
Differential Diagnosis of Parkinsonism

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ABSTRACT: The diagnosis of Parkinson's disease is predominantly clinical, based on a combination of the cardinal features of tremor, bradykinesia and rigidity. The differential essentially lies between other conditions resulting in tremor, of which essential tremor is the commonest, and other akinetic-rigid syndromes. These include progressive supranuclear palsy, multiple system atrophy, toxins and other degenerative disorders, including diffuse Lewy body disease and corticobasal degeneration. The key clinical features of these disorders and a practical diagnostic approach are briefly reviewed in this article.

R SUM : Diagnostic différentiel du parkinsonisme. Le diagnostic de la maladie de Parkinson est avant tout clinique et basé sur une combinaison de manifestations dont le tremblement, la bradykinésie et la rigidité. Le diagnostic différentiel regroupe d'autres entités comportant du tremblement, dont le tremblement essentiel est la plus fréquente, et d'autres syndromes akinéto-rigides. Parmi ces derniers, mentionnons la paralysie supranucléaire progressive, l'atrophie multisystémique, les toxines et les autres maladies dégénératives, incluant la maladie diffuse à corps de Lewy et la dégénérescence corticobasale. Nous revoyons dans cet article les principales manifestations cliniques de ces maladies et nous proposons une approche diagnostique pratique.

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The cardinal features of Parkinson's disease are tremor, bradykinesia, rigidity and postural/gait disturbance. Other conditions may mimic individual or any combination of these manifestations (Table).

TREMOR

The typical tremor of Parkinson's disease is maximal at rest, often asymmetric and approximately 3-5 Hz. The hands are preferentially affected, but with more advanced disease, the legs, chin and head may be involved. The most important differential is essential tremor (ET), which is frequently bilateral (although often somewhat asymmetric) and characteristically maximal in sustaining antigravity postures. Kinetic tremor may also be present. The hands are most frequently involved, although some patients may have relatively isolated involvement of the head or voice. Voluntary movements of the opposite limbs may not uncommonly bring out a mild degree of cogwheeling (Froment's sign) in ET, so this cannot be used as a totally reliable differentiator from Parkinson's disease. Similarly, postural and kinetic tremor may both be seen in Parkinson's disease. The frequency of essential tremor may be somewhat higher in some patients (5-7 Hz; 8-12 Hz in the case of exaggerated physiological tremor) than parkinsonian tremor, but this is also not a reliable differentiator. Probably the best ways to separate the diagnoses are on the basis of the handwriting (micrographic in Parkinson's disease) and by asking the patient to walk. This will typically accentuate parkinsonian tremor, whereas ET will often be attenuated, as the limb is fully dependent and therefore at rest. Although the typical rest tremor of Parkinson's disease is generally unresponsive to ethanol, in contrast to ET, this distinction is not always a reliable diagnostic feature.

AKINETIC-RIGID SYNDROMES

Progressive supranuclear palsy

This condition typically onsets in the 7th decade and can be very difficult to diagnose in the early stages. In retrospect, one can often obtain a history of fairly longstanding postural instability and "dizziness". Visual complaints are often attributed to "diplopia", which may be worse on looking down. As time progresses, the typical picture becomes much more obvious. Facial dystonia gives rise to a surprised look and pseudobulbar affect may be prominent (as may spastic dysarthria and dysphagia).

The cardinal feature of the disorder, *without which the diagnosis cannot be made during life*, is the supranuclear gaze disturbance. This preferentially affects saccadic eye movements, particularly downgaze. Pursuit movements may be relatively preserved, particularly in the early stages of the disorder. Therefore, if the diagnosis is being entertained, careful examination of both voluntary saccades and optokinetic nystagmus are mandatory. Another suggestive feature is the presence of macro-square wave jerks. Nystagmus is not a feature of PSP. Blepharospasm and lid levator inhibition (leading to so-called "apraxia of eye opening") are also common neuro-ocular manifestations.

Rigidity is typically lead-pipe rather than cogwheel, reflecting the lack of tremor in this disorder, and typically affects axial extensor muscles more than appendicular musculature, in

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contrast to Parkinson's disease. Limb involvement is generally fairly symmetrical, again in contrast to PD, although highly asymmetric dystonia has been described.¹ Bradykinesia and postural instability may be quite profound, even in the absence of much limb rigidity. Tremor is not a feature and its presence should suggest either a different diagnosis or superimposed ET.

The family history is usually negative in PSP. MRI may demonstrate quadrigeminal atrophy and prominence of quadrigeminal and interpeduncular cisterns as well as the cerebral aqueduct. MRI has also allowed the delineation of a PSP-like syndrome due to multiple small infarcts,² although there are frequently clinical clues to suggest this diagnosis. Clinical research criteria for diagnosing PSP have recently been published.³

System degenerations

Under this category, we will consider a spectrum of disorders including the Shy-Drager syndrome, striatonigral degeneration, olivopontocerebellar atrophy and multiple systems atrophy. The clinical and pathological overlap between these disorders is in general so large that until a reliable biochemical or genetic marker is determined which allows their separation, it generally makes more sense to consider them as a group. This means, however, that the clinicians and pathologists involved have a special responsibility to carefully examine and document the entire spectrum of nervous system abnormalities.

