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Diagnostic criteria for Parkinson's disease

Abstract The diagnosis of Parkinson's disease is not easy. Developments in basic research have indicated pathophysiological links among parkinsonian syndromes that are still classified as independent entities. On the other hand, genetic studies are dividing forms that fit into the clinical diagnosis of Parkinson's disease. The diagnostic criteria used in current practice are by no means satisfactory, but cannot yet be replaced by new comprehensive criteria based on laboratory evidence.

Key words Parkinson's disease • Diagnosis • Clinical features

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Parkinson's disease (PD) is just one of several parkinsonian syndromes. The criteria used to define PD have varied over time and to some extent across studies performed at the same time. Many studies published 10 or more years ago grouped parkinsonism of any cause. Even when modern diagnostic criteria are applied, identification of early disease is difficult, since up to 80% of substantia nigra pars compacta may be lost before any clinical signs are apparent [1].

Three phases of the disease can be distinguished.

The pre-clinical period, when the degenerative process is ongoing, but no symptoms can be detected. This is thought to correspond to the phase when the number of degenerated neurons has not yet reached the threshold for clinical recognition. This may last from few to many years.

The prodromal period, when initial symptoms are not specific. For example, depression, anxiety, fibromyalgia, or shoulder pain may begin some months or even years before the onset of diagnostic symptoms.

The symptomatic period, when parkinsonian symptoms are evident.

Many individuals with asymptomatic PD may remain in the pre-clinical period and be undiagnosed at death [2]. Clinically diagnosed PD does not always show typical pathological changes on postmortem examination. Surveys of postmortem findings in cases clinically diagnosed as PD found typical postmortem neuropathology in only 80% of cases [3, 4]. These results probably overestimate the actual misdiagnosis rate, however, since autopsy is most likely performed when there is a question of clinical diagnosis.

During the symptomatic period, PD relentlessly progresses. The cardinal signs consist of tremor, bradykinesia, rigidity, and postural instability. In addition to these signs, there are many motor and non-motor manifestations of PD, including cognitive, sensory, and autonomic disturbances. Within PD, there are different subgroups with relatively specific clinical patterns. For example, several studies have now demonstrated that patients with tremor as the dominant parkinsonian symptom generally have less bradykinesia and slower progression of the disease than those with postural instability

and gait difficulty as the dominant features [5]. The latter group generally is older, is more likely to be cognitively impaired, and has a more rapidly progressive course than the tremor group. Age is also an important variable with reference to classification of PD. It has become increasingly recognized that early onset PD (before age 40 years) is often genetically determined [6]. Autosomal recessive forms of early onset parkinsonism are caused by mutations in the parkin gene (*PARK2* locus) on chromosome 6q [7]. In Europe, mutations in the parkin gene explain almost half of the families with recessive parkinsonism and onset before age 45 years [8]. Recent evidence indicates that susceptibility to late-onset (otherwise typical) PD may also derive from specific mitochondrial DNA haplotypes. One of the intriguing questions is whether the different subgroups represent variations of the same disease, namely PD, or whether they are etiologically distinct entities.

Pathologically PD is defined as a neurodegenerative disorder characterized chiefly by depigmentation of the substantia nigra and by the presence of Lewy bodies (LBs). These criteria, however, are too restrictive and simple, and they do not take into account the heterogeneous clinical and pathological presentation of PD and the overlap with other parkinsonian disorders, each with presumably distinct etiology. In the absence of a specific biological marker for PD, the differentiation of PD from other parkinsonian disorders rests on clinicopathological criteria that have yet to be rigorously tested and validated. Recent studies have shown that certain populations of neurons are more vulnerable than others and the neuronal loss in PD is not uniform. For example, the ventrolateral part of the substantia nigra that projects chiefly to the putamen is more affected than the dorsal part [2]. Although pigmented neurons in the substantia nigra degenerate more than the non-pigmented neurons [9], the other brain stem catecholaminergic neurons seem to degenerate regardless of the degree of melanin pigmentation [10]. LBs, eosinophilic cytoplasmic inclusions with an unstained halo, represent the typical histological hallmark of PD. Because these inclusions have been typically found in PD and they are usually absent in most other neuronal degenerations, they are useful in differentiating PD from other parkinsonian disorders. In contrast to PD, brains of patients with pathologically proved multiple system atrophy (MSA) [11] were found to have distinct glial cytoplasmic inclusions [12]. Notwithstanding their morphological dissimilarity, both LBs and glial cytoplasmic inclusions contain α-synuclein [13]. Furthermore, α-synuclein gene mutations cause familial PD in rare families [14], and these mutations may be pathogenic by altering the properties of α-synuclein, thereby promoting the formation of α-synuclein filaments that aggregate into LBs.

