and symptoms present. Tremor is the most apparent clinical symptom and mostly begins at one end and gets worse with precipitating factors like stress, exhaustion and cold weather. It may be confused with the more common essential tremor, but it can be distinguished by noting whether the tremor occurs mainly in rest (Parkinson's disease) or with motion (essential tremor). Essential tremor normally occurs in both limbs, while Parkinson's disease patients generally have a one-sided tremor that can affect one arm or leg. Bradykinesia is usually the symptom with the most trouble.

Patients report slowness in carrying out their daily living activities, including dressing, walking and doing household chores. Writing may become micrographic, with the size of a character increasingly smaller as the author continues to write. It is beneficial to watch a patient get up from a chair and walk. Parkinson's disease patients can need to force themselves up, take longer to get up or fall backwards. Very early features of the disease may be reduced arm swing, flexed posture and a shuffling gait. Muscle rigidity on passive movement is typical of Parkinson's disease but must be differentiated from the rigidity arising from, for example, upper motor neuron lesions in patients with a stroke.

In Parkinson's disease, passive joint movement reveals continuous resistance throughout the whole range of motion, the rigidity of the so-called "lead pipe." With upper motor neuron lesions the muscles, after an initial period of rigidity and resistance to movement, suddenly relax or give way, the so-called "clasp-knife" rigidity. Additionally, patients with Parkinson's disease may show a cogwheel type of rigidity. Here the muscles, on passive movement, have a ratchet-like feel. If rigidity and cogwheeling are not present when the patient is relaxed, the signs may be brought on by having the patient open and close their contralateral hand during the examination (Table 1).

Diagnostic Considerations

Parkinson's disease, and essential tremor, are the most common tremor disorders. If a patient is shaking, the clinician should pay careful attention to the areas of the body involved, the positions / conditions in which the tremor occurs (i.e., rest, postural, kinetic, intention), and the magnitude of the tremor. Looking for possible related signals, too, is important. For symptoms of parkinsonism (bradykinesia, weakness, postural instability), dystonia, and other neurological signs, the patient should be checked.

An upper extremity tremor of 8-12 Hz (postural/kinetic) which is temporarily relieved by drinking alcohol is typical of essential tremor, while the occurrence of pill-rolling rest tremor, bradykinesia, and rigidity is consistent with Parkinson's disease and argues against essential tremor. Careful attention to the history is needed in patients with parkinsonism to exclude secondary causes such

as medication, toxins, or trauma. Medicines that block receptors of striatal dopamine, such as metoclopramide and neuroleptics, can cause parkinsonism caused by the medication. Parkinsonism can also be caused by other chemicals, such as MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) and manganese (at high exposure).

Consider assessing osteoporosis and osteopenia in patients with parkinsonism. In a meta-analysis of 23 studies, Tornsey and colleagues found evidence that individuals with Parkinson's disease have an increased risk of osteoporosis and osteopenia (2014). For example, a pooled analysis of 2 of the studies indicated that the odds ratio for developing osteoporosis in patients with Parkinson's disease was 2.61 compared to healthy controls, although the increase was lower in men than in women. Review of 14 studies showed that bone mineral densities were significantly lower in patients with Parkinson's disease in the hip, lumbar spine, and femoral back, although researchers concluded that bone fracture risk was doubled in Parkinson's patients after an analysis of 9 studies (Tornsey et al, 2014).

Early clinical findings indicating an atypical parkinsonism instead of Parkinson's disease include the following (Suchowersky et al., 2006):

- Falls at presentation or early in the disease.
- Poor response to levodopa
- Symmetry at disease onset
- Rapid disease progression
- No tremor
- Dysautonomia (e.g. urinary incontinence, fecal incontinence, catheterization for urinary retention, persistent erectile failure, prominent symptomatic orthostatic hypotension)

The atypical parkinsonisms are usually associated with little or no tremor, difficulty in speaking and balance relatively early, and little or no response to dopaminergic drugs. Multiple system atrophy (MSA) is relatively symmetric and characterized by parkinsonism, often with some combination of autonomic, corticospinal, and cerebellar dysfunction. Progressive supranuclear paralysis (PSP) is relatively symmetrical and characterized by early-fallen parkinsonism (often in the first year) and a supranuclear gaze palsy in which the patient has difficulty with voluntary down-gaze. Corticobasal ganglionic degeneration (CBD) is generally very asymmetric and has both cortical (difficulty recognizing items, apraxia) and basal ganglionic (usually marked stiffness in an arm) characteristics.

Lewy body disorder is characterized by severe cognitive impairment within 1 year of the parkinsonism onset. Hallucinations are common. Patients with an onset of parkinsonism before age 40 should be tested for Wilson disease, starting with serum ceruloplasmin measurement and Kayser-Fleischer rings ophthalmological assessment.

