Parkinson's disease

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The diagnosis of Parkinson's disease (PD) is clinical and there are no biological markers to confirm it during life.[1] Confirmation is possible only post mortem. There are no accepted neuropathological criteria for PD[2] and there is an ongoing debate on whether PD is a single entity.[3,4] This is because of the description of genetic forms of PD with clinical features typical of sporadic PD but pathological features distinct from it.[5] Early accurate diagnosis of PD may be important for institution of disease course -modifying treatments when they become available, for prognostication and for research purposes.[6] Recognizing early PD is not easy. It is also well known that in the early stages of the disease, PD and other forms of degenerative parkinsonism share common features and clinical distinction may be difficult.[7] The certainty of diagnosis increases as the disease advances and in specialist clinics.[8] Even though PD is considered as a predominantly motor disorder, non-motor symptoms occur at all stages of the disease[9] and may even antedate it.[10,11] However, the diagnosis of PD rests on motor signs. The three cardinal motor manifestations of PD which are essential to make a diagnosis are rest tremor, rigidity, and bradykinesia.

Rest tremor (4-6 Hz) tremor occurring when the limb is fully supported). It can be brought out by mental stress, during walking, or while performing alternating finger taps with the opposite hand. Some patients have postural tremor but appears only after a latency of seconds to a minute of assuming the outstretched posture of arms (re-emergent tremor).[12] This feature, if present, helps to differentiate PD tremor from postural tremor due to other causes, e.g. essential tremor (ET) in which tremor appears immediately on assuming the posture. Typically, rest tremor of the hands in PD has a pill rolling appearance and abates during action. In the head region, tremor occurs in the lips, chin, and jaw but is infrequent in the neck. About 75% of PD patients have tremor during the course of their illness.[13]

Rigidity (resistance offered to passive flexion-extension or rotation movement of major joints with the patient sitting relaxed. It does not include cog-wheel rigidity caused by tremor). Rigidity in PD is lead pipe-like, is present throughout the range of movement, and is not velocity dependent. In PD, rigidity involves both neck and limbs while in progressive supranuclear palsy (PSP) there is a disproportionate axial preponderance of rigidity.[14]

Bradykinesia (slowness of initiation of voluntary movements with progressive reduction in speed and amplitude of repetitive actions). It is tested by asking the patient to do repeated finger taps, alternate pronation and supination of forearm, opening and closing of fist and foot taps. Look for speed, regularity, arrests of ongoing movement and slowness. Fatiguing or gradual reduction in amplitude during continued activity and arrests are typical of true bradykinesia.

Postural instability (not due to cerebellar, vestibular, posterior column or visual dysfunction). In the clinic this may be demonstrated by the "pull test." This is assessed from the response to the sudden strong posterior displacement produced by a pull on shoulders while the patient stands erect with eyes open and feet slightly apart. The patient is prepared for the test and can have a few practice runs. Many experts do not consider postural instability by itself for the early diagnosis of PD as it is seldom present in early stages and is nonspecific. Onset with postural instability and gait disturbance (PIGD) tends to be more often due to atypical parkinsonism.[15]

Although several clinical criteria have been proposed for PD, most have not been evaluated for reliability and validity. The United Kingdom Parkinson's disease Society Brain Bank Clinical Diagnostic Criteria[16] [Table 1] is based on a retrospective clinico- pathological study and has been tested

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in autopsy confirmed cases and found to have an accuracy of around 75% to 80%.[17] The misdiagnosis in the remaining cases was from conditions such as multiple system atrophy (MSA), progressive supranuclear palsy (PSP), vascular parkinsonism and Alzheimer's disease. These criteria are useful for improving diagnostic accuracy but may not be useful in monosymptomatic and early stages of PD.[18] Early PD can have a wide variety of presentations including non-specific symptoms like generalized stiffness, pain and paresthesia, reduced appetite, constipation, sleeplessness, shoulder pain, and reduction in volume of voice or more specific ones like tremor during anxiety, sense of inner tremor, reduced arm swing, reduced facial expression, personality changes noticed by others, slowness, monotonous speech, micrographia, problems with fine motor task, dragging of leg, dystonia of limbs (especially in young onset PD due to Parkin mutations), mood changes, decreased smell, and increased salivation.[19-21] Response to treatment may support the diagnosis. Excellent response to levodopa and levodopa-induced chorea are seen more often in PD but can occur in MSA[22] where it wanes with time. Orofacial dystonia, spontaneous or levodopa induced, is often seen in MSA. Partial response to levodopa can be seen in PSP[23] and other atypical parkinsonism.

In order to address the issue of improving the early diagnosis of PD, Calne *et al.* proposed a designation of escalating levels of diagnostic confidence [Table 2].[24] Three categories were defined.

