Parkinson’s Disease: An update on Pathophysiology, Epidemiology, Diagnosis and Management
Part 4: Differential Diagnosis and Patient Assessment

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Abstract

Early symptoms of PD are subtle and occur gradually. Patients may be tired, or experience a general malaise. Many may feel a little nervous or may have trouble getting out of a chair. We can note that they talk too softly or that they look messy and spidery in their handwriting. They may lose track of a word or thought or they may, for no obvious cause, feel irritable or discouraged. This early period can last a long time before the symptoms appear more classic and obvious. The onset of symptoms will take several years to go unnoticed. Symptoms usually impact only one side of the body for one or two years, then move to the other side. Tremor is always first detected, which usually causes the doctor’s first appointment. Nevertheless, there is no tremor in up to 30 per cent of patients; this may lead to a misdiagnosis. In this review the approach to assessment and differential diagnosis of Parkinson disease are discussed.

Key words: Parkinson’s disease, differential diagnosis, patient assessment
Early PD signs are mild, and gradually occur (Jankovic, 2008). Patients may be tired, or experience a general malaise. Many may feel a little nervous or may have trouble getting out of a chair. We can note that they talk too softly or that they look messy and spidery in their handwriting. They may lose track of a word or thought or they may, for no obvious cause, feel irritable or discouraged. This initial phase can last a long time before the symptoms appear more classic and obvious.

The first to note changes could be friends or family members. We can see that the face of the person lacks speech and movement (“masked face”) or that the person stays for a long time in a certain position, or usually does not move an arm or leg. Perhaps they see the individual appears rigid, erratic and unusually slow.

The beginning of symptoms will take several years to become noticeable. Warning symptoms include finger stiffness or a sore shoulder followed by tense muscles. Pain could be a feature of that (Jankovic 2008). Symptoms usually impact only one side of the body for one or two years, then move to the other side. Tremor is always first detected, which usually causes the doctor’s first appointment. Nevertheless, there is no tremor in up to 30 per cent of patients; this may lead to a misdiagnosis. When the disease progresses, the tremor that most patients feel may begins to interfere with everyday activities.

Patients may not be able to keep utensils straight, or may find it difficult to read a newspaper due to trembling. Once the patient is comfortable the tremor can get worse. Shaking is most pronounced a couple of seconds after hands rest on a table.

The clinical image between patients with PD can be extremely varied, allowing different motor subtypes to be defined: ‘tremor dominant,’ ‘postural instability and gait difficulty’ (PIGD) or ‘indeterminate.’ The interest in the identification / definition of PD subtypes is focused on their potential correlation with etiological or prognostic aspects and treatment response: for example, tremor-dominant PD was associated with slower progression and less impairment compared with PIGD (Fereshtehnejad & Postuma, 2017).

Even though PD has traditionally been described as a movement disorder, NMSs are an essential aspect of the clinical picture. NMSs differ from dysphagia and sialorrhoea to autonomic, gastrointestinal, sleep, auditory, cognitive, and neuropsychiatric conditions. NMSs continue to be under-identified by patients and under-researched by doctors; but, if correctly assessed, they are identified by the majority of patients and have a direct effect on health-related quality of life (HRQoL) and disability (Schapira et al., 2017, Balestrino & Martinez-Martin). Many other symptoms – known as ‘prodromal / premotor symptoms’ – may occur even 10 years before the diagnosis and onset of motor symptoms: hyposmia, fatigue, constipation, and rapid eye movement sleep behavior disorder (RBD) are the most commonly recognized, which can include visual changes, anxiety, and other autonomic disturbances (Postuma et al., 2012). The prodromal phase of PD offers a rare opportunity to recognize those at high risk of developing PD and prior to the onset of severe neurodegeneration, offering valuable insight into the mechanisms of the disease and its development, and a potential therapeutic window for neuroprotective treatments; hence efforts have been made to increase the identification of this period.

Wide population studies such as PRIPS (Prospective Assessment of Risk Factors for Idiopathic Parkinson’s Syndrome), PARS (Parkinson At-Risk Syndrome Study), TREND (Tubinger Assessment of Risk Factors for Early Detection of Neurodegeneration) and Rotterdam Studies have helped to classify prodromal markers of PD. (Postuma et al., 2019). Online-based screening studies, such as the general population PRE-DICT-PD and the GBA mutation carriers RAP- SODI, are currently under way. The diagnostic criteria for the prodromal phase of PD have recently been revised, and a web-based prodromal PD risk calculator that enables individuals to measure the probability of prodromal PD is now available, but should be used with caution and only in clinical settings (Heinzel et al., 2019).