The differential Diagnoses include the following

Alzheimer Disease
 Cardioembolic Stroke
 Chorea in Adults
 Cortical Basal Ganglionic Degeneration Dementia with
 Lewy Bodies Dopamine-Responsive Dystonia Essential
 Tremor
 Pantothenate Kinase-Associated Neurodegeneration
 (PKAN) Huntington Disease
 Lacunar Syndrome
 Multiple System Atrophy
 Neuroacanthocytosis
 Neurological Manifestations of Vascular Dementia Normal
 Pressure Hydrocephalus Olivopontocerebellar Atrophy
 Parkinson-Plus Syndromes Progressive Supranuclear
 Palsy Striatonigral Degeneration

Available Investigations that Help with Diagnosis

Practical laboratory testing for PD are not available; the diagnosis is based on the clinical characteristics or excluding other causes of parkinsonism. However there are some promising developments in radiology.

Examination

A focused examination to assess whether a patient has symptoms and signs that may suggest other forms of parkinsonism than Parkinson's disease (Table 1) should be performed. To rule out progressive supranuclear paralysis, it is important to evaluate changes in vertical eye movement. To rule out multiple system atrophy,

postural blood pressure changes, other autonomic abnormalities including a history of bladder instability, and cerebellar features such as early gait instability should be evaluated. Although falls and swallowing problems are consistent with late Parkinson's disease, they may be suggestive of progressive supranuclear palsy or multiple system atrophy if they occur early and are accompanied by a lack of treatment response. Early dementia and other characteristics may suggest dementia to the Lewy body, corticobasal degeneration or parkinsonism to the vascular. Patients with early onset parkinsonism (aged < 40 years) should always be assessed for Wilson's disease with serum copper and ceruloplasm level measurement, 24-hour copper excretion urine collection, and Kayser–Fleischer ring slit-lamp examination,

Imaging

While PD is a clinical condition, imaging can help in diagnosing differentials. Magnetic Resonance Imaging (MRI) is not useful for diagnosing PD; its usefulness depends on excluding ischemic, inflammatory, neoplastic and infectious causes or other forms of parkinsonism.

Typical findings of MRI in atypical parkinsonism include 'hot cross bun sign' in MSA, 'hummingbird sign' and 'morning glory sign' in PSP, front-temporal atrophy in FTD and asymmetric cortical atrophy in CBD; fluorodeoxyglucose positron emission tomography (FDG-PET) may reveal hypo-metabolism in the same areas of CBD and FTD atrophy (Deutschländer et al., 2017).

Recommendations for Imaging in the Diagnosis of Parkinson Disease

<i>Imaging modality</i>	<i>American Academy of Neurology</i>	<i>National Institute for Health and Clinical Excellence</i>	<i>Scottish Intercollegiate Guidelines Network</i>
Fludeoxyglucose positron emission tomography	Evidence insufficient to make recommendation	Use only in research settings	Not recommended
Magnetic resonance imaging	Possibly useful to distinguish Parkinson disease from multisystem atrophy	Not recommended for diagnosis of Parkinson disease Consider for diagnosis of parkinsonian syndromes	Not recommended for routine diagnosis of idiopathic Parkinson disease
Single-photon emission computed tomography	Possibly useful to distinguish Parkinson disease from essential tremor	Distinguish Parkinson disease from essential tremor	Distinguish Parkinson disease from nondegenerative parkinsonism or other tremor disorders
Ultrasonography	Evidence insufficient to make recommendation	No recommendation	Not recommended

Advances in neuroimaging research including transcranial Doppler ultrasonography (Alonso-Cánovas et al., 2014), positron emission tomography (PET), single-photon computed tomography (SPECT), morphometric MRI tests, tractography, functional MRI and perfusion imaging are used to distinguish Parkinson's idiopathic disease from other parkinsonian disorders (Stoessl et al., 2011).

Radionuclide imaging modalities such as PET and SPECT have become the best approach for assessing the metabolism and deficiency of dopamine, using a dopamine transporter ligand. Tracer absorption in the posterior or dorsal striatum is limited, which is asymmetric in Parkinson's disease (Stoessl et al. 2011. Stoessl et al. 2014).

No evidence of dopaminergic deficit on dopamine transporter SPECT and fluorine-18 fluoro-L- dopa PET imaging scans will be available to a subgroup of patients suspected of having new-onset Parkinson's disease (Marek et al., 2014). Disease development, through imaging or clinical tests, is low in this group of patients, as is their risk of developing idiopathic Parkinson's disease (Marek et al., 2014). However, a few may eventually be diagnosed with Parkinson's disease, based on clinical progression, imagery and genetic evidence and a positive response to levodopa (Erro et al., 2016).

Ultrasounds may detect abnormal SN hyperechogenicity in patients with PD; however, this technique's sensitivity and specificity for the diagnosis of PD is suboptimal (75% and 70% with atypical parkinsonism and 78% and 85% with ET) (Shafieesabet et al., 2017).

