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Differential Diagnosis of Parkinsonism

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Parkinsonism refers to a clinical syndrome characterized by a variable combination of tremor, bradykinesia or akinesia, rigidity, and postural instability. In general, two of these four features must be present to make a diagnosis of parkinsonism. However, the situation is complicated by rare cases of pure akinesia in the absence of tremor and rigidity that have the classic pathology of Parkinson's disease (PD) (1). Within the rubric of parkinsonism there are a myriad of disorders, some yet unclassified (Table 1).

The most common cause of parkinsonism is PD. Pathologically, PD is characterized by nigral cell loss and Lewy bodies in the remaining neurons, and the term "Lewy body parkinsonism" is sometimes used synonymously with PD. Some researchers consider it most appropriate to refer to even the pure clinical picture of PD as "Parkinson's syndrome" on the premise that PD may not be one disease. Whereas the purists demand the presence of Lewy bodies at autopsy to diagnose PD, these inclusions may not be present in some inherited forms of otherwise classical PD. Currently, one such condition, the "parkin parkinsonism" has been mapped to chromosome 6 (2). This autosomal recessive parkinsonism of juvenile onset differs pathologically from sporadic disease in that no Lewy bodies are found in

TABLE 1 Classification of Parkinsonism

Primary Parkinson's disease
Sporadic
Familial
Secondary Parkinsonism
Drug-induced parkinsonism (DIP)
Toxin-induced parkinsonism
Infectious
Creutzfeld-Jakob disease (CJD)
Metabolic
Structural
Tumor
Subdural hematoma
Vascular
Other Degenerative Disorders
Progressive supranuclear palsy (Steele-Richardson-Olzewaski syndrome) (PSP)
Multiple-system atrophy (MSA)
Shy-Drager syndrome (SDS)
Olivopontocerebellar atrophy (OPCA)
Striatonigral disease (SND)
Cortical basal ganglionic degeneration (CBGD)
Dementia with Lewy bodies (DLB)
Hereditary degenerative diseases
Spinocerebellar ataxias (SCA)
Hallervorden-Spatz disease
Huntington's disease
Neuroacanthocytosis
Wilson's disease
X-linked dystonia-parkinsonism (Lubag)

the substantia nigra at autopsy. The clinical picture can be similar to idiopathic PD, including the presence of tremor (3). Two other forms of inherited parkinsonism, one with the locus on the long arm of chromosome 4 and the other with the locus on chromosome 2p13, have been described where typical Lewy body pathology is found (4,5).

In the absence of a known biological marker, the challenge facing the clinician is to make an accurate diagnosis of PD and differentiate it from other similar conditions. This review will give a practical approach to the differential diagnosis of parkinsonism and examine the diagnostic accuracy

of PD. Because PD is the most common cause of parkinsonism, it is useful to review the typical clinical picture of PD.

THE TYPICAL CLINICAL PICTURE OF PD

The onset of PD is gradual and the course slowly progressive, albeit at different rates in different individuals. In most series, 65–70% of the patients present with an asymmetrical tremor, especially of the upper extremity (6). After a variable delay, the disorder progresses to the other side with bilateral bradykinesia and gait difficulty that takes the form of festination and, in advanced cases, freezing. Postural instability and falls tend to be a late feature. Eye movements may show saccadic pursuit, and the upgaze may be limited, especially in the elderly. Downgaze is normal. Autonomic disturbances are common but in early disease are not severe. Depression may occur early in the disease, but dementia as a presenting manifestation is not a feature of PD. Several signs should ring alarm bells when considering a diagnosis of PD. These include early severe dementia, early severe autonomic dysfunction, gaze difficulty (especially looking down), upper motor neuron or cerebellar signs, stepwise deterioration, and apraxia (Table 2).

CONDITIONS MIMICKING PARKINSONISM

The first step is to differentiate other conditions that may be confused with parkinsonism. Essential tremor (ET) is more common than PD and results in tremor that affects the head and neck and the upper extremities (7). The tremor is absent at rest except in most severe cases and is increased by maintained posture and voluntary movement. Mild cogwheeling may be present, but bradykinesia is not a feature (Table 3). The confusion occurs when a patient with a long history of ET begins to develop signs of bradykinesia or a rest tremor. Patients with PD may have a prominent action tremor adding to the diagnostic uncertainty. In addition there are elderly patients with ET who exhibit mild bradykinesia (8). Whether patients with ET are at an increased risk to develop PD is debatable (9). Psychomotor slowing in a severely depressed individual may resemble PD, but there is no tremor and patients improve with antidepressant therapy. Frequently depression and PD coexist.

