Cardinal Features of Early Parkinson’s Disease


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PARKINSONIAN SYNDROME AND THE DEFINITION OF PARKINSON’S DISEASE

Nearly two centuries ago James Parkinson described a disorder of the elderly under the eponym of “shaking palsy” (1). Over the years the constellation of symptoms and signs of this clinical entity came to be known as “Parkinson’s disease.” However, the vast clinical experience and emergence of newer diagnostic methods over the past century have forced neurologists to modify their view of this clinical syndrome. It has become evident that the clinical findings described by Parkinson occur in a setting where several different causes can be identified or where the findings are part of other progressive neurodegenerative disorders. Therefore the clinical entity described by Parkinson has been termed parkinsonism or the parkinsonian syndrome (2) (Table 6-1). Thus it is doubtful whether “Parkinson’s disease” is a single entity (2,3) and whether “idiopathic parkinsonism” (IP) may be a suitable name for what is really a syndrome of unknown origin (2). With the advent of modern genetic techniques, a small subgroup of patients who have a familial form of parkinsonism have had their underlying genetic abnormalities identified (4–6).

There is no generally acceptable definition of IP. However, for research purposes, one needs to have a uniform and generally accepted set of inclusion and exclusion criteria. Takahashi and Calne (7) proposed a working definition of IP as a syndrome comprising a combination of the triad – tremor, rigidity, and akinesia, with inclusion and exclusion criteria (Table 6-2).

AGING AND PARKINSON’S DISEASE

Parkinsonian features are seen with normal aging (8–10). Duncan and Wilson (11) noted that almost all elderly people (without any neurologic disorder) attending a day care and nearly one-half of the neurologically “normal” elderly people seen in a community had at least one feature (excluding impaired postural reflex) of parkinsonism. It is difficult to distinguish this apparently “normal” variant of aging from early IP. Old age is the most consistently recognized risk factor for parkinsonism, and its incidence and prevalence increases with age (12). Prevalence has been reported to be 1 percent in patients 60 years or older and 2.6 percent in those over 85 years of age (13).

Like many other, but not all, parts of the central nervous system, there are age-related changes in the nigrostriatal dopaminergic pathways. These are due to (1) age-related, localized neuronal death, and (2) generalized loss of neuronal plasticity (14). There is a decrease in the enzymes involved in dopamine synthesis, especially during the first 20 years of life.
Table 6-1 Classification of Parkinsonism

<table>
<thead>
<tr>
<th>Classification of Parkinsonism</th>
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<tbody>
<tr>
<td>Idiopathic Parkinsonism (commonly known as Parkinson’s Disease)</td>
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<tr>
<td>Late-onset (&gt;40 years; generally sporadic)</td>
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<tr>
<td>Early-onset (&lt;40 years; often familial)</td>
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<tr>
<td>Young-onset (&gt;21 years)</td>
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<tr>
<td>Juvenile (&lt;21 years)</td>
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<td>Parkinsonism due to identifiable cause</td>
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<td>Virus (e.g., encephalitis lethargica)</td>
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<td>Toxins (e.g., carbon monoxide, manganese, methylphenyltetrahydropyridine)</td>
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<tr>
<td>Drugs (e.g., phenothiazines, reserpine, butyrophenones, metoclopramide)</td>
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<tr>
<td>Vascular (multi-infarct)</td>
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<tr>
<td>Tumors of basal ganglia</td>
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<tr>
<td>Normal pressure hydrocephalus</td>
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<tr>
<td>Hemiparkinsonism-hemiatriphathy</td>
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<tr>
<td>Metabolic</td>
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<td>Wilson’s disease</td>
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<tr>
<td>Hepatocerebral degeneration</td>
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<tr>
<td>Hallervoden-Spatz disease</td>
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<tr>
<td>Hypoparathyroidism</td>
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<tr>
<td>Parkinsonism in other neurodegenerative disorders</td>
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<tr>
<td>Progressive supranuclear palsy</td>
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<tr>
<td>Cortical-basal gangionic degeneration</td>
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<tr>
<td>Disorders with cerebellar/autonomic/pyramidal manifestion:</td>
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<tr>
<td>Multiple system atrophy</td>
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<tr>
<td>Striatonigral degeneration</td>
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<td>Shy-Drager syndrome</td>
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<tr>
<td>Olivopontocerebellar atrophy</td>
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<tr>
<td>Machado-Joseph disease</td>
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<tr>
<td>Disorders with prominent and often early dementia:</td>
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<tr>
<td>Diffuse cortical Lewy body disease</td>
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<tr>
<td>Alzheimer’s disease with parkinsonism</td>
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<tr>
<td>Parkinsonism-dementia-ALS complex of Guam</td>
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<tr>
<td>Pallidopontonigral degeneration/disinhibition-dementia-parkinsonism-amyotrophy complex</td>
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</tbody>
</table>