These imaging techniques are still considered experimental, and at the time of initial presentation of patients with early Parkinson's disease, studies to assess their positive predictive value were not conducted to identify their clinical value. Because current management strategies would not change due to a quick diagnosis of Parkinson's disease, most experienced clinicians choose to follow the patient's clinical course and make treatment decisions based on the needs of the individual patient, rather than relying on any information obtained from neurological imaging.

Lumbar Puncture

Where signs of normal-pressure hydrocephalus (NPH) are observed (e.g., incontinence, ataxia, dementia), lumbar puncture should be considered. Clinical signs in NPH improve characteristically after removal of around 20 mL of cerebrospinal fluid.

Dopa-responsive dystonia ought to be contemplated in patients with juvenile-onset dystonia and parkinsonism, especially those with diurnal symptom fluctuations. A trial of levodopa in such patients is critical. Measurement of CSF concentrations of biopterin, neopterin and neurotransmitter metabolites of homovanillic acid (HVA), 5-hydroxyindoleacetic acid (5-HIAA), and 3-methoxy-4-hydroxyphenylglycol (MHPG) are additional measures for this disorder. A modified pattern of decreases in these compounds is observed in both forms of dopa-responsive dystonia.

In the cross-sectional analysis of 63 drug-naive patients with early-stage PD and 39 healthy controls, the CSF levels of Alzheimer's biomarkers β -amyloid 1-42 ($A\beta$ 1-42), total tau (T-tau), tau phosphorylated threonine 181 (P-tau181), and α -synuclein in the PD patients were lower than in the controls. $A\beta$ 1-42 and P-tau181 were important predictors of Parkinson's disease and the extent of the motor dysfunction was correlated with T-tau and α -synuclein. In particular, lower concentrations of $A\beta$ 1-42 and P-tau181 were associated with the postural instability – gait disturbance – dominant PD phenotype, but were not linked to the tremor-dominant or intermediate phenotypes (Kang et al., 2013).

Autopsy

Autopsy confirmation is the sole conclusive method of diagnosis. The UK Brain Bank Criteria were developed to improve the accuracy of the Parkinson's disease clinical diagnosis (Hughes et al., 1992). This study evaluated the presenting clinical features in 100 cases which predicted confirmation of the disease by autopsy. They found that the best predictors of pathological diagnosis were the unilateral onset of symptoms with features including tremor, and at least one of bradykinesia and rigidity with a good initial response to L-dopa. A specific neurological disease was diagnosed at autopsy in 24 percent of the cases relative to those diagnosed during childhood.

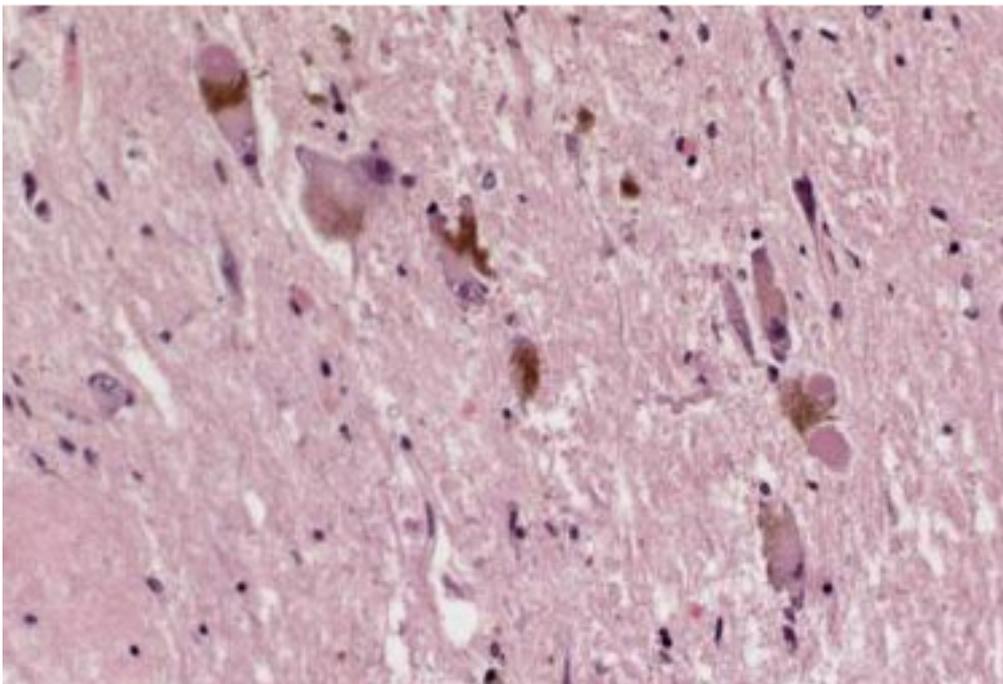
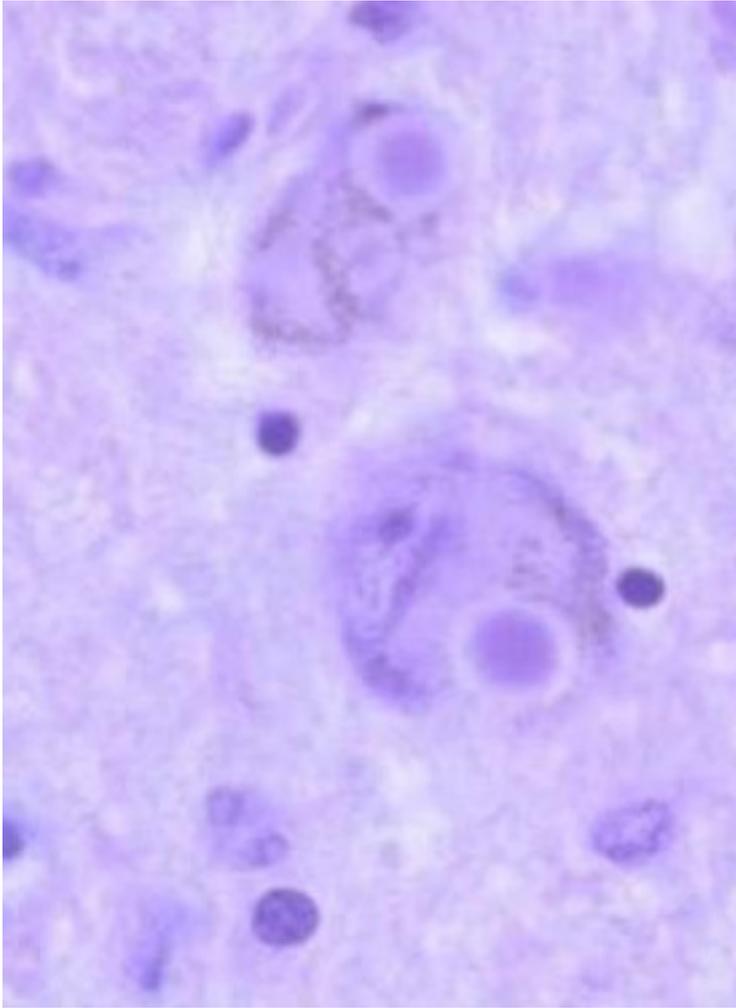
Lewy bodies are eosinophilic intracytoplasmic inclusions, often with halos, which are easily seen in pigmented neurons, as shown in this histologic slide (Figure 1). They contain polymerised alpha-synuclein; thus, alpha synucleinopathy is Parkinson's disease.

