Review Article

Accuracy in the clinical diagnosis of parkinsonian syndromes

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Summary: This review of Parkinson's disease and related disorders emphasizes the difficulties of distinguishing between variants of the parkinsonian syndrome. Characteristic clinical features may remain absent for many months, but accuracy of diagnosis may be improved by considering certain presenting symptoms and signs. The main characteristics of various parkinsonian syndromes are reviewed and their major distinguishing features are emphasized. Future improvement in the precision of clinical diagnosis, especially early in the course of parkinsonian syndromes, will depend on selecting out patients with Parkinson's disease using positive diagnostic criteria.

Introduction

Idiopathic Parkinson's disease is the foremost of a variety of disorders characterized by slowness of movement and muscular stiffness¹ (Table I). Many are degenerative diseases in which loss of nigro-striatal neurones and dopaminergic input to the striatum are responsible for the parkinsonian disorder. Another common mechanism is pharmacological interference by dopamine receptor antagonists acting at the post-synaptic striatal dopamine receptor. The variety of pathologies embraced by the parkinsonian syndromes is illustrated by one neuropathological study of 67 unselected parkinsonian cases.² Only 29 (43%) had pathology consistent with Parkinson's disease, which is cell loss in the substantia nigra with Lewy inclusion bodies in remaining cells. The rest had findings compatible with a number of other parkinsonian syndromes. In most other studies restricted to patients with Parkinson's disease the frequency of this pathology is reported in 70%³ to 96%,⁴ reflecting inaccuracy in clinical diagnosis or inconsistent pathology.

A recent study has been done to examine whether Lewy bodies are found in the substantia nigra of all persons dying with Parkinson's disease.⁵ A retrospective clinical diagnosis of Parkinson's disease was made in a selected group of 78 patients.

Seventy-four showed loss of pigmented cells in the substantia nigra with Lewy bodies in some of the remaining cells. Two brains without these inclusions had the pathology of striatonigral degeneration⁶ and two had the pathology of post-encephalitic parkinsonian syndrome.⁷ Lewy bodies are not associated with the pathology of these disorders so that Parkinson's disease can be diagnosed and defined according to pathological criteria as a parkinsonian disorder with Lewy bodies in the substantia nigra.

Table I Causes of parkinsonian syndromes

Idiopathic Parkinson's disease
Drug-induced neuroleptics, reserpine
Striatonigral degeneration (multiple system atrophy)
Steele-Richardson-Olszewski syndrome
Alzheimer's disease
Atherosclerotic vascular disease
Communicating hydrocephalus
Post-encephalitic parkinsonian syndrome
Trauma
Tumours
Carbon monoxide poisoning
Corticobasal degeneration
Juvenile parkinsonian syndrome
MPTP
Basal ganglia calcification
Wilson's disease

Refer to Fahn¹ for a more comprehensive list.

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Many parkinsonian disorders have clinical features which are not seen in Parkinson's disease, but the conditions that most commonly cause confusion include striatonigral degeneration and drug-induced parkinsonian syndrome. The difficulties in diagnosis lie in the fact that in the early months or years of a parkinsonian disorder features diagnostic of atypical syndromes may be absent.

Parkinson's disease is traditionally diagnosed in two stages. Firstly by identifying a parkinsonian syndrome, by recognising any two of bradykinesia, muscular rigidity, rest tremor and postural instability. Secondly by using a mental checklist of exclusion criteria (Table II), which may provide evidence for the alternative diagnoses (listed in Table I and discussed below). Some clinicians might argue that the current diagnostic success rate of 75–90% for Parkinson's disease is acceptable provided that surgically treatable conditions, such as communicating hydrocephalus and tumours, are excluded. A trial of L-dopa and a treatment diagnosis, as a responder or non-responder, is usually considered the next step. However, an uncritical approach to diagnosis is inappropriate, because 'benign' and specifically treatable disorders such as essential tremor or drug-induced parkinsonian syndrome can be difficult to diagnose even by experienced clinicians. Awareness of the course of a disease will readily identify remediable complications, such as those of confusion or dementia resulting from drug therapy, infection or subdural haematoma. Repeated clinical examinations and accurate documentation of signs may be necessary to assess response to L-dopa therapy and to identify fresh clinical signs incompatible with a diagnosis of Parkinson's disease alone. Diagnostic accuracy is also essential for epidemiological work, drug trials, neurochemical and pathological studies, for which rating scales for documenting stages of disease severity are valuable.⁸