Drug-Induced Parkinsonism

Drug-induced parkinsonism (DIP) is a common complication of antipsychotic drug use, with a reported prevalence of 15–60% (10). In one study,

TABLE 2 Features Indicating an Alternate Diagnosis to Parkinson's Disease

Early or predominant feature	Disease
Young onset	Drug- or toxin-induced parkinsonism, Wilson's disease, Hallervorden-Spatz disease
Minimal or absent tremor	PSP, vascular parkinsonism
Atypical tremor	CBGD, MSA
Postural instability	PSP, MSA
Ataxia	MSA
Pyramidal signs	MSA, vascular parkinsonism
Amyotrophy	MSA, parkinsonism dementia of Guam
Symmetric onset	PSP, MSA
Myoclonus	CBGD, CJD, MSA
Dementia	DLB
Apraxia, cortical sensory loss	CBGD
Alien limb sign	CBGD
Gaze palsies	PSP, OPCA, CBGD, DLB, PSG
Dysautonomia	MSA
Hallucinations (non–drug related)	DLB
Acute onset	Vascular parkinsonism, toxin-induced, psychogenic
Stepwise deterioration	Vascular parkinsonism

PSP = progressive supranuclear palsy; CBGD = cortiobasal ganglionic degeneration; MSA = multiple system atrophy; CJD = Creutzfeld-Jakob disease; DLB = dementia with Lewy bodies; OPCA = olivopontocerebellar atrophy; PSG = progressive subcortical gliosis.

TABLE 3 Differentiating Essential Tremor from Parkinson's Disease

	Essential tremor	Parkinson's disease
Body parts affected	Arms > Head > Voice > Legs	Arms > Jaw > Legs
Rest tremor	−	+++
Postural tremor	+++	+
Kinetic tremor	+++	±
Tremor frequency	7–12 Hz	4–6 Hz
Bradykinesia	−	++
Cogwheel rigidity	±	++
Family history	++	±
Response to beta blockers	+	−
Response to levodopa	−	++
Postural instability	−	+

51% of 95 patients referred for evaluation to a geriatric medicine service had parkinsonism associated with prescribed drugs (11). Frequently these patients are misdiagnosed as PD and treated with dopaminergic drugs without any benefit. In a community study, 18% of all cases initially thought to be PD were subsequently diagnosed as DIP (12).

The symptoms of DIP may be indistinguishable from PD. DIP is often described as symmetrical, whereas PD is often asymmetrical. However, one series found asymmetry of signs and symptoms in DIP in 30% of patients (13). Patients with DIP are as varied in their clinical manifestations as patients with PD. Some patients have predominant bradykinesia, while in others tremor is dominant. Postural reflexes may be impaired. Festination is uncommon and freezing is rare (13,14).

When the patient is on a dopamine blocking agent (DBA), it is difficult to distinguish underlying PD from DIP. If possible, the typical DBAs should be stopped or substituted with atypical antipsychotics and the symptoms and signs of DIP should resolve within a few weeks to a few months. In fact, it could take up to 6 months or more for signs and symptoms to resolve completely (15). If there is urgency in making the diagnosis, cerebrospinal fluid dopamine metabolites may be studied. These are low in untreated PD but are relatively normal or increased in DIP. However, this test may not always be helpful clinically (16). One study utilizing 6-fluorodopa positron emission tomography (PET) scanning showed that a normal PET scan predicted good recovery from DIP upon cessation of DBA and an abnormal PET scan was associated with persistence of signs in some but not all patients (17). DIP should be considered, and inquiry should be made about intake of antipsychotic drugs and other DBAs like metoclopramide (Table 4).

Progressive Supranuclear Palsy

Progressive supranuclear palsy (PSP), also known as Steele-Richardson-Olszewski syndrome, is easy to diagnose in advanced stages (18,19). However, diagnostic confusion may occur early in the disease and in cases that have atypical features. Typically, the disorder presents with a gait disturbance with resultant falls in over half the cases (20). Measurable bradykinesia in the upper extremities may not be present initially. The clinical features of PSP consist of supranuclear gaze palsy, especially involving the downgaze, with nuchal extension and predominant truncal extensor rigidity. Varying degrees of bradykinesia, dysphagia, personality changes, and other behavioral disturbances coexist. Patients often exhibit a motor recklessness and get up abruptly out of a chair (Rocket sign), even if this results in a fall.