PD is basically a clinical diagnosis. Recently the Movement Disorders Society revised the diagnostic criteria for PD (Postuma et al., 2015) (Table 1). Table 2 & 3 summarizes the principal differential diagnoses.

Secondary Parkinsonism

Parkinsonism can be due to basal ganglia lesions with different etiologies – such as ischemic, neoplastic, or infective. A sudden onset and the co-occurrence of other symptoms in those cases should suggest a diagnosis other than PD. Exposure to toxins (carbon monoxide, manganese) or drugs such as dopamine-blocking agents (anti-psychotics but also metoclopramide), tetrabenazine, calcium channel blockers, amiodarone and lithium may cause parkinsonism; the second most common cause of parkinsonism after PD is drug-induced parkinsonism (DIP). Accurate diagnosis is necessary for better management and appropriate prognosis. Motor characteristics that can help distinguish it from PD are symmetric symptoms, oromandibular dyskinesias, and no or limited response to levodopa; however, DIP motor characteristics may be similar to PD. Hyposmia appears to be the most effective NMS to differentiate between DIP and PD, although the founding factors (age, smoking, and cognitive impairment) may complicate its assessment. Withdrawal of the causative medication for 6 months could lead to symptom improvement, but this is not always feasible or successful (Brigo et al 2014).

Essential Tremor (ET)

ET’s key clinical characteristic is a 5–12 Hz frequency postural and/or action tremor with symmetric presentation.
that includes the hands, head (‘yes–yes’ or ‘no–no’) and/or voice more frequently. Rest tremor can be present but it increases during movement as compared to PD. Patients display tremulous handwriting rather than micrography as in PD. In addition to tremor, mild signs of the cerebellar, cognitive dysfunction, psychological symptoms and sensory problems were often identified. The disease is usually slowly progressive; its symptoms may be mitigated by alcohol, propranolol and primidone, while they are ineffective in PD. ET shows an autosomal dominant inheritance and patients often report a positive family experience (Bhatia et al., 2018). Some overlapping features were described between PD and ET, and misdiagnosis is relatively common (Shahed & Jankovic 2007).

**Atypical Parkinsonism**

Multiple system atrophy (MSA) is a neurodegenerative disease portrayed by autonomic dysfunction and cerebellar signs and/or parkinsonism. Motor symptoms of MSA include an akinetic-rigid parkinsonism with, in contrast to PD, a symmetric distribution and no or limited response to levodopa; pyramidal symptoms (extensor plantar responses and hyperreflexia), cerebellar signs (dysarthria, dystaxia, nystagmus, ataxia) and oculomotor dysfunction (impaired smooth pursuit movement, dysmetric saccades, represssion of vestibulo-ocular reflex) may happen. Classic resting tremor is rare; a jerky poly-mini myoclonus can be seen in patients instead. Neck (anterocollis or laterocollis) or orofacial dystonia may happen, particularly when levodopa is prescribed. Dysautonomic features are common from early stages of the disease; they include urogenital, cardiovascular (orthostatic hypotension and its effects such as syncope and postural dizziness), respiratory (stridor, sleep-related breathing disturbances, respiratory failure), gastrointestinal and sudomotor symptoms. Dementia may ensue at the later stages of the illness. MSA is pathologically a synucleinopathy; neurodegeneration affects the striatonigral and/or olivopontocerebellar structures more commonly (Stamelou & Bhatia, 2015, Deutschlander, et al., 2017).

Various forms of progressive supranuclear palsy (PSP) were identified. The classic PSP phenotype is known as Richardson syndrome; it typically has an axial akinetic-rigid parkinsonism with no or moderate reaction to levodopa, postural anomalies (head and trunk hyperextension / retrocollis, not camptocormia as in PD), gait abnormalities (broad-based gait and freezing), postural instability, and falls from the initial stage of the disease (rather than in a later stage as in PD). The typical symptom of PSP is the supranuclear palsy of the vertical gaze, which is absent in PD; other indications of oculomotor dysfunction include slowing down (especially downward) vertical saccadic movements and eyelid opening apraxia (which cause a compensatory overactivity of the frontal muscle and lead to a typical ‘surprised’ expression). Despite the supranuclear aspect of gaze palsy, the vestibulo-ocular reflex is retained. Certain characteristics include pseudobulbar palsy, dementia of the sub-cortical form, symptoms of frontal release and perseverance of the motor that are absent in PD. A characteristic of PSP patients is ‘motor recklessness,’ described as no caution in walking / standing / moving despite loss of balance and frequent falling. Pathologically, PSP is a tauopathy disease linked with irregular tau protein aggregates and its hallmark characteristic is ‘tufted astrocytes;’ neurodegeneration affects subcortical structures such as the SN, the subthalamic nucleus (STN) and the midbrain (Stamelou & Bhatia, 2015, Deutschlander, et al. 2017).