Idiopathic Parkinson's disease

The age of onset can range from 20 years upwards, but the disease is more common in middle and late age. The mean age of onset is about 60 years and the disease duration 10 years, possibly with an additional 2 to 4 years with L-dopa treatment. A number of vague, isolated, fluctuating or persistent symptoms often precede parkinsonian signs by many months (Table III). These provide opportunities for misdiagnosis as they are not specific to Parkinson's disease or any other parkinsonian syndrome. In some patients the onset

appears to be abrupt and may be attributed to stressful physical or emotional life events. With relief from stress, symptoms may remit, only to reappear weeks or months later. A number of early signs may be suggestive (Table III), but confident diagnosis of a parkinsonian syndrome depends on identifying at least two of bradykinesia, rest tremor, muscular rigidity and impaired postural reflexes. First symptoms of Parkinson's disease are often

Table II Criteria that exclude or question a diagnosis of Parkinson's disease

Criteria that exclude Parkinson's disease

Oculogyric crises
Gaze palsy
Several affected relatives
Poor or absent response to L-dopa
Cerebellar signs
Peripheral neuropathy
Autonomic neuropathy
Complete remission of symptoms/signs*

Criteria that place the diagnosis in doubt

Neuroleptic medication
Dementia at onset
Evidence of arteriosclerosis
Unexplained pyramidal signs

*Minor fluctuation and apparent remission of symptoms may occur at the onset.

Table III Early symptoms and signs of Parkinson's disease*

Early symptoms

Fatigue following exertion, lethargy, depression
Restlessness, anxiety
Drooling, constipation,
Low volume or hoarse voice
Small handwriting
Muscle cramps, pains, stiffness
Difficulty rising from chair or turning in bed
Difficulty with balance or turning, especially in the elderly
Slowness over daily activities

Early signs

Expressionless face
Slow movement with decrement in amplitude and disintegration of continued or repeated movement
Reduced movement – including blink rate, arm swing on walking, spontaneous gestures
Loss of automatic and emotional control of expression
Positive glabellar tap
Axial or proximal rigidity on synkinesis
Pseudohemiparesis

*These symptoms and signs occur in other parkinsonian syndromes.

tremor or difficulty in walking in the elderly, and tremor or muscular stiffness in younger patients. Tremor at rest has been shown in pathological studies to be fairly specific for Parkinson's disease^{9,10} and about 70% of patients may show it.¹¹ Onset with unilateral symptoms is common and persistent asymmetry affecting the side of onset most is characteristic.¹² L-Dopa consistently produces moderate or good improvement, and this may increase for some months.¹³ In a series of 400 patients with Parkinson's disease 15% did not show a beneficial therapeutic response to L-dopa, suggesting that they had other parkinsonian disorders, many of which are not generally responsive to L-dopa.¹⁴ No patient with uncomplicated Parkinson's disease, defined pathologically, has been shown to have a negative response to L-dopa.

A multitude of additional parkinsonian symptoms and signs, for example, alterations of speech, facial appearance and handwriting, do not appear to have any predictive diagnostic value,¹⁵⁻¹⁷ and their presence does not therefore justify the term 'typical' Parkinson's disease. However, information obtained from clinico-pathological studies suggests that certain features are more common in Parkinson's disease (Table IV). These need to be elaborated and justified, but form the basis of a third stage in the diagnostic process. They act as positive diagnostic criteria, three or more of which, for example, might justify a diagnosis of clinically definite Parkinson's disease.