Characteristic pathological findings in Parkinson's disease include neuronal degeneration containing neuromelanin, especially in the substantia nigra and the locus ceruleus. Surviving neurons often have eosinophilic cytoplasmic inclusions, called Lewy bodies (see image below). The primary biochemical defects are the loss of striatal dopamine resulting from the degeneration of dopamine-producing cells in the substantia nigra, as well as cholinergic neuron hyperactivity in the caudate nucleus.

Alpha-synuclein is one of Lewy bodies' main structural components; all Lewy bodies stain for alpha-synuclein, and most stain for ubiquitin. Lewy bodies with peripheral halos and thick cores are compact, eosinophilic, cytoplasmic inclusions. The presence of Lewy bodies within the substantia nigra pigmented neurons is indicative of Parkinson's disease, but not the pathognomonic one. Also found are Lewy bodies in the cortex, nucleus basalis, locus ceruleus, spinal cord intermediolateral column and other areas.

According to the Braak hypothesis, Lewy body pathology in the brain starts in the olfactory bulb and lower brainstem and slowly ascends to affect dopamine neurons in the substantia nigra and ultimately the cerebral cortex (Brakk et al., 2004). Lewy body pathology is also observed in the gut and heart autonomous nerves.

Figure 1. Lewy bodies in the locus coeruleus from a patient with Parkinson disease



Biomarkers

There are currently no proven clinically relevant biomarkers. The α -synuclein cerebrospinal fluid levels may predict cognitive decline, but do not correlate with motor progression (Stewart et al., 2014).

How is the diagnosis made?

Diagnosis of Parkinson's disease is currently based on historical clinical features and examination, and over time, based on dopamine agent reaction and motor fluctuation (Suchowersky et al., 2006). Mild, early illness can be hard to recognize as it usually starts subtly. It is particularly difficult to detect PD in older people because aging can cause similar problems, such as loss of balance, slow movement, muscle stiffness, and stuffy posture.

Motor manifestations of the condition (Table 1) begin asymmetrically, and typically involve a resting tremor, a soft voice (hypophonia), masked facies (initially described as a reduced blink rate), small handwriting (micrography), stiffness (rigidity), slow motion (bradykinesia), shuffling steps and balance difficulties. A classic symptom is a resting tremor, usually affecting one upper limb, although 20 percent of patients do not have it; (Jankovic, 2008) 30 percent may first be trembling at a lower limb, and there may also be a resting lip, jaw, or even tongue shaking. (2012 by Baumann). Tremors of the head and voice are rare, and in such cases one should consider essential tremor in the differential diagnosis (Jankovic, 2008). Of all the main characteristics, bradykinesia has the strongest correlation with dopamine deficiency (Vingerhoets et al 1997).