TABLE 4 Drugs Known to Cause Parkinsonism

Generic name	Trademark
Chlorpromazine	Thorazine
Thiordazine	Mellaril
Mesoridazine	Serentil
Chlorprothixine	Taractan
Trifluprомazine hydrochloride	Vesprin
Carphenazine maleate	Proketazine
Acetophenazine maleate	Tindal
Prochlorperazine	Compazine
Piperacetazine	Quide
Butaperazine maleate	Repoise maleate
Perphenazine	Tilafon
Molindone hydrochloride	Moban
Thiothixene	Navane
Trifluoperazine hydrochloride	Stelazine
Haloperidol	Haldol
Fluphenazine hydrochloride	Prolixin
Amoxapine	Asendin
Loxapine	Loxitane, Daxolin
Metoclopramide	Reglan
Promazine	Sparine
Promethazine	Phenergan
Thiethylperazine	Torecan
Trimeprazine	Temaril
Combination drugs	Etrafon, Triavil

Extraocular movement (EOM) abnormalities are very characteristic but may not be present at the onset of the illness or for several years. Rarely a patient with PSP may die without developing EOM abnormalities (21). EOM abnormalities consist of square wave jerks, instability of fixation, slow or hypometric saccades, and predominantly a downgaze supranuclear palsy (22,23). Generation of a saccade in the direction opposite to a stimulus (antisaccade test) is frequently abnormal in PSP (23). The oculocephalic responses are present in early disease but may be lost with advancing disease, suggesting a nuclear element to the gaze palsy. Bell's phenomenon may be lost in advanced cases. Some patients with PSP have a limb dystonia that can be asymmetrical (24). This can cause confusion with corticobasal ganglionic degeneration (CBGD), which will be discussed subsequently. Rest tremor is rare but has been reported in pathologically confirmed PSP (25).

PSP differs from PD radiologically in that in advanced cases there is atrophy of the mid-brain tectum and tegmentum with resultant diminution of the anteroposterior (AP) diameter of the midbrain (26,27). There may be dilatation of the posterior third ventricle and sometimes a signal alteration may be seen in the tegmentum of the midbrain (28). PET scanning utilizing 6-fluorodopa may distinguish PSP from PD in that the uptake diminished equally in both the caudate and putamen, whereas in PD the abnormalities are largely confined to the putamen (29). PET scan using raclopride binding shows that the D2 receptor sites are diminished in PSP, whereas in PD these are normal (30).

Clinically CBGD, dementia with Lewy bodies (DLB), progressive subcortical gliosis (PSG), multiple system atrophy (MSA), and even prion diseases have been misdiagnosed as PSP because of the presence of supranuclear gaze palsies (31–34). PSP also needs to be distinguished from other causes of supranuclear gaze palsy including cerebral Whipple's disease, adult-onset Niemann-Pick type C, and multiple cerebral infarcts (35–37). The presence of prominent early cerebellar symptoms or early, unexplained dysautonomia would favor MSA over PSP (38), and the presence of alien limb syndrome, cortical sensory deficits, focal cortical atrophy on MRI would favor CBGD (39). The clinical diagnostic criteria proposed by Litvan et al. may be helpful (40,41).

Multiple System Atrophy

This term, originally coined by Graham and Oppenheimer (42), refers to a variable combination of parkinsonism, autonomic, pyramidal, or cerebellar symptoms and signs. MSA can be subdivided into three types: striatonigral degeneration (SND), olivopontocerebellar atrophy (OPCA), and Shy-Drager syndrome (SDS) (43). All subtypes of MSA may have parkinsonian features. It is especially difficult to differentiate PD from SND. SND was originally described by Van Eecken et al. (44). The parkinsonian features of MSA consist of progressive bradykinesia, rigidity, and postural instability (43). In a clinicopathological report, one of four patients had a rest tremor characteristic of PD (45). Although symptoms are usually bilateral, unilateral presentations have been described (46). Useful clinical clues for the diagnosis of MSA include disproportionate anterocollis and the presence of cold blue hands. The autonomic failure is more severe than that seen in idiopathic PD and occurs early in MSA.