Drug-induced parkinsonian syndrome

Drugs responsible include pre-synaptic dopamine depleting agents and post-synaptic dopamine receptor blocking agents. In the past drug-induced parkinsonian syndromes have been considered almost solely the result of high dose neuroleptic therapy, which causes a symmetrical bradykinetic syndrome with minimal tremor. About 15% of young persons on large doses develop this syndrome within a few weeks. There is now greater awareness of a syndrome indistinguishable from

Parkinson's disease occurring in older patients treated with small doses of less potent drugs. For example, 48 of 95 patients admitted to a department of geriatric medicine with a parkinsonian syndrome had consumed neuroleptics.¹⁸ Tremor was present in 40%, bradykinesia in 80% and falls or inability to walk were frequent. At least 6 months without medication may be required to distinguish drug-induced from idiopathic disease.

Striatonigral degeneration

Striatonigral degeneration causes a parkinsonian syndrome, but olivopontocerebellar atrophy and degeneration of the autonomic nervous system, which coexist, may cause additional cerebellar signs and autonomic failure (multiple system atrophy).¹⁹ Cases in which striatonigral degeneration dominate the pathology may be difficult or impossible to distinguish from Parkinson's disease.

In a personal review of clinical findings in 56 pathologically confirmed cases of striatonigral degeneration the sex ratio was 43% male and 57% female, the mean age of onset was 55 years (range 41-75), and the mean duration 4.8 years (range 0.5-11). Rest tremor alone was recorded in only 14%, another 25% had tremor of undisclosed type and another 14% had intention tremor. Asymmetry of signs was documented in 21%, but persistent asymmetry was uncommon, being recorded in one case for 4 years²⁰ and another case for 9 years before becoming generalized.²¹ Twenty-seven patients received L-dopa and most failed to respond, but a modest short-lived response was obtained in three and a further three cases responded for 6 months. Another patient responded for 3 years.²² Bradykinesia was improved most of all, followed by rigidity, but the effect on postural hypotension was variable. A modest improvement in parkinsonian disability was described in the early L-dopa era,²³ but the extent to which the L-dopa response in terms of fluctuations in motor performance mimics that in Parkinson's disease may not be fully appreciated.²⁴

The essential features of this disorder comprise both cerebellar signs and autonomic failure, associated with a parkinsonian disorder, but the diagnosis may be suspected at an early stage if the patient is of the appropriate age, if there is a poor response to L-dopa and if autonomic failure or cerebellar features are present.

Steele-Richardson-Olszewski syndrome

Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy) can also be difficult to

Table IV Positive criteria for Parkinson's disease

Unilateral onset
Rest tremor
Persistent asymmetry affecting the side of symptom onset most
Excellent response to L-dopa
Severe L-dopa-induced chorea
L-dopa response for 5 years or more
Clinical course of 10 years or more

distinguish from Parkinson's disease, especially early in its course, although the presenting symptoms are often different. In a personal review of 57 cases coming to autopsy the most common symptoms in order of frequency were unsteady gait and frequent falls, visual difficulties involving focussing and reading, double vision, personality change comprising irritability, forgetfulness, emotional lability, mental slowing (bradyphrenia), dementia, depression; and also dysarthria and dysphagia. A recent clinical analysis of 52 patients identified similar features.²⁵ Early pathological studies were almost totally dominated by male cases, but the disparity is now less obvious with 65% male and 35% female, mean age of onset 58 years (range 47–69 years, in 19 pathologically verified cases), and duration of illness 5.3 years (range 1.5–12 years in 19 cases). Characteristic signs are supranuclear paralysis of gaze, cervical and axial dystonia, and pseudobulbar palsy, but these can take up to nine years to appear.^{26–28} Atypical presentations are not uncommon and ophthalmoparesis or cervical dystonia may remain absent.^{29,30} Mental slowing can be marked, as can speech disorder with stuttering palilalia and anarthria. Pyramidal and cerebellar signs also occur. Mild postural limb tremor is recorded in 1 in 10 cases, but rest tremor in only one.³¹ Response to L-dopa at some time during the illness, occurs in 20–25% and provides short-lived improvement in bradykinesia, but beneficial effects on ophthalmoparesis and dystonia are unusual.