The diagnosis was formalized using the criteria of the UK Parkinson's Brain Bank Disease Society (Jankovic, 2008), with diagnostic accuracy of up to 90 percent (Table 2) (Hughes et al., 1999). Patients with PD would live for 20 years or longer, depending on the age at the beginning; the mortality rate is around 1.5 times that of ordinary people of the same age. Death from PD is usually caused by a concurrent unrelated disease, or by the effects of decreased mobility, aspiration, or increased fall with subsequent physical injury.

How do early and late-onset disease differ in presentation?

Patients with early Parkinson's disease are less likely to experience gait disturbance as the symptom presenting, but have more pronounced stiffness and bradykinesia than those with late onset disease (Gomez et al., 1997). In one study, resting tremor presentation occurred in 41 percent of patients with early-onset disease and 63 percent of patients with late-onset disease (Gibb & Lees, 1988), but further studies did not show a consistent difference between early and late-onset Parkinson's disease for tremor onset (Ferguson et al., 2016).

Motor and Non Motor Symptoms

PD is a disease of the motor system. The four main symptoms are tremor (trembling) in the hands, arms, legs, mouth, and face; weakness or rigidity of the limbs and

trunk; bradykinesia (slow motion); and postural instability (impaired balance and coordination) (Jankovic, 2008; Ahlskog, 2001).

Parkinson's disease often has a variety of non-motor symptoms; some may precede diagnosis, while others may appear early or late (Table 2) after diagnosis which is made on the basis of motor functions. Table 2 lists the frequencies of early non-motor symptoms that may precede the diagnosis of Parkinson's disease including constipation, rapid eye movement, sleep behavior disorders, depression, and olfactory impairment. Red flags indicating an alternative diagnosis to Parkinson's disease idiopathic, such as another parkinsonian conditions.

The disorder is chronic and progressive but, in the same way, it does not affect everyone. For some patients PD can appear to be progressing faster than in others. Some patients become severely disabled; others experience only minor motor functional disruptions. The motor and non-motor symptoms are listed in detail in Table 2.

Motor (Physical) Symptoms

Tremor. For some patients, tremor is the primary symptom, but it may only be a minor complaint for others, for whom other symptoms may be more troubling. Typically the tremor associated with PD takes the form of a back-and-forth rhythmic motion of the thumb and forefinger at three beats per second. This is sometimes referred to as "pill rolling." Tremor usually begins in a hand, though a foot or jaw may be affected first. When the hand is in repose or the patient is under stress, it is most obvious. In 75 percent of patients, tremor may affect only one part or side of the body, particularly early in the disease; tremor can become more generalized in later stages. Tremor is rarely impaired, and typically disappears during sleep, or improves with deliberate motion.

Although tremor is the most common initial symptom in Parkinson's disease, occurring in about 70 percent of patients, to make the diagnosis it does not need to be present. Tremor is most commonly described as shakiness or nervousness by patients, and usually starts at one upper extremity and may be intermittent at first. Tremor at the upper extremity generally starts in the fingers or thumb but it can also begin in the forearm or wrist. The tremor may spread to the lower ipsilateral extremity or the upper contralateral extremity after several months or years until it is more generalized; but asymmetry is generally retained. Tremor can vary significantly, arising only with stress, anxiety or fatigue. Classically, the Parkinson's disease tremor is a resting tremor (occurring in a resting position with the limb) and disappears with the action or use of the limb, but this is not seen in all patients. The tremor can initially be observed during such activities as eating or reading a newspaper. Though Parkinson's disease is a rare cause of tremor that affects the head or neck, chin, lip or tongue tremors are not uncommon. The amplitude, as with other tremors, increases with stress and resolves during sleep.

Rigidity. Most patients with PD suffer from resistance to motion. A major principle of body movement is that it has an opposing muscle in all muscles. Movements are not only possible because one muscle becomes more active but also because the opposing muscle relaxes. Rigidity comes about when the delicate equilibrium of competing muscles is disrupted in response to signals from the brain. The muscles remain continuously tensed and contracting in such a way as to make the person feel stiff or weak. Rigidity is the increased muscle resistance to passive motion, and it often has a quality of “cogwheeling” (Jankovic, 2008). As the examiner moves a limb, it resists, then in slow, step-like motions it gives way as if it were being driven by a cogwheel (Michigan Parkinson Foundation, 2008).

Bradykinesia. The loss of spontaneous and automatic movement is especially disturbing as it is unpredictable; the patient can move effortlessly at one stage but will require support at the next. This could well be the disease’s most impaired and distressing symptom, as the patient is unable to make quick daily movements. Activities that could easily be done before — such as washing or dressing—may take several hours to complete.

Bradykinesia means slow motion. Bradykinesia symptoms are varied, and can be described in different ways by patients. These may include a subjective sense of weakness, with no true weakness on physical examination; loss of dexterity, sometimes described by patients as the “message not reaching the limb;” fatigue; or ache when repeated actions are carried out.