The response to levodopa is usually not as dramatic or sustained in MSA as in PD (47). However, it must be noted that several patients with MSA may initially respond to levodopa, but the benefit usually declines within one or 2 years of treatment (48). Levodopa-induced dyskinesias may

occur in MSA. These dyskinesias typically involve the face and neck but may involve the extremities as well (49,50). It is clear, therefore, that the presence of levodopa dyskinesias cannot be used to make a definite diagnosis of PD. The situation is further complicated by the fact that patients with PD may develop autonomic dysfunction including postural hypotension, urinary problems, constipation, impotence, and sweating disturbances. This autonomic dysfunction in PD may be worsened by dopaminergic therapy. Autonomic dysfunction tends to be severe in MSA and occurs early (51). Stridor can occur early in MSA but not in PD (52). Urinary symptoms are very common in MSA. On urodynamic testing, there is a combination of detrusor hyperreflexia and urethral sphincter weakness (53). In addition, neurogenic anal and urethral sphincter abnormalities are very common in MSA (54). However, this finding is not diagnostic and may occur in other conditions like PSP (55). Neuroimaging may show nonspecific abnormalities like diffuse hypointensity involving the putamen, but more specific findings include a strip of lateral putaminal hyperintensity or pontine atrophy with an abnormal cross sign in the pons. (56).

Dementia with Lewy Bodies

In this disorder, Lewy bodies are found in widespread areas of the neocortex as well as the brain stem and diencephalic neurons (57). Some of these patients may have associated neurofibrillary tangles consistent with coincidental Alzheimer's disease. The parkinsonian syndrome of DLB may be indistinguishable from PD. However, these patients have early-onset dementia and may have hallucinations, delusions, and even psychosis in the absence of dopaminergic therapy (58,59). Another characteristic feature is wide fluctuations in cognitive status. Rarely, the patients with DLB may develop supranuclear gaze palsy, resulting in confusion with PSP (31,32). Some patients respond partially and temporarily to dopaminergic therapy. Occasionally the response to levodopa is robust. The electroencephalographic (EEG) recording in DLB may be abnormal with background posterior slowing and frontally dominant burst activity that is not a feature of PD.

Corticobasal Ganglionic Degeneration

Rebeiz et al. initially described this disorder as corticodentatonigral degeneration with neuronal achromasia (60). CBGD typically presents in the 6th or 7th decade with slowly progressive unilateral, tremulous, apraxic, and rigid upper limb (61). The disorder tends to be gradually progressive with progressive gait disturbances, cortical sensory loss, and stimulus

sensitive myoclonus resulting in a "jerky useless hand" (62–64). Jerky useless lower extremity is uncommon but may occur. Rarely these patients may develop Babinski signs and supranuclear gaze palsy.

When typical, the clinical picture is distinct and easily recognizable. However, atypical cases may be confused with PSP, and the myoclonic jerking may be confused with the rest tremor of PD. The gait disturbance typically consists of slightly wide based apraxic gait rather than the typical festinating gait of PD. Fixed limb dystonia may be prominent and strongly suggests CBGD, but some patients with PSP may also have asymmetrical limb dystonia (24). Patients with CBGD do not benefit from levodopa, and the course is relentlessly progressive.

Rare cases of the parietal form of Pick's disease may be confused with CBGD (65). The clinical spectrum of CBGD has recently been expanded to include early-onset dementia and aphasia (66), but in general these patients have a conspicuous absence of cognitive deficits. The magnetic resonance image (MRI) in CBGD shows focal atrophy especially in the parietal areas (67), and the PET scan shows asymmetrical decrease of regional cerebral metabolic rates for glucose utilization (68).

Frontotemporal Dementia with Parkinsonism

Frontotemporal dementia (FTD) is characterized by profound behavioral changes and an alteration in personality and social conduct with relative preservation of memory (69,70). Extrapyramidal symptoms are common, and parkinsonism occurs in 40% of patients (71). Akinesia, rigidity, and a shuffling gait are the most common signs with typical tremor being rare (72). PET scan reveals an equal decrease in fluorodopa uptake in the caudate and the putamen as opposed to PD, where putamen is preferentially involved. (72). This disorder should be easy to distinguish from PD but may be confused with DLB and other disorders causing dementia and parkinsonism. Tables 5 and 6 summarize some of the differential diagnostic features.