The diagnosis of Steele–Richardson–Olszewski syndrome is strongly suggested in patients with a parkinsonian disorder and supranuclear paralysis of downgaze, but supranuclear ophthalmoplegia occurs in a variety of disorders, including degenerative diseases,³² so that characteristic signs (postural instability with backward falls, extreme bradyphrenia), cervical dystonia or pseudobulbar palsy are also necessary features.

Alzheimer's disease

A slight shuffling gait and posture of flexion are common in the late stages of Alzheimer's disease, but a true parkinsonian syndrome has not been clearly described in uncomplicated cases. Mild signs of motor slowing and muscular stiffness were reported in 40 of 65 patients, 27% of whom also had tremor of undisclosed type.³³ Rest tremor, which is a non-specific sign of Parkinson's disease, has been reported in 4% (71 patients),³⁴ and 10% (143 patients)³⁵ of patients.

Atherosclerotic vascular disease

Atherosclerosis is still said to be the cause of parkinsonian states, but a true parkinsonian syndrome in the absence of Lewy body pathology has not been described. Bilateral strokes produce a clinical picture resembling a bradykinetic-rigid syndrome, but without rest tremor. Facial masking, bilateral pyramidal signs and a pseudobulbar palsy with speech disturbance are not uncommon. Additional signs include dementia and urinary incontinence.

Bilateral subcortical vascular disease confined to white matter, either focally (lacunar infarcts) or diffusely (Binswanger's disease), usually produces clinical features that constitute only a fragment of the parkinsonian syndrome. Typically such patients have hypertension, an ataxic-parkinsonian (broad-based shuffling) gait and facial masking, but other signs may be lacking.³⁶

Extensive, striatal infarction might cause a true bradykinetic-rigid syndrome,³⁷ but pathologically studied cases have not been reported.

Communicating hydrocephalus

Clinical features of communicating hydrocephalus are similar to those of subcortical vascular disease. An unsteady, shuffling gait with a tendency to fall is common in the early stages. Urinary incontinence and dementia may follow. Features such as hypomimia, slowing of movements and muscular stiffness may occur, but tremor is unusual. Tremor at rest was recorded in two patients (not studied pathologically), but disappeared following the insertion of a CSF shunt.³⁸

Post-encephalitic parkinsonian syndrome

There are very few survivors of the original cohort of persons affected by the encephalitis lethargica epidemic of 1917–1925, but the condition remains of interest because of the relatively selective effect of the putative viral agent on the substantia nigra and the rare sporadic cases that still occur.^{39–45}

Pathologically the brains show neuronal inclusions called neurofibrillary tangles in the substantia nigra, but the inflammatory process is often widely spread through other parts of the brain and spinal cord. A reasonably confident retrospective diagnosis depends on a history of definite encephalitis between 1917 and 1925, associated with lethargy, sleep disorder, eye signs or behavioural change. Onset of a parkinsonian

syndrome within 5 years of encephalitis, which occurred in 50% of patients,⁴⁶ is another sensible guide. Occasionally oculogyric crises followed mild or subclinical illness, and provided support for the diagnosis. The range of additional signs was greater than in Parkinson's disease and included chorea, multiple tics, persistent sleep disorder, ocular palsies, mental disturbance and palilalia. In long survivors the parkinsonian syndrome was often milder, more chronic and more slowly progressive, with unilateral rest tremor and rigidity persisting for 10–40 years.¹¹ When L-dopa became available it gave significant improvement in well over half the cases, but beneficial effects and adverse effects, such as dyskinesias, occurred at about one half the dose used in Parkinson's disease.