The most common motor characteristics of corticobasal degeneration (CBD) are asymmetric rigidity and bradykinesia, which can occur in conjunction with dystonia and myoclonus (typically distal and sensitive to stimulation) differently from PD. A distinguishing sign of CBD is the ‘alien limb phenomenon,’ reported by about 50% of patients: the limb may involuntarily assume positions, grab objects or interfere with the actions of the non-affected limbs. Tremor is rare, and an action / postural tremor is present, rather than a resting tremor as in PD. CBD also has cortical symptoms such as dementia (usually affecting frontal and parietal functions), apraxia, and cortical sensory impairment, usually absent in PD. However CBD presentation is highly variable and can overlap with other diseases, and it is estimated that its clinical diagnostic accuracy is particularly low (< 50 percent). Pathologically, CBD is a tauopathy; its signature characteristic is the development of ‘astrocytic plaques;’ the neurodegeneration primarily affects the SN and the front-parietal cortex (Stamelou & Bhatia, 2015, Deutschlander, et al. 2017).

**Other Parkinsonisms**

Dementia of Lewy Body –DLB’s main clinical characteristics include cognitive impairment, with alertness and concentration disturbances, parkinsonism, visual hallucinations and Rem Sleep Behavioral Disorder (RBD). Parkinsonism occurs in nearly 85 per cent of patients; it is typically milder than in other atypical parkinsonisms and PD; axial symptoms such as postural disturbances, gait disorder and postural dysfunction are prevalent; tremor is rare. Essentially, cognitive dysfunction occurs at or within 1 year of parkinsonism. Cognitive impairment is characterized by attention deficits, executive function and visuospatial ability, while memory and language are spared relatively. Many clinical characteristics include dysautonomy, repeated dropping, prolonged daytime sleepiness, susceptibility to the neuroleptics, hyposmia and mood disorders. Hallucinations are typically extremely vivid and informative. Alertness and attention variations are rather common, and help eliminate PD. DLB is a synucleinopathy; its pathological features are neuronal inclusions of a-synuclein (LBs and Lewy neurites), and neuronal failure. DLB comprises three types of a-synuclein pathology: predominant brainstem, limbic (or transitional), and neocortical. Alzheimer’s disease pathology is overlapping (Walker et al., 2015).

The second most frequent cause of neurodegenerative dementia before age 65 (after Alzheimer’s disease) is Fronto-Temporal Dementia (FTD). There are specific variants with FTD and they are graded based on clinical characteristics. In the behavioral type (bvFTD), parkinsonism is more pronounced; the most pronounced
motor symptoms are bradykinesia, parkinsonian gait, rigidity, postural stiffness, and resting tremor. For FTD cases with C9orf72 mutations, a cause of FTD-amyotrophic lateral sclerosis (FTD-ALS), parkinsonism is often common; it is usually symmetrical and rigid-akinetic. The presence of early behavioral or cognitive symptoms may assist in the diagnosis of differentials. FTD pathology is complex and classified in pathological inclusions according to the predominant protein: tau (4R and/or 3R tau), TDP-43 or FET (Baizabal-Carvallo & Jankovic, 2016).

Other degenerative diseases such as Wilson disease (WD) and Huntington disease (HD) can cause parkinsonism. Wilson disease is a recessive, autosomal, monogenic disorder. The causative gene, ATP7B, encodes a P-type ATPase that carries copper. Hepatic and/or neurological symptoms are characteristic of WD. Usually, neurological symptoms in WD begin in the second or third decade of life; however, both late onset (> 70 years of age) and infancy onset have been identified. The combination of wing-beating tremor or flapping tremor and dysarthria strongly indicates WD diagnosis; other neurological signs include parkinsonism, other types of tremor (an abnormal, jerky, dystonic tremor; rest, motion, or intention tremor), dystonia, and orofacial dyskinesias. Often reported were pyramidal features, hallucinations, psychotic symptoms and irregular vertical smooth pursuit. WD may present with acute liver failure or chronic liver disease, but WD is not exempt from the absence of liver disease. The presence of Kayser – Fleischer rings and the low concentrations of serum ceruloplasmine are sufficient to establish the diagnosis. Precise diagnosis of WD is critical, since it is a treatable disorder and pre-symptomatic treatment is also mandatory in relatives with pre-clinical WD biochemical or genetic evidence. Treatment options include copper chelators, zinc salts, or both; life-long medical therapy is required. Introduction of WD therapy can be associated with an initial deterioration of clinical characteristics and requires close monitoring (Poujois & Woimant, 2019).