Toxin-Induced Parkinsonism

In general, these disorders are uncommon and may pose less of a differential diagnostic problem. 1-Methyl-4-phenyl-1,2,3,6-tetrahydopyridine (MPTP)–induced parkinsonism is distinct from DIP in that it is irreversible and is due to the destruction of the substantia nigra neurons (73). The clinical features have some similarities to PD, except that the onset is abrupt and the affected individuals are younger than typical PD (74,75). These patients respond to levodopa with early levodopa-induced fluctuations (76). The patients may worsen gradually even in the absence of continued exposure to the toxin

TABLE 5 Differential Diagnosis of Parkinson's Disease

	PD	PSP	MSA	CBGD	DLB
Symmetry of deficit	+	+++	+++	−	+
Axial rigidity	+	+++	++	+	+
Limb dystonia	+	+	+	++	+
Postural instability	++	+++	++	+	++
Vertical gaze palsy	+	+++	+	++	+
Dysautonomia	+	−	++	−	+
Levodopa response	+++	−	+	−	++
Asymmetrical cortical atrophy	−	−	−	++	−
Hallucinations (nondrug)	−	−	−	−	+

PD = Parkinson's disease; PSP = progressive supranuclear palsy; MSA = multiple system atrophy; CBGD = corticobasal ganglionic degeneration; DLB = dementia with Lewy bodies.

TABLE 6 MRI Features of Some Cases of Parkinsonism

	PD	PSP	MSA (OPCA)	MSA (SND)	CBGD
Cortical atrophy	+	+	±	+	++
Putaminal atrophy	−	−	−	++	−
Pontine atrophy	−	+	+++	−	−
Midbrain atrophy	−	++	+	−	−
Cerebellar atrophy	−	−	++	−	−
High putaminal iron	−	−	+	+	−

PD = Parkinson's disease; PSP = progressive supranuclear palsy; MSA = multiple system atrophy; OPCA = olivopontocerebellar atrophy; SND = striatonigral degeneration; CBGD = corticobasal ganglionic degeneration.

(77). In manganese poisoning, the patients may have symptoms very similar to PD, including soft speech, clumsiness, and impaired dexterity; however, the patients have a peculiar cock-walk gait in which they swagger on their toes (78,79). They may also have limb and truncal dystonia that is very unusual in untreated PD. Dementia and cerebellar dysfunction may occur, and these patients do not respond well to dopaminergic drugs. Patients with manganese exposure who develop otherwise typical PD had an earlier age of onset as compared to controls (80).

Parkinsonism as a result of carbon monoxide intoxication has been well described (81,82). The parkinsonism may be delayed after the acute episode. These patients often show a slow shuffling gait, loss of arm swing, retropulsion, bradykinesia, rigidity, and, occasionally, a rest tremor. The pull test tends to be markedly abnormal. The computerized tomography (CT) scan or MRI scan may show necrotic lesions of the globus pallidus (83,84). There may also be associated white matter lesions that may progress without further exposure to carbon monoxide (85). Other toxins that have been reported to cause parkinsonism include carbon disulfide (86), cyanide (87,88), and methanol (89,90). These patients often have an acute onset and in some cases show basal ganglia lesions on neuroimaging. Posthypoxic parkinsonism has an acute evolution following a bout of severe prolonged hypoxia. A variable degree of intellectual deterioration often accompanies posthypoxic parkinsonism, and the patients usually do not have rest tremor.

Posttraumatic Parkinsonism

Isolated head trauma is rarely a cause of parkinsonism (91). Parkinsonism may be seen in the setting of diffuse severe cerebral damage after brain injury (92). However, repeated minor trauma to the head, as in boxers (dementia pugilistica), may be complicated by the late onset of dementia, parkinsonism, and other clinical features (93,94). Obviously, the boxers are not immune to developing PD as they get older. However, the onset of parkinsonism and dementia in a professional boxer would be very suggestive of dementia pugulistica. The imaging studies may show a cavum septum pellucidum and cerebral atrophy. A PET study using 6-fluorodopa showed damage to both the caudate and the putamen in posttraumatic parkinsonism, whereas in PD the putamen is more severely involved.

Multi-Infarct Parkinsonism

Arteriosclerotic or multi-infarct parkinsonism is a debatable entity (95). Patients typically have predominant gait disturbance with slightly wide-based gait with some features of gait apraxia and frequent freezing (96).

These patients have lower-body parkinsonism, and they usually lack the typical rest tremor or signs in the upper extremity (97). The gait disorder may not be distinct from senile gait, and a similar gait disorder may also be seen in patients with Binswanger's disease (98,99). Levodopa responsiveness is uncommon but has been demonstrated occasionally in patients with pathologically confirmed multi-infarct parkinsonism.

The proposed criteria for the diagnosis of vascular parkinsonism include acute or subacute onset with a stepwise evolution of akinesia and rigidity along with vascular risk factors (100). This should be supplemented by at least two or more infarcts in the basal ganglia on neuroimaging. In some cases there may be more widespread MRI white matter abnormalities. Spontaneous improvement in symptoms and signs without dopaminergic therapy is suggestive of vascular parkinsonism.