These disorders may frequently present with the symptoms of typical parkinsonism. In contrast to PSP, tremor may be present. In the early stages, there may be a response to levodopa, although this is not generally as well sustained as in idiopathic Parkinson's disease and complications of treatment may occur earlier.

Autonomic disturbances can of course occur during the course of Parkinson's disease or may be related to pharmacological treatment, but prominent abnormalities early in the course of the illness should suggest one of these conditions. Postural hypotension should be assessed after asking the patient to stand for 2 minutes. In contrast to autonomic failure, drug-induced hypotension is often transient and associated with reflex tachycardia. While incontinence is not generally a presenting feature, frequency and urgency may be present if specifically sought. Impotence is similarly often present early but not volunteered as a symptom.

The eye movements may be affected, particularly in olivopontocerebellar degeneration. Breakdown of smooth pursuit may be more marked than in Parkinson's disease, and there may be nystagmus, ophthalmoparesis and fixation instability (square wave jerks), but the latter features are not as marked as in PSP. Some variants of OPCA may be associated with optic atrophy.

The system degenerations may be associated with amyotrophy (rare), ataxia or corticospinal tract abnormalities such as spasticity, increased reflexes and Babinski signs. Such findings are not compatible with pure Parkinson's disease and their presence should suggest one of the system degenerations or a concurrent problem such as cervical spondylosis. The same is true of sensory abnormalities. Other characteristic features include antecollis, stridor (due to paralysis of laryngeal abductors), facial myoclonus and prominent levodopa-induced facial dystonia.^{4,5}

For those diagnostic "splitters", the choice of diagnosis among these conditions will be based upon the precise constellation of clinical findings. Thus, typical parkinsonism with promi-

nent autonomic dysfunction in the early stages may suggest Shy-Drager syndrome. Parkinsonism without tremor, combined with autonomic dysfunction may suggest striatonigral degeneration, whereas ataxia with or without corticospinal tract or sensory abnormalities may suggest OPCA. It is clear that the separation is quite artificial, and it is indeed worth remembering that 2 of the original 4 cases of striatonigral degeneration had concomitant OPCA!

With the exception of some variants of OPCA, the family history is usually negative. MRI scanning may be of assistance, revealing pontine, olivary and cerebellar atrophy in OPCA and abnormal striatal iron deposition in striatonigral degeneration;⁶ however, the appearance may be non-specific and sensitivity is relatively low.

Extrapyramidal dysfunction in association with a variety of other abnormalities, including ataxia, corticospinal tract findings, sensory abnormalities and amyotrophy can occur as a manifestation of dominantly inherited Azorean disease (Machado-Joseph disease).⁷ Like a number of the other dominantly inherited spinocerebellar ataxias, this condition is due to a triplet expansion.^{8,9}

GAIT DISTURBANCE

Postural disturbances and abnormalities of gait are key features of Parkinson's disease. Not uncommonly, one may see patients with a gait which is reminiscent of parkinsonism, in that the steps are small and shuffling. In typical Parkinson's disease, the base is narrow, but in these patients there may be a relatively broad base, suggestive of midline cerebellar disease, but without true ataxia. This combination of features suggests frontal lobe disorders, and may be seen with communicating hydrocephalus, multiple (lacunar) infarcts, cerebral atrophy or, rarely, subdural hematoma or tumours. The gait does not usually respond to levodopa treatment and CT or MRI scanning will settle the diagnosis. This appearance has also been referred to as "lower half Parkinsonism", in association with multiple lacunar infarcts.¹⁰

OTHER CONDITIONS PRESENTING AS PARKINSONISM

Drugs and other toxins

The single most important cause to exclude is the use of neuroleptic agents, including metoclopramide (domperidone is relatively devoid of extrapyramidal effects in most patients). Rarely, one will see patients taking reserpine-containing antihypertensive agents. If Parkinsonism persists following withdrawal of neuroleptics, one has to consider the possibility that they simply uncovered latent disease which would have eventually developed in any case. Neuroleptic-induced tremor may be more rapid and more postural than that of idiopathic Parkinson's disease, but this is far from reliable, and it is worth remembering that neuroleptics may result in asymmetric findings. Calcium channel blockers, particularly cinnarizine and flunarizine, have been associated with parkinsonism as well.^{11,12}

MPTP is a very uncommon cause of parkinsonism, but chronic amphetamine abusers may rarely develop a state of dopamine depletion. Intravenous drug abusers are at risk of HIV infection, which may result in a variety of movement disorders,¹³ as well as heightened sensitivity to the effects of neuroleptics.¹⁴