Facial bradykinesia is characterized by decreased blink rate and expression of the face. Speech can become quieter, less pronounced or more monotonous. In more advanced instances, voice is slurred, poorly articulated, and hard to comprehend. Drooling is a rare initial symptom in isolation, but is commonly reported later in the course of the disease (especially at nighttime drooling).

Truncal bradykinesia leads to slowness or difficulty rising from a chair, getting into bed, or walking. If it affects walking, patients can take smaller steps and the cadence of the gait is decreased. Some patients experience a transitory inability to walk, as if their feet were frozen to the ground. This “freezing” is commonly seen in more advanced disease patients; it is more prominent as patients attempt to navigate doorways or narrow areas and may result in patients being trapped behind furniture or unable to easily cross a door threshold.

Bradykinesia may cause weak, effortful handwriting (i.e., micrography) in the upper extremities, and trouble using the hand for fine dexterous tasks such as using a key or kitchen utensils. Unilateral bradykinesia in the lower extremities usually causes the foot to scuff on the ground, as it is not picked up during swinging of the leg. That can also be described as one leg dragging.

Postural instability. Balance and coordination impairment causes patients to lean forward or backward, and fall easily. Patients who lean backward tend to step backward (retropulsion) when pushed from the front or when beginning to walk. There may establish a stooped posture in which the patient’s head is bent and the shoulders drooped. Walking may be impacted as the disease progresses. Patients may stop in mid-stride and “freeze” in place, possibly even overturn, or they may walk with a series of fast, tiny steps as if they were hurrying to maintain balance (festination).

Dystonia

Dystonia is a common initial symptom of young-onset Parkinson’s disease, described as the onset of symptoms before age 40. In Parkinson’s disease, dystonia usually consists of a foot involuntary turning in (inversion) or down (plantar flexion), often associated with cramping or leg pain. The big toe may also get dorsiflexion. Another common dystonia in Parkinson’s disease is arm and elbow adduction which causes the hand to rest in front of the abdomen or chest. Dystonic postures can wax and wane, with tiredness or exertion.

It is debatable whether stooped posture is due to truncal dystonia. One study suggests that the stooped posture may be due to vertebral fractures resulting from vitamin D deficiency with compensatory hyperparathyroidism (Sato et al . , 2011). Supplementation with vitamin D may reduce the risk of stooped postures.

Non-Motor Symptoms

Many symptoms can be treated with medicine or physical therapy that is necessary. No one can predict what symptoms an individual patient may encounter, and the severity of the symptoms often varies among patients. None of these symptoms are fatal but affect life quality (Jankovic, 2008).

Emotional changes. Some people with PD get anxious and insecure. Maybe they don’t want to travel or socialise. Some are losing their motivation and becoming apathetic and dependent on family. Others can become pessimistic or uncharacteristically irritable. Loss of memory and slow thinking may occur, but the ability to reason remains intact. Whether people are actually suffering from intellectual loss or PD dementia is still a controversial area under study.

Dysphagia. In later stages of the disease, muscles used for swallowing can function less efficiently. Food and saliva may accumulate in the mouth and at the back of the throat, which may cause choking or drooling. Drugs such as levodopa and apomorphine can frequently alleviate these problems.

Dysarthria. About 50 per cent of all patients with PD have speech problems. They can speak too tenderly or in a monotonous voice, hesitate to talk, slur or repeat their words, or talk too quickly. A speech therapist can ease some of these problems.

Urinary problems or constipation. Bladder and bowel problems in some patients can be caused by improper functioning of the autonomic nervous system, which regulates smooth muscle activity, and adverse drug effects. Some patients may become incontinent while others may have difficulty urinating. Constipation may occur because the gastrointestinal (GI) tract functions more slowly; inactivity, consuming a bad diet, or drinking too little fluid may also cause this. It can be chronic, and may be severe enough to require hospitalization in exceptional cases. Patients should not allow constipation to last for more than a couple of days before taking measures to relieve it.

Skin problems. It is normal for the skin of the patient to become oily, especially on the front and on the nose sides. The scalp can get oily too, contributing to dandruff. The skin may in other cases become very dry. Such problems are the result of an adaptive nervous system that is not functioning properly. It could be helped with standard dermatological treatments. Excessive sweating, which is also normal, is typically controllable with PD medications.

Fragmented sleep. Problems with sleep include difficulty staying asleep at night, restless sleep, nightmares and daytime drowsiness. Whether these symptoms are linked to PD or the drugs used for treating PD is uncertain. Patients can never take the sleep aids over-the-counter without consulting a doctor.

Thinking. Bradyphrenia can occur, or a slowing of the ability to think (Hirsch, 2008). Just as it takes more time to step up from a chair, it may take more time for patients to reply intelligently. Information processing takes longer, and this can lead to disappointment for patients and carers alike. Bradyphrenia may be misinterpreted as deliberate behavior, lack of interest, or even stubbornness, but it is vital to understand that the condition is triggered by changes in the brain.