Some patients with multiple cerebral infarction have a clinical picture characterized by gaze palsies, akinesia, and balance difficulties consistent with PSP. In fact, one study found that 19 out of 58 patients with a clinical diagnosis of PSP had radiographic evidence of multiple small infarcts in the deep white matter and the brainstem (35).

Parkinsonism with Hydrocephalus

Patients with hydrocephalus have varying degrees of hypomimia, bradykinesia, and rigidity in the absence of tremor. This may occur in high-pressure as well as in normal-pressure hydrocephalus (NPH) (101). High-pressure hydrocephalus rarely poses any diagnostic difficulties because of the relatively acute onset in the presence of signs of raised intracranial pressure. However, NPH may be more difficult to distinguish from PD in some cases. The classic triad of NPH includes a subacute onset of dementia, gait difficulty, and urinary incontinence (102). The gait is slightly wide based with features of gait apraxia or slight ataxia. Rarely, levodopa responsiveness has been demonstrated (103). In some patients the gait might improve over the next few hours to days by the removal of cerebral spinal fluid (104).

Parkinsonism Due to Structural Lesions of the Brain

Blocq and Merinesco were the first to report a clinicopathological correlation of midbrain tuberculoma involving the substantia nigra and contralateral parkinsonism (105,106). In most cases the responsible lesions have been tumors, chiefly gliomas and meningiomas. Interestingly, these are uncommon in the striatum and have usually involved the frontal or parietal lobes. Subdural hematoma may present with subacute onset of parkinsonism, with some pyramidal signs at times (107). Other rare causes of

parkinsonism and structural lesions have included striatal abscesses (108) and vascular malformations. However, the structural lesions are easily confirmed by neuroimaging. Occasionally parkinsonism has been reported in patients with basal ganglia calcifications that usually occur in primary hypoparathyroidism. The calcification should be obvious on neuroimaging (109).

Infectious and Postinfectious Causes of Parkinsonism

The classic postencephalitic parkinsonism is now exceedingly uncommon. It was characterized by a combination of parkinsonism and other movement disorders. Particularly characteristic were "oculogyric crises," which resulted in forceful and painful ocular deviation lasting minutes to hours. Other causes of oculogyric crises are Tourette's syndrome, neuroleptic induced acute dystonia, paroxysmal attacks in multiple sclerosis, and possibly conversion reaction. The parkinsonism may improve with levodopa, but response deteriorates quickly. Parkinsonism rarely occurs as a sequelae of other sporadic encephalitides. Human immunodeficiency virus (HIV) dementia has also been reported with parkinsonian features. Other infectious causes include striatal abscesses and neurosyphilis.

Psychogenic Parkinsonism

Compared to other psychogenic movement disorders like tremor, psychogenic parkinsonism is uncommon (110). A tremor of varying rates with marked distractibility along with inconsistent slowness and the presence of feigned weakness and numbness might lead to the correct diagnosis.

PARKINSONISM IN YOUNG ADULTS

The onset of parkinsonism under the age of 40 is usually called young-onset parkinsonism. When symptoms begin under the age of 20, the term "juvenile parkinsonism" is sometimes used (111). Under the age of 20, parkinsonism typically occurs as a component of a more widespread degenerative disorder. However, Parkin parkinsonism may present with dystonia and parkinsonism in patients under the age of 20.

Dopa-Responsive Dystonia

There is a significant overlap in young patients with dystonia and parkinsonism. Patients with young-onset parkinsonism manifest dystonia that may be responsive to dopamingeric drugs (112). However, the response may deteriorate upon long-term follow-up. Patients with hereditary dopa-responsive dystonia have an excellent and sustained response to low doses of

levodopa (113). In addition, PET scan shows markedly reduced 6-fluorodopa uptake in patients with young-onset PD, whereas the fluorodopa uptake is normal in patients with dopa-responsive dystonia (114). Patients with dopa-responsive dystonia have a guanosine triphosphate (GTP)–cyclohydrolase deficiency that is not a feature of PD in young adults.