1. Clinically possible: Presence of any one of tremor, rigidity, or bradykinesia could qualify for clinically possible PD. Impairment in postural reflexes was not included. Tremor must be of recent onset and may be rest or postural.
2. Clinically probable: Two of the cardinal features of rest tremor, rigidity, bradykinesia, or impaired postural reflexes are required to make this diagnosis. Alternatively, asymmetrical rest tremor, asymmetrical rigidity, or asymmetrical bradykinesia alone may be sufficient.
3. Clinically definite PD: A combination of three of the features - rest tremor, rigidity, bradykinesia or impairment in postural reflexes - is required to make the diagnosis of PD clinically definite. Alternatively, two of the features are sufficient if one of the first three displays asymmetry. Laboratory support for the diagnosis could be applied to each category. However, these criteria have not been validated in pathologically confirmed cases.

There are certain conditions which are commonly mistaken for PD, especially in the early stages of PD. ET can have rest tremor[25] and also cogwheel type of rigidity. ET can be asymmetric; however, long-duration asymmetric postural tremor is more likely to be due to PD than ET.[26] The distinguishing features between the tremor of PD and ET are shown in Table 2. The other conditions producing rest tremor include dystonic tremor (tremor in a dystonic body part, irregular and abolished in certain positions), tardive tremor related to neuroleptic exposure, and Wilson's disease. The slowness of activities seen in hypothyroidism may be mistaken for bradykinesia. The slowness of activities and reduced facial expression in depression can resemble PD. Slowness of activities, slow gait, instability, and hypomimia of the elderly may also resemble PD. Diagnosis of PD should be made carefully in very old people in whom the presence of a rest tremor may be the most specific sign.[27]

PD needs to be differentiated from the secondary causes of parkinsonism. Vascular parkinsonism results from infarcts

Table 1: UK Parkinson's disease society brain bank clinical diagnostic criteria[16]

Inclusion criteria	Exclusion criteria	Supportive criteria
Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions)	History of repeated strokes with stepwise progression of parkinsonian features.	(Three or more required for diagnosis of definite PD)
	History of repeated head injury	Unilateral onset
	History of definite encephalitis	Rest tremor present
	Oculogyric crises	Progressive disorder
	Neuroleptic treatment at onset of symptoms	Persistent asymmetry affecting side of onset most
	More than one affected relative	Excellent response (70–100%) to levodopa
	Sustained remission	Severe levodopa-induced chorea
	Strictly unilateral features after 3 years	Levodopa response for 5 yr or more
	Supranuclear gaze palsy	Clinical course of 10 yr or more
	Cerebellar signs	
	Early severe autonomic involvement	
	Early severe dementia with disturbances of memory, language, and praxis	
	Babinski sign	
	Presence of cerebral tumor or communicating hydrocephalus on CT scan	
	Negative response to large doses of levodopa (if malabsorption excluded)	
	MPTP exposure	

And at least one of the following:
- Muscular rigidity
- 4-6 Hz rest tremor
- Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction

Table 2: Distinguishing features between tremor of Parkinson's disease and essential tremor

Feature	PD	ET
Tremor type	Predominantly rest; re-emergent postural tremor	Predominantly postural (immediate)
Tremor frequency	4-6 Hz	8–12 Hz
Tremor characteristics	Supination–pronation	Flexion–extension
Unilateral/bilateral	Usually unilateral to begin with	Usually bilateral
Areas involved	Head and voice tremor not usually seen	Head and voice tremor are usually seen
Response to alcohol	No	Common
Positive family history	Rare (less than 10%)	Usual (17–100% of patients in various series)

involving frontal lobe, deep subcortical white matter, and basal ganglia. The patients are more likely to present with gait difficulty and postural instability rather than tremor. They usually have a history of stroke and report risk factors for stroke. Focal signs like pyramidal signs and vascular dementia may co-exist. The patients usually have a more upright posture, wide based stance, and well-preserved arm swing compared to PD. Response to levodopa therapy is usually poor.[28] A variety of drugs including neuroleptics, dopamine receptor blocking agents, dopamine depletors (tetrabenazine), and calcium channel blockers can cause drug-induced parkinsonism (DIP). This could develop 1 to 3 months after introduction of a D2 receptor blocker neuroleptic or an increase in dose and generally resolves in weeks to months after discontinuation. Freezing and festination are rare in DIP. DIP is often difficult to differentiate from PD; useful clues for differentiation include parkinsonism associated with tardive dyskinesia or akathisia , symmetric signs, action greater than resting tremor and presence of a low-frequency, high-amplitude jaw tremor ("Rabbit syndrome").[29-31] The classical features of normal pressure hydrocephalus include gait disturbance, urinary incontinence and cognitive changes; however the triad is seen only in advanced cases.[32] Bradykinesia of upper limbs is seen in around 50% and frank parkinsonism, usually symmetrical, in less than 15% of patients.[33] Rest tremor and upper limb rigidity are rare. Gait is more wide-based and apractic in NPH. Gait difficulty is not usually overcome by stepping over examiners foot as it happens in PD. Wilson's disease is yet another cause for parkinsonism; most cases also have other signs like coarse "wing beating" tremor, dystonia, a "mixed" dysarthria, and neurobehavioral disturbances. Investigations like serum copper and ceruloplasmin measurement, slit lamp examination for Kayser–Fleischer ring, 24 h urinary free copper estimation, and liver biopsy are helpful in establishing the diagnosis in suspected cases. Infections (SSPE, mycoplasma pneumonia, HIV, viral encephalitis), metabolic disturbances (hyperparathyroidism), toxins (MPTP, manganese, carbon monoxide, cyanide, methanol), anoxia, and structural lesions (frontal, temporal, brainstem and posterior fossa space occupying lesions causing hydrocephalus) are relatively rare causes of secondary parkinsonism.