Pressing on an adult who has cognitive issues causes tension and typically makes matters worse. Patients may find it hard to think about other ways of doing things or move from one subject to another. These alterations in cognition may be mistaken as intentional, and may label the individual as rigid or inflexible. A portion of the brain involved in this sort of thinking may be affected in some patients.

Language. Substantial changes in language are uncommon in PD but subtle changes can occur. Talking also is slower, and it eliminates spontaneous expression. Patients cannot participate in conversation as much as they do, if at all. Such adjustments can be misinterpreted as being insensitive and lead to poor communication.

Cognitive Changes and Dementia. Some PD-patients shift their mood and cognitive abilities. The most common improvements include the slow thought and information processing. There may be a reduction in the capacity to produce new ways of solving problems. While memory

changes are less frequent, some people with PD forget where and when they got the information but remember the information itself. In certain cases, dementia occurs, and age progression is a risk factor. In these patients depression is often under-diagnosed. Regardless of the type of cognitive changes encountered, if symptoms are to be handled accurate assessment is important.

Alterations may occur in one's ability to think, reason, and remember, and several factors may contribute to these differences (Hirsch, 2008). Cognitive changes can affect the everyday lives of patients just as much as, and sometimes more, than the physical (motor) effects of PD (Marsh, 2008). Although the importance of addressing cognitive and other non-motor symptoms is increasingly recognized by physicians, many still focus primarily on treating physical symptoms and cognitive changes may remain undertreated or untreated. An objective evaluation of cognitive changes is required to develop a suitable plan for care.

A small number of patients may experience severe and drastic changes in memory, reasoning ability, language, and attention (Marsh, 2008, Galvin, 2006). As people age, there is an increased risk of a progressive decline in their ability to think and remember. When dementia occurs, patients require better treatment and supervision.

Depression. Depression is an additional potential cause of cognitive changes in PD patients, and is more severe in these patients than in the general population; within one year of the onset of PD symptoms, 25 percent of PD patients experience depression (Hirsch, 2008). Depressive condition progression is unlikely to be due to problems adapting to the disorder on its own. Some PD symptoms are similar to depression symptoms (e.g., lack of interest in activities, exhaustion, weight shift and social withdrawal). This similarity will lead to depression in those with PD being undertreated. In addition, patients may not even acknowledge being depressed. On a more optimistic note, depression can be managed and controlled by combining antidepressant medications with cognitive-behavioral therapy. Depression can have serious negative consequences if left untreated, interfering with cognition and, consequently, quality of life.

Adverse Drug Reactions

There are several forms of treatment available for managing PD symptoms. Managing PD symptoms, however, is becoming more complicated as the disease progresses. Developing adverse effects and improvements in the steady reaction to medications present various problems for patients, their families and health care providers. Alterations in cognitive ability can unfortunately be a potential side effect of all drugs used to treat PD. Hence, patients need to know which side effects are associated with the drugs they take. If there is a cognitive decline a health care provider should be immediately notified.

Natural history and prognosis

Treatments currently available are symptomatic and don't stop neurodegeneration. Although pharmacological therapy provides good symptom control in the initial stages of the disease, some levodopa-resistant symptoms (such as falls and freezing, dysarthria, dysphagia and choking, dementia, hallucinations, daytime sleepiness and urinary incontinence) appear in the later stages of the disease, leading to increased disability in advanced PD. Additionally, complications associated with pharmacological treatment add additional difficulties in managing the advanced PD stages.

Parkinson's disease caused serious impairment or death in 25 percent of patients within 5 years of diagnosis, 65 percent within 10 years, and 89 percent within 15 years before levodopa was introduced. Parkinson's disease mortality rate was 3-fold that of the general population balanced for age, sex, and ethnic origin. The mortality rate decreased by approximately 50 percent with the introduction of levodopa, and longevity was extended by many years. It is believed to be attributed to the symptomatic effects of levodopa, since there is no strong evidence to indicate that levodopa impedes the disease's progressive development (Frank et al., 2006; Thobois et al., 2005).

Parkinson's disease patients experience gradual loss in motor and cognitive function and increased mortality. Risk factors for a faster decrease in motor function include older age at diagnosis, and prominent bradykinesia and diagnostic rigidity. Prominent diagnostic tremor can predict slower progression of the disease (Suchowersky And et al., 2006). Dementia incidence increases with Parkinson's disease patient age and duration, with 60 per cent of patients having the disease developing dementia within 12 years of diagnosis (Buter et al., 2008). In a Dutch longitudinal cohort of 6,969 men and women, the relative mortality rate was 1.8 (de Lau et al., 2005). In a community-based cohort in Norway, men with Parkinson's disease at age 70 had eight years of median life expectancy, and women with Parkinson's disease at age 70 had 11 years of median life expectancy (Buter et al., 2008).