Wilson's Disease

Wilson's disease may present primarily with a neuropsychiatric impairment. It should be considered in every case of young-onset parkinsonism because it is eminently treatable and the consequences of nonrecognition can be grievous. Most common neurological manifestations are tremor, dystonia, rigidity, dysarthria, drooling, and ataxia. A combination of parkinsonism and ataxia is particularly indicative of neurological Wilson's disease (115). Parkinsonism is the most prevalent motor dysfunction, whereas about 25% of the patients present with disabling cerebellar ataxia, tremor, or dysarthria (116). Typically, the tremor involves the upper limbs and the head and rarely the lower limbs. It can be present at rest, with postural maintenance, and may persist with voluntary movements. The classic tremor is coarse and irregular and present during action. Holding the arms forward and flexed horizontally can emphasize that the proximal muscles are active (wing-beating tremor). Less commonly, tremor may affect just the tongue and the orofacial area (117). Dystonia is also quite common. The characteristic feature is an empty smile due to facial dystonia. Dysarthria is very common and may take the form of a dystonic or a scanning dysarthria. Approximately 30% of the patients present with behavioral and mental status changes (118). The psychiatric disorder may take the form of paranoid symptoms sometimes accompanied by delusional thinking and hallucinations. Early presentation may be a decline in memory and school performance. Patients may develop anxiety, moodiness, disinhibited behavior, and loss of insight. A characteristic feature is inappropriate laughter. Although eye movements are typically normal, some cases of Wilson's disease may show a saccadic pursuit, gaze distractibility, or difficulty in fixation (119). Macrosaccadic oscillations have been personally observed in a patient with Wilson's disease, and the abnormal eye movements disappeared after successful therapy. Kayser-Fleischer (KF) rings due to copper deposition in the cornea may be easy to recognize in patients with a light-colored iris, but in patients with brown irides these rings may be very difficult to see. Usually the ring is golden-brown in color and involves the whole circumference of the cornea. However, in the early stages the ring may be more apparent in the upper than the lower pole. Rarely these rings can be unilateral. KF rings are best appreciated by a

careful slit-lamp examination done by a competent neur-ophthalmologist. Typically the absence of KF rings on the slit-lamp examination rules out neurological Wilson's disease. However, there are reports of patients with typical Wilson's disease without any KF rings (120,121).

Radiologically, advanced cases of Wilson's disease may have cavitation of the putamen (122). However, putaminal lesions are not specific for Wilson's disease. Other causes of putaminal cavitation or lesions include hypoxic ischemic damage, methanol poisoning, mitochondrial encephalomyopathy, and wasp-sting encephalopathy. Nearly half the patients with neurological Wilson's disease have hypodensities of the putamina on CT scans in contrast to patients with hepatic disease, who frequently have normal CT scans (123). MRI is more sensitive, and almost all patients with neurological features have some disturbance on T_2-weighted images in the basal ganglia with a pattern of symmetrical, bilateral, concentric-laminar T_2 hyperintensity, and the involvement of the pars compacta of the substantia nigra, periaqueductal gray matter, the pontine tegmentum, and the thalamus (124). The hepatic component of Wilson's disease may cause increased T_1 signal intensity in the globus pallidus (125). In the adult age group, the basal ganglia lesions may be different from those in the pediatric group; the putaminal lesions may not be present; the globus pallidus and substantia nigra may show increased hypointensity on T_2-weighted images. Cortical and subcortical lesions may also be present with a predilection to the frontal lobe. However, rare cases of neurological Wilson's disease may have normal MRI (126). PET scanning may show a reduction of 6-fluroudopa uptake (127).

The most useful diagnostic test is serum ceruloplasmin and a 24-hour urinary copper excretion supplemented by a slit-lamp examination for KF rings. Unfortunately, not all patients with Wilson's disease have a low ceruloplasmin level (128). Measurement of liver copper concentration makes a definitive diagnosis. Normally, it is between 50–100 μg/g of tissue, and in patients with Wilson's disease it may be over 200 μg/g (129).

Hallervorden-Spatz Disease

Hallervorden-Spatz disease (HSD) is usually a disease of children, but young adults may be affected. Typically, the disease occurs before the age of 20. Facial dystonia tends to be prominent, coupled with gait difficulty and postural instability. Patients may have night blindness progressing to visual loss secondary to retinitis pigmentosa. Other extrapyramidal signs include choreoathetosis and a tremor that has been poorly characterized. Cognitive problems include impairment of frontal tasks and memory disturbances. Psychiatric manifestations have been reported in HSD. CT scans in HSD

are often normal, but low-density lesions have been described in the globus pallidus. MRI, especially using a high field strength magnet, shows decreased signal intensity in the globus pallidus with a central hyperintensity. We have termed it the "eye of the tiger sign" (130).