Table - Features of Parkinsonism due to Degenerative Disease

	PD	PSP	MSA&SCA's	Lewy Body Disease	CBGD	Juvenile HD
Corticospinal/corticobulbar abnormalities	–	++	+	–	+	+
Eye movement abnormalities	Breakup of smooth pursuit	Supranuclear gaze palsy, MSWJ, blepharospasm, “apraxia” of eye opening	Mild SN gaze paresis, nystagmus	May have SN palsy	May have SN palsy	Prominent slowing, impaired saccades
Autonomic	Mild, late	Minimal except bladder	Prominent, early	May be prominent	May occur	Not a major feature
Postural instability	Late	Prominent, early	May be prominent			Prominent
Cognitive changes	Not prominent early	Subcortical dementia	Variable	Visual spatial dysfunction, fluctuating course, hallucinations	Variable; prominent apraxia, cortical sensory loss	Prominent

MSA = multiple systems atrophy; SCA = spinocerebellar ataxia; CBGD = cortical basal ganglionic degeneration; MSWJ = macro square wave jerks; SN = supranuclear

Manganese¹⁵ and carbon disulfide can result in akinesia and rigidity, generally in association with more widespread nervous system dysfunction, and result from specific industrial exposures. Survivors from carbon monoxide, cyanide or methanol intoxication may have some features of parkinsonism. n-hexane and other solvent exposures have been linked to the development of parkinsonism.^{16,17}

Other degenerative diseases associated with parkinsonism

Parkinson's disease frequently results in cognitive impairment. Prominent cognitive dysfunction occurring early in the course of the illness, and in particular the presence of positive psychiatric manifestations (hallucinations and delusions), fluctuating course and visual-spatial impairment, should suggest the possibility of diffuse Lewy body disease, which may also be associated with supranuclear gaze disturbance and autonomic dysfunction.^{18,19}

Parkinsonism may be associated with motor neuron disease and dementia as part of Guamanian Parkinson-ALS syndrome. Neuroacanthocytosis (a term preferable to choreoacanthocytosis) may result in a variety of neurological manifestations, including mild cognitive impairment, parkinsonism, tics, chorea, eating dystonia and amyotrophy with absent ankle jerks. Acanthocytes (detected by examination of a wet blood smear) are seen in the absence of lipoprotein abnormalities. CT or MRI scans may reveal caudate atrophy, the CK is often elevated, and the family history is frequently positive.

Cortical basal ganglionic degeneration (with neuronal achromasia) is an increasingly recognized syndrome in which asymmetric rigidity is associated with apraxia, cortical sensory disturbances, cognitive impairment, supranuclear gaze disturbance and a variety of involuntary movements, including focal reflex

myoclonus and semipurposeful movements of which the patient is aware, but over which he/she has no control (“alien limb” syndrome). Response to therapy is poor.²⁰⁻²³ Although the diagnosis is predominantly clinical, [¹⁸F]fluoro-2-deoxyglucose positron emission tomography may help, revealing widespread and asymmetric cortical and subcortical hypometabolism.²⁴ It has more recently been recognized that there may be a much greater clinical and pathological overlap than previously appreciated among disorders associated with abnormal tau-immunoreactivity, including corticobasal degeneration, Pick's disease and progressive supranuclear palsy.^{25,26}

Parkinsonism onset in a young individual should lead to a consideration of juvenile (rigid) Huntington's disease (Westphal variant). As a general rule, any extrapyramidal disorder onset in a young person should also trigger a search for Wilson's disease, including slit lamp examination and determination of plasma copper and ceruloplasmin. Hallervorden-Spatz disease may produce akinesia-rigidity, dystonia, chorea or myoclonus and is associated with retinitis pigmentosa, peripheral neuropathy and recessive inheritance. MRI may reveal abnormal iron deposition in the basal ganglia as well as periventricular demyelination. Some forms have been associated with sea blue histiocytes.

Other rare causes of parkinsonism

Parkinsonism due to epidemic encephalitis lethargica has virtually disappeared. This disorder was associated with tics, dystonia (particularly oculogyric crisis, which is otherwise seen following neuroleptic use), eye movement abnormalities, sleep disorders and psychiatric disturbance. Sporadic cases of encephalitic parkinsonism are still encountered.²⁷ Parkinsonism has been reported following central pontine myelinolysis and Type 3 GM1 gangliosidosis.

DIAGNOSTIC APPROACH

This is really based on the history and physical examination. Clinicopathological studies indicate that initial diagnostic accuracy is approximately 65% and this increases to 76% with the benefit of followup.^{28,29} A sustained (more than 2 years) and unequivocal response to levodopa is highly predictive of predominant degeneration of nigral compacta neurons, with relative preservation of the striatum.³⁰ This response can often be predicted based on an acute challenge with levodopa or apomorphine. Other supportive clinical features include unilateral onset, rest tremor, prolonged duration and levodopa-induced chorea. Strongly positive family history, early age of onset or atypical features should prompt laboratory investigation - in most cases, MRI, slit lamp examination, plasma copper and ceruloplasmin will suffice.

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