Whereas LBs are regarded as hallmark intracytoplasmic neuronal inclusions of PD, they also occur in the most-common subtype of Alzheimer's disease (AD) known as the LB variant of AD. Numerous cortical LBs are also the defining brain lesions of dementia with LBs, which is similar to AD clinically, but distinct from AD pathologically [15, 16]. Nonetheless, the accumulation of α-synuclein into filamentous inclusions appears to play a role in the pathogenesis of several progressive neurological disorders including PD, dementia with LBs, Down's syndrome, familial AD, LB variant of AD, sporadic AD, MSA, and other synucleinopathies.

The vast majority (up to 80%) of patients with hypokinetic movement disorders have presumed PD. Their diagnosis is still based on clinical criteria, with the exception of obtaining a genetic diagnosis when possible. The most commonly used criteria for PD are summarized in the flow chart proposed by the UK Brain Bank [17] (Fig. 1, Table 1). These criteria require verification of the occurrence of exclusion criteria and consideration of a parkinsonian syndrome other than PD before affirming a diagnosis of probable PD.

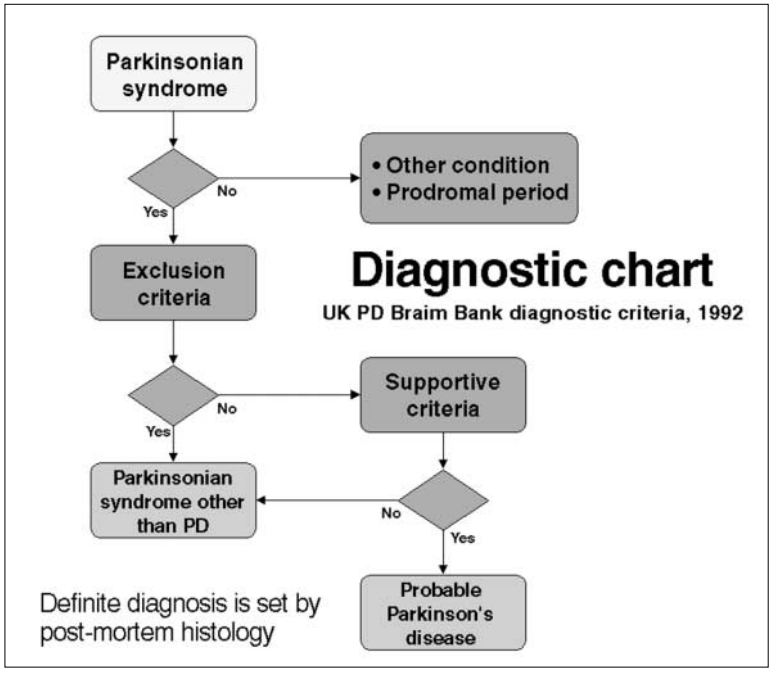

Fig. 1 Flow chart for the diagnosis of Parkinson's disease (PD) based on the criteria set by the UK PD brain bank [17]

Table 1 Exclusion criteria for Parkinson's disease [17]

History of repeated strokes with stepwise progression of parkinsonian features
History of repeated head injury
History of definite encephalitis
Oculogyric crises (unless drug-induced)
Neuroleptic treatment at onset of symptoms
Sustained remission
Supranuclear gaze palsy
Cerebellar signs
Early severe autonomic involvement
Early severe dementia
Babinski sign
Presence of cerebral tumor or communicating hydrocephalus on CT scan
Negative response to an adequate dose of levodopa

CT, computed tomography

Table 2 Clues suggesting atypical parkinsonism

Early onset of, or rapidly progressing, dementia
Rapidly progressive course
Supranuclear gaze palsy
Upper motor neuron signs
Cerebellar signs-dysmetria, ataxia
Severe urinary incontinence
Early symptomatic postural hypotension

Secondary parkinsonism is thought to represent 8.2% of all our parkinsonian patients. The causes include environmental exposure (e.g., drugs or toxins) and other factors (trauma, metabolic derangement, infection, stroke, brain tumor). 'Lower body' parkinsonism, a condition in which upper body motor function is relatively preserved while gait is markedly impaired, is often associated with multiple lacunar infarctions and may represent one form of vascular parkinsonism [18]. Medications known to cause parkinsonism include dopamine receptor blocking drugs, such as antipsychotics and antiemetics (e.g., meloclopramide), dopamine-depleting drugs, such as reserpine, tetrabenazine, and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), and alpha-methyldopa. Drug-induced parkinsonism was noted in 4% of all our parkinsonian patients. Rare causes of parkinsonism include pseudodegenerative diseases, such as Huntington's disease, Wilson's disease, Hallervorden-Spatz disease, and familial basal ganglia calcification.

The UK brain bank criteria also state that a diagnosis of definite PD can only be made by autopsy (Table 1). Therefore, patients with a full-house clinical picture will be classified as affected by probable PD.

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