Differentiation of PD from other neurodegenerative causes of Parkinsonism is important from the treatment and prognostication point of view. MSA is characterized by a combination of varying degrees of parkinsonism, early and prominent autonomic dysfunction, and cerebellar dysfunction. Parkinsonism is predominant in MSA-P and cerebellar dysfunction is more prominent in MSA-C.[34] Red flags that suggest MSA are disproportionate anterocollis (chin on chest), severe lateroflexion of trunk, head and neck (Pisa syndrome), orofacial dystonia that are spontaneous or L-dopa induced, irregular action and postural tremor of hands, severe hypophonic quivering high pitched dysarthria, emotional incontinence, nocturnal strider, or excessive snoring. Dementia and behavioral changes are not usually seen.[35] MRI may be supportive. Patients with PSP present with progressive unexplained and unexpected falls or tendency to fall (backwards or in any direction) within 1 year of onset of parkinsonism.[36] Vertical supranuclear gaze paresis (any downward or moderate to severe upgaze) is characteristic. The parkinsonism is generally symmetric with axial more than appendicular rigidity, behavioral and cognitive changes, early dysphagia, and dysarthria.[37] MRI may be supportive. Cortico-basal degeneration (CBD) results in progressive cortical dysfunction such as asymmetric ideomotor or constructional apraxia, alien limb phenomenon, cortical sensory loss, focal myoclonus, apraxia of speech, or nonfluent aphasia. Extrapyramidal dysfunction such as asymmetric appedicular rigidity that is levodopa unresponsive and asymmetric appendicular dystonia is also part of the clinical picture.[38] MRI findings may support the diagnosis. Dementia with Lewy bodies (DLB) is a dementia syndrome associated with visual hallucinations, fluctuating levels of attention, and spontaneous parkinsonism. Dementia precedes motor symptoms or occurs within 1 year. The parkinsonism is symmetric with early gait and postural instability.[39] Moderate L-dopa response may be seen. In Alzheimer's disease, parkinsonism follows dementia, is symmetric, and rest tremor is rare. Dementia of AD is dominated by early and severe memory impairment. Clinical features which suggest an alternative diagnosis other than PD in a patient presenting with parkinsonism are listed in Table 3.

There is no diagnostic test which can reliably differentiate PD from other causes of parkinsonism. Acute levodopa challenge (with 250 mg/25 mg of levodopa/carbidopa) and assessment for changes in Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) score of 30% or more have a sensitivity of around 70% and specificity of around 80% for predicting an eventual diagnosis of PD.[40] Around 30% will have false positive or false negative results. Subcutaneous apomorphine challenge (1-4.5 mg of apomorphine given subcutaneously)[41] has similar utility but apomorphine is not freely available in India. Patients need to be pre-treated with domperidone for 2-3 days to prevent dopaminergic side effects.

Decreased smell in standardized smell identification tests (like the University of Pennsylvania Smell Identification Test - UPSIT) may be useful to discriminate PD from PSP and CBD. The smell is preserved in these conditions unlike PD in which there is moderate to severe impairment of smell. MSA and PD have overlapping levels of impairment.[42,43]

Significant overlap in levels of impairment does not allow reliable distinction between PD and atypical parkinsonism based on neuropsychological testing, electro-oculogram, sphincter and urethral EMG or autonomic function tests.[44]

Conventional and advanced MR modalities may help distinguish PD from atypical parkinsonism. However, the

Table 3: Baseline features that suggest an alternative diagnosis other than PD

- Mild or no tremor, particularly absence of rest tremor
- Severe bradykinesia at onset
- Symmetric signs and rapid progression
- Postural instability, gait difficulty and freezing at onset or early in the disease (within 3 years)
- Falls at presentation or early in the course
- Slowing of saccades or supranuclear palsy(other than upgaze restriction)
- Dementia preceding motor symptoms or in the first year
- Hallucinations unrelated to medicines early in the disease
- Severe and symptomatic dysautonomia unrelated to medicines

*A combination of features is more suggestive of an alternative diagnosis than a single odd feature.

evidence is insufficient and MRI has low sensitivity.[44] Iodine-123 meta-iodobenzylguanidine (MIBG) cardiac imaging is normal in multiple system atrophy and PSP, while it is abnormal in PD.[45] However, the level of evidence is currently not considered high enough to recommend for routine diagnostic purposes. Hyperechogenicity of substantia nigra detected by brain ultrasonography has been shown to differentiate PD from atypical parkinsonism.[46-49] Evidence is not strong to recommend it for routine diagnostic purposes. Beta CIT and IBZM SPECT can differentiate PD from ET[44] but are not freely available.

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