Huntington disease is a neurodegenerative disorder with autosomal dominant inheritance, instigated by an extended repeat of the CAG trinucleotide in the gene encoding the huntingtin protein (HTT). The disorder features a mixture of motor, cognitive, and behavioral characteristics. Motor features in HD include repetitive gestures, such as chorea, and voluntary movement disorder, such as incoordination and bradykinesia. Cognitive deficiency in HD is portrayed by problems in mental flexibility, concentration, preparation, cognitive slowing, and awareness of emotion problems. Psychiatric symptoms include depression, apathy, irritability, paranoia and obsessive – compulsive behaviors. Juvenile HD, also known as Westphal type, can resemble PD: behavioral and cognitive abnormalities are often the first sign and the motor picture is characterized by dystonic hypokinesia and bradykinesia; chorea is uncommon in the first decade and occurs only in the second decade; epileptic fits are frequent (Bates et al., 2015). Current HD management focuses on the management of symptoms, but disease-modifying therapies such as antisense oligonucleotides designed to inhibit HTT messenger RNA give promising results in trials (Tabrizi et al., 2019).

Parkinsonism can also occur in neurodegenerative diseases with brain iron accumulation – such as Haller-vorden-Spatz disease – and some forms of spinocerebellar ataxias: in these cases, a positive family history, young age at onset, concurrent clinical features and instrumental findings should lead the neurologist to consider other causes than PD.

Parkinsonism can also occur in neurodegenerative diseases with accumulation of brain iron, such as Haller-vorden-Spatz disease, and certain forms of spinocerebellar ataxia: in these cases, a positive family history, early age, concurrent clinical characteristics and instrumental findings should lead the neurologist to consider causes other than PD.

Conclusion

The assessment of the suspected Parkinson patient is a delicate process. It entails good knowledge of the differential of the disease, good listening and observation skills. In addition to cooperative patient and caregiver.

References


**Table 1. New diagnostic criteria for Parkinson disease from Movement Disorder Society**

The essential criterion is parkinsonism defined as: bradykinesia in combination with at least 1 of rest tremor or rigidity.

**Diagnosis of clinically established PD**

1. Absence of absolute exclusion criteria
2. At least two supportive criteria, and
3. No red flags

**Diagnosis of clinically probable PD**

1. Absence of absolute exclusion criteria
2. Presence of red flags counterbalanced by supportive criteria
   - If one red flag is present, there must also be at least 1 supportive criterion
   - If two red flags are present, at least 2 supportive criteria are needed
   - No more than two red flags are allowed for this category

**Supportive Criteria**

1. Clear and dramatic beneficial response to dopaminergic therapy. During initial treatment, patient returned to normal or near-normal level of function. In the absence of clear documentation of initial response, a dramatic response can be classified as:
   a) Marked improvement with dose increases or marked worsening with dose decreases. Mild changes do not qualify. Document this either objectively (>30% in UPDRS III with change in treatment) or subjectively (clearly documented history of marked changes from a reliable patient or caregiver).
   b) Unequivocal and marked on/off fluctuations, which must have at some point included predictable end-of-dose wearing-off.
2. Presence of levodopa-induced dyskinesia
3. Rest tremor of a limb, documented on clinical examination (in past, or on current examination)
4. The presence of either olfactory loss or cardiac sympathetic denervation on MIBG scintigraphy

**Absolute exclusion criteria**

1. Cerebellar abnormalities, such as cerebellar gait, limb ataxia or cerebellar oculomotor abnormalities
2. Downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades
3. Diagnosis of probable behavioural variant fronto-temporal dementia or primary progressive aphasia, defined according to consensus criteria within the first 5 years of disease
4. Parkinsonian features restricted to the lower limbs for more than 3 years
5. Treatment with a dopamine receptor blocker or a dopamine-depleting agent in a dose and time-course consistent with drug-induced parkinsonism
6. Absence of observable response to high-dose levodopa despite at least moderate severity of disease
7. Unequivocal cortical sensory loss, clear limb ideomotor apraxia, or progressive aphasia
8. Normal functional neuroimaging of the presynaptic dopaminergic system
9. Documentation of an alternative condition known to produce parkinsonism and plausibly connected to the patient’s symptoms, or the expert evaluating physician, based on the full diagnostic assessment, feels that an alternative syndrome is more likely than PD