For Parkinson's disease, life expectancy declines (odds ratio 2.56, i.e. mortality risk is 2.56 times greater than comparable age-groups without Parkinson's disease), and medical therapies do not tend to change mortality or postpone the onset of non-motor symptoms (Clarke, 2010). Although progression is slower in early-onset disease patients and there is longer absolute survival, this occurs at the expense of increased years of loss of life (11 years lost in early-onset disease v. 4 years in late-onset illness). (Ferguson and others, 2016). Late-onset Parkinson's disease is associated with quicker development of the disorder and cognitive impairment (Reid et al., 2011), which could be due to a lack of cell death compensatory strategies (Ferguson et al, 2016). Long-term outcome data are lacking in the older population (Logroschino, 2016).

The American Academy of Neurology states that the following clinical characteristics can help predict the risk of Parkinson's disease progression (Suchowersky et al., 2006):

- Older age at onset and initial rigidity/hypokinesia can be used to predict (1) a more rapid rate of motor progression in those with newly diagnosed Parkinson disease and (2) earlier development of cognitive decline and dementia; however, initially presenting with tremor may predict a more benign disease course and longer therapeutic benefit from levodopa
- A faster rate of motor progression may also be predicted if the patient is male, has associated comorbidities, and has postural instability/gait difficulty (PIGD)
- Older age at onset, dementia, and decreased responsiveness to dopaminergic therapy may predict earlier nursing home placement and decreased survival

Conclusion

Parkinsonism and PD are frequent in older patients. In the differential diagnosis of patients who have falls. Family physicians should consider parkinsonism, when symptoms show general functional decline. Functional declines are normal among older vulnerable patients. The functional deterioration differential diagnosis is broad and involves side effects of the drug, congestive heart failure, unrecognized dementia or depression, and other common and uncommon diseases.

Parkinson's disease (PD) and parkinsonism sometimes have an unspecific history, and experienced physicians may initially miss the PD's physical characteristics unless considered in the differential diagnosis. Idiopathic PD is the most common form of parkinsonism but recognizing other causes of parkinsonism is important for family physicians. This paper aims to examine the diagnostically relevant features of PD and to explain certain causes of parkinsonism.

PD is associated with an increased risk of death from all causes and a reduction in life expectancy and serious disability. In the advanced phase of the disease, the majority of patients lose autonomy; levodopa-resistant symptoms are the most accurate predictors of nursing home placement and mortality.

Table. 1 Criteria of the UK Parkinson's Disease Society Brain Bank for diagnosing Parkinson disease**Bradykinesia and at least one of the following:**

- Rigidity
- Resting tremor (4–6 Hz)
- Postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction

Exclusion of other causes of parkinsonism**At least three of the following supportive (prospective) features:**

- Unilateral onset
- Persistent asymmetry primarily affecting the side of onset
- Resting tremor (hand, leg or jaw; low frequency (4–5 Hz), asymmetric, disappears with action)
- Excellent response to levodopa (70%–100%)
- Progressive disorder
- Severe levodopa-induced chorea (dyskinesias)
- Levodopa response for five years or more
- Clinical course of 10 years or more

Early motor features	Early non-motor features (may precede the diagnosis)	Late features (usually develop 5–10 years after disease onset)	Late non-motor features
<ul style="list-style-type: none"> • Difficulty turning in bed • Frozen shoulder • Stiffness, numbness or pain in limb • Micrographia • Difficulty with fine finger movements (bradykinesia) • Tremor of hand, jaw, foot • Decreased facial expression • Decreased arm swing, dragging a leg • Soft voice ("Do people ask you to repeat yourself over the phone?") 	<ul style="list-style-type: none"> • Constipation (30%) • REM sleep behavior disorder (50%, often preceding the diagnosis by median of 14 years) • Depression occurs with a prevalence of 35% in Parkinson disease, and 10%–15% will have depression at the time of diagnosis • Olfaction impairment (most consistent non-motor feature predicting Parkinson disease); up to 97% of patients 	<ul style="list-style-type: none"> • Motor fluctuations • Dyskinesia (complication of dopaminergic treatment, more so with levodopa); typically choreiform, involving the neck, head, limbs and trunk • Gait freezing • Falls 	<ul style="list-style-type: none"> • Dysphagia (50% at 15 years) neuropsychiatric symptoms (50% at 15 years), including hallucinations, sleep disturbance and dementia • Autonomic disturbances (70%–80%), including sweating, orthostasis, sialorrhea and urinary dysfunction • Seborrheic dermatitis (usually involving the forehead, with flaky oily skin)

Note: HR = hazard ratio REM = rapid eye movement.

The risk of synucleinopathy (i.e., Parkinson disease, multiple system atrophy, Lewy body dementia) in patients with REM sleep behavior disorder was reported to be 30% at 3 years, rising to 66% at 7.5 years. Advanced age (HR 1.07), olfactory loss (HR 2.8), abnormal colour vision (HR 3.1), subtle motor dysfunction (HR 3.9) and nonuse of antidepressants (HR 3.5) identified higher risk of disease conversion.

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