Juvenile Huntington's Disease

This autosomal dominant neurodegenerative disorder typically presents with chorea, difficulty with gait, and cognitive problems. However, the "Westphal variant" of the disease affecting the young may manifest bradykinesia, tremulousness, myoclonic jerks, and occasionally seizures and cognitive disturbances (131). Eye movement abnormalities including apraxia of eye movements can be remarkable in this setting. When coupled with a lack of family history, these young patients may be confused with young-onset PD, but neuroimaging and gene testing should easily distinguish the two.

Hemiparkinsonism Hemiatrophy Syndrome

These patients have a longstanding hemiatrophy of the body and develop a progressive bradykinesia and dystonic movements around the age of 40 (132,133). Ipsilateral corticospinal tract signs may be found, which are not a feature of PD. Neuroimaging reveals brain asymmetry with atrophy of the contralateral hemisphere with compensatory ventricular dilatation. Regional cerebral metabolic rates are diminished in the hemisphere contralateral to the clinical hemiatrophy in the putamen and the medial frontal cortex, whereas in idiopathic PD the regional cerebral metabolic rates are normal or increased contralateral to the clinically affected side (134).

X-Linked Dystonia Parkinsonism (Lubag)

This inherited disorder usually occurs in the Philippines. However, rare cases are seen in other parts of the world (135). Typical age of presentation is around the age of 30–40 years. Focal dystonia or tremor is the initial finding followed by other parkinsonian features. Rarely parkinsonian features may precede dystonia. Clinically this disorder is differentiated from idiopathic PD by the presence of marked dystonia and the pattern of inheritance.

Neuroacanthocytosis

This is a rare cause of parkinsonism and typically presents with a hyperkinetic movement disorder including chorea, tic-like features, and

polyneuropathy. MRI shows a characteristic atrophy of the caudate and a hyperintensity in the putamen on T_2-weighted images, and acanthocytes are revealed on a fresh blood smear (136).

DIAGNOSTIC CRITERIA FOR PARKINSON'S DISEASE

From the preceding discussion it is obvious that there are a large number of disorders that can be confused with PD. In an effort to improve diagnostic accuracy, several sets of clinical diagnostic criteria for PD have been proposed (137–140). Table 7 lists the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria (UKPDBBCDC).

The first clinicopathological study found that only 69–75% of the patients with the autopsy-confirmed diagnosis of PD had at least two of the three cardinal manifestations of PD: tremor, rigidity, and bradykinesia (140). Furthermore, 20–25% of patients who showed two of these cardinal features had a pathological diagnosis other than PD. Even more concerning, 13–19% of patients who demonstrated all three cardinal features typically associated with a clinical diagnosis of PD had another pathological diagnosis.

Rajput et al. reported autopsy results in 59 patients with parkinsonian syndromes (141). After a long-term follow-up period, the clinical diagnosis of PD was retained in 41 of 59 patients. However, only 31 of 41 (75%) patients with clinically determined PD showed histopathological signs of PD at autopsy examination.

A third series was comprised of 100 patients with a clinical diagnosis of PD, who had been examined during their life by different neurologists using poorly defined diagnostic criteria. When autopsies were performed (mean interval between symptom onset and autopsy = 11.9 years), PD was found in 76 patients. The authors reviewed the charts of these patients and then applied the accepted UKPDBBCDS clinical criteria for PD requiring bradykinesia and at least one other feature, including rigidity, resting tremor, or postural instability, and focusing on clinical progression, asymmetry of onset, and levodopa response. Sixteen additional exclusion criteria were also applied (Table 7). With the application of these diagnostic criteria, 89 of the original 100 patients were considered to have PD, but, again, only 73 (82%) were confirmed to have PD at autopsy. When the authors reexamined the patients with all three cardinal features (excluding the postural instability), only 65% of patients with an autopsy diagnosis of PD fit this clinical category.

The authors have reexamined the issue. They studied another 100 patients with a clinical diagnosis of PD that came to neuropathological examination. Ninety fulfilled pathological criteria for PD. Ten were

TABLE 7 United Kingdom Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria

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

misdiagnosed: MSA (six), PSP (two), postencephalitic parkinsonism (one), and vascular parkinsonism (one). They next examined the accuracy of diagnosis of parkinsonian disorders in a specialist movement disorders service (144). They reviewed the clinical and pathological features of 143 cases of parkinsonism, likely including many of the patients previously reported (143). They found a surprisingly high positive predictive value (98.6%) of clinical diagnosis of PD among the specialists. In fact, only 1 of 73 patients diagnosed with PD during life was found to have an alternate diagnosis. This study demonstrated that the clinical diagnostic accuracy of PD may be improved by utilizing stringent criteria and a prolonged follow up

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