**Red Flags**

1. Rapid progression of gait impairment requiring regular use of wheelchair within 5 years of onset
2. A complete absence of progression of motor symptoms or signs over 5 or more years unless stability is related to treatment
3. Early bulbar dysfunction: severe dysphonia or dysarthria (speech unintelligible most of the time) or severe dysphagia (requiring soft food, nasogastric tube or gastrostomy feeding) within first 5 years
4. Inspiratory respiratory dysfunction: either diurnal or nocturnal inspiratory stridor or frequent inspiratory sighs
5. Severe autonomic failure in the first 5 years of disease. This can include orthostatic hypotension or severe urinary retention or urinary incontinence in the first 5 years of disease (excluding long-standing or small amount stress incontinence in women) that is not simply functional incontinence. In men, urinary retention must not be attributable to prostate disease, and must be associated with erectile dysfunction.
6. Recurrent (>1/year) falls because of impaired balance within 3 years of onset
7. Disproportionate anterocollis (dystonic) or contractures of hand or feet within the first 10 years
8. Absence of any of the common non-motor features of disease despite 5 years’ disease duration. These include sleep dysfunction (sleep-maintenance insomnia, excessive daytime somnolence, symptoms of REM sleep behaviour disorder), autonomic dysfunction (constipation, daytime urinary urgency, symptomatic orthostasis), hyposmia or psychiatric dysfunction (depression, anxiety or hallucinations)
9. Otherwise unexplained pyramidal tract signs, defined as pyramidal weakness or clear pathological hyperreflexia (excluding mild reflex asymmetry and isolated extensor planter response)
10. Bilateral symmetric parkinsonism. The patient or caregiver reports bilateral symptom onset with no side predominance, and no side predominance is observed on objective examination

Table 2. Differential diagnosis in parkinsonism

<table>
<thead>
<tr>
<th>Parkinson disease</th>
<th>Secondary parkinsonism</th>
<th>Atypical parkinsonism</th>
<th>Neurodegenerative disease</th>
<th>Other diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporadic</td>
<td>Drug induced</td>
<td>Multi-systemic atrophy</td>
<td>Dementia with Lewy bodies</td>
<td>Wilson disease</td>
</tr>
<tr>
<td>Familial/genetic</td>
<td>vascular</td>
<td>Progressive supranuclear palsy</td>
<td>Alzheimer disease with</td>
<td>Huntington disease</td>
</tr>
<tr>
<td>Toxic</td>
<td>Corticobasal syndrome</td>
<td>Prion disease</td>
<td>Kufor Rakeb syndrome</td>
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<tr>
<td>Neoplastic</td>
<td>Frontotemporal Dementia</td>
<td>SCA3</td>
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<tr>
<td>Infective</td>
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<td></td>
<td>Dopa-responsive dystonia</td>
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<td>Normal pressure hydrocephalus</td>
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<td>X-linked parkinsonism dystonia</td>
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<tr>
<td>Trauma</td>
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<td>Neurodegeneration with brain iron accumulation</td>
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<td>Liverfailure</td>
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<td>Fragile X-associated ataxia-tremor-parkinsonism</td>
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Table 3: Differential diagnosis of Parkinson’s disease

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Differentiating clinical features</th>
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</thead>
<tbody>
<tr>
<td>Progressive supranuclear palsy</td>
<td>Oculomotor dysfunction with vertical gaze abnormalities, axial rigidity, falls during the early stages of disease, pseudobulbar palsy, swallowing dysfunction, cognitive impairment, apraxia of eyelid opening, parkinsonism with lack of or transient response to L-dopa, rapid progression, dysarthria</td>
</tr>
<tr>
<td>Multiple system atrophy</td>
<td>Postural hypotension and autonomic dysfunction (Shy-Drager variant), cerebellar dysfunction (olivopontocerebellar atrophy variant), parkinsonism with lack of or transient response to L-dopa (striatognial degeneration variant), falls during the early stages of disease, swallowing dysfunction, rapid progression, neck flexion, myoclonus, dysarthria</td>
</tr>
<tr>
<td>Vascular parkinsonism</td>
<td>Lower body presentation with freezing gait during the early stages of disease, pyramidal tract signs, cognitive dysfunction, relative lack of response to L-dopa</td>
</tr>
<tr>
<td>Diffuse Lewy body disease</td>
<td>Early dementia, hallucinations with L-dopatherapy, fluctuating level of alertness, sensitivity to extrapyramidal side effects of neuroleptics</td>
</tr>
<tr>
<td>Corticobasal degeneration</td>
<td>Apraxia, cortical sensory signs, myoclonus, unilateral presentation, dystonia, cognitive impairment, lack of response to L-dopa</td>
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References (continued)