On rare occasions today it would be reasonable to entertain the diagnosis of an encephalitis lethargica-like illness if a similar form of encephalitis was closely followed by a parkinsonian syndrome or by oculogyric crises, in the absence of neuroleptic medication. Slow or absent progression of disease in long survivors and the often dramatic effect of L-dopa are important distinguishing features.⁴⁷ The presence of oligoclonal bands of immunoglobulin in the cerebrospinal fluid may be helpful diagnostically.^{41,43,44}

Trauma

Repeated head trauma after years of boxing produces various combinations of dementia, pyramidal and cerebellar signs and a parkinsonian syndrome (pugilistic parkinsonism). Pathologically neurofibrillary tangles develop in the brainstem, including the substantia nigra, and medial temporal cortex, but other widespread abnormalities of the ventricles, corpus callosum, septum pellucidum and cerebellum occur.⁴⁸

Tumours

Gliomas or meningiomas (and other mass lesions) particularly in the brainstem and frontal lobes, with or without hydrocephalus, may cause a parkinsonian syndrome, but additional signs are usual. For example frontal lobe tumours produce gait disturbance, urinary incontinence, dementia, muscular rigidity, facial hypomimia and occasionally rest tremor.

Carbon monoxide poisoning

A parkinsonian disorder most often results from

acute poisoning following attempted suicide sufficient to produce coma. After recovery from coma there is a complex neurological picture with dementia, pyramidal signs and parkinsonian features.⁴⁹ Rarely the syndrome is more specific, as reported in a 50 year old woman who exhibited tremor at rest, but did not show a response to L-dopa.⁵⁰ As with other anoxic-type injuries there is relatively selective necrosis of the globus pallidus and the putamen.

Other parkinsonian syndromes

Corticobasal degeneration is increasingly recognized as a disorder with a variety of clinical manifestations, which may resemble those of the Steele–Richardson–Olszewski syndrome. The original report of three patients in their sixth and seventh decades described stiffness of limbs, choreiform movements, dystonia, supranuclear gaze palsy, cerebellar and pyramidal signs, in addition to parkinsonian features.⁵¹ Important areas of pathological change include the parietal cortex and substantia nigra.

Juvenile parkinsonian syndrome, also recognized by the terms hereditary dystonia with diurnal fluctuations and Segawa disease, is another syndrome receiving increasing attention as the cause of a slowly progressive disorder with foot dystonia, parkinsonian features and an excellent response to L-dopa.⁵²

The toxic effects of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) have been confined to drug addicts in Maryland and California who inadvertently synthesized the compound during their attempts to develop a potent pethidine analogue.^{53,54} Young addicts who injected this compound developed an irreversible syndrome with bradykinesia, rigidity and occasionally rest tremor. This was accompanied by the gamut of signs seen in Parkinson's disease, particularly flexed posture, facial seborrhoea, drooling of saliva and difficulty with initiation of movements. There have been good responses to L-dopa, but drug-induced dyskinesias develop early. Neither moderate intellectual deterioration nor progression of disease have satisfactorily been shown over at least two years of follow-up.⁵⁵ Structural damage is concentrated in the nigrostriatal system and locus coeruleus, so as a model of a relatively selective insult to the substantia nigra the future course of the parkinsonian syndrome may resemble that following encephalitis lethargica.

Basal ganglia calcification demonstrated by plain skull X-ray or at post-mortem is usually asymptomatic.

matic, but modern imaging techniques detect many milder examples. In a few cases there is a clear association with parathyroid-related disorders, usually any cause of hypoparathyroidism. Occasionally this is associated with a parkinsonian syndrome, which is L-dopa resistant.⁵⁶ In one case of post-operative hypoparathyroidism there was a festinant gait, masked face, bilateral pill-rolling tremor and rigidity of neck and limbs,⁵⁷ signs which apparently disappeared after intravenous calcium.

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