(15,16), a decrease in the dopamine concentration (17,18) most profound from age 60 to 90 years (18), and a fall in the dopamine receptors as documented from postmortem (19) and positron emission tomographic (PET) studies (20). Fearnley and Lees (21) reported a linear fallout of neurons in the substantia nigra with advancing age at a rate of 4.7 percent of the initial number per decade. Idiopathic parkinsonism is clearly not simply a consequence of aging or accelerated aging, as both the extent and pattern of cell loss in the substantia nigra are different in the two conditions. Neuronal loss in IP is curvilinear in contrast to aging, where it is linear, and a 45 percent neuronal loss occurs in the first decade of disease, which is 10-fold greater than that could be accounted for by normal aging (21–23). Neuronal loss in aging is selective and is greatest in the dorsal tier of the substantia nigra followed by the medioventral tier and least in the lateroventral tier, which is reverse of that seen in IP (21). The age-related attrition of dopaminergic nigral neurons is independent of the pathology of IP, so that these two causes of neuronal death are additive rather than multiplicative (22). Aging must contribute to the appearance and progression of the symptoms of IP (14). The early progression of IP is more rapid in elderly subjects because of a lower “neuronal reserve” (22). The pattern of clinical features is also influenced by the age of onset of IP: young patients often present with dystonic features, whereas those with a later onset have more postural imbalance and difficulty in walking (24–26). This is probably due to the difference in the topography of pathologic changes within the nigrostriatal system seen in aging and IP.

**CLINICAL FEATURES**

**Onset of Symptoms**

It is a matter of speculation as to when IP begins. As is the case with other diseases, there is a delay between the onset of the pathologic changes in the nigrostriatal
tripping after walking a distance, and clumsiness of
to get out of a low chair, dragging of feet or
is often strengthened by symptoms such as inability
suggest a neuromuscular disorder. The latter suspicion
disturbances – dysesthesias and paraesthesias – may
and tightness of muscles, cramps or vague sensory
energy, easy fatigability, myalgia, arthralgia, stiffness
loss of
even normal aging. The symptoms are often related
to the occupation and lifestyle of the patients. Loss of
pathways and the onset of clinical manifestations. The cause for most patients may be a transient
event rather than a prolonged process (27,28). The
average age of onset of IP is 55 years (29), although a
subset of patients, particularly those with a prominent
genetic component to their etiology, may have onset
before 40 years (early-onset parkinsonism). The onset
is usually insidious and the course is slowly progressive.
Initially, symptoms are often intermittent and may be
present only during stress. Repeated traumatic events
can cause parkinsonism (30). Asymmetry of symptoms
is common, and the initial pattern of asymmetry
persists, although the deficit on each side progresses
(28). The asymmetry is not related to handedness.
Extrapyramidal motor symptoms are usually taken
to mark the onset of this disease. However, it is well
known that many patients, on retrospective analysis,
realize that they had several nonmotor symptoms,
before the diagnosis of IP could be made (31).

**Early Nonspecific Features**
The early symptoms of IP are usually nonspecific and
may be seen in many other neurologic syndromes or
even normal aging. The symptoms are often related
to the occupation and lifestyle of the patients. Loss of
ergy, easy fatigability, myalgia, arthralgia, stiffness
and tightness of muscles, cramps or vague sensory
disturbances – dysesthesias and paraesthesias – may
suggest a neuromuscular disorder. The latter suspicion
is often strengthened by symptoms such as inability
to get out of a low chair, dragging of feet or
tripping after walking a distance, and clumsiness of
hands. The patient or his relatives may notice that
a longer time is needed by the patient to do his
daily activities such as taking a shower, shaving,
dressing, cooking, or eating. Before the emergence of
classical rest tremor, there may be a feeling of internal
tremulousness and transient appearance of postural
tremor in one or both hands, especially in stressful
situations. Deterioration in handwriting, in the form of
a gradual decrease in the size of letters (micrographia)
may be noticed. Inability to achieve high notes can be
an early complaint of singers; others may complain
of hypophonia after speaking for a while. There are
reports of sleep disturbances and bad dreams preceding
emergence of IP (32). Further early manifestations that
have been reported include dizziness, constipation,
seborrheic dermatitis, decreased perception of smell,
sudden transient weakness of limbs, dystonic posturing
of a limb or hemidystonia, sweating disturbances, and
bladder dysfunction. Change in personality, difficulty
in concentrating, slowed thinking (bradyphrenia),
mood changes especially depression, and impaired
cognition may be mistaken for a primary psychiatric
disorder or early dementia.

**Cardinal Features**

Tremor at rest, rigidity, bradykinesia, and abnormal-
ities of posture, gait, and balance are the cardinal
manifestations of IP. In the early stages, any combina-
tion of tremor, rigidity, or bradykinesia may be present
and a neurologic examination may be required to elicit
these signs.

**Tremor**
Approximately 70% of patients notice tremor as the
first symptom (33). Tremor is classically described to be
present at rest. Characteristically, the tremor is 3–5 Hz
rhythmic “pill-rolling” movements of the thumb
and forefinger (biplanar) and has varying amplitude.
There is abduction and adduction of the thumb and
flexion and extension of the metacarpophalangeal and
interphalangeal joints. At a later stage the tremor may
spread to the proximal joints of the limb causing
pronation–supination movements of the forearm and
to and fro movement of the arm. Onset of tremor is
usually in one of the hands (34) and it progresses to
involve the other upper limb or ipsilateral lower limb.
Rarely, onset is in one or both lower limbs. Onset of
tremor in the upper limbs is nearly 10 times more
common than in the lower limbs (12). Tremor may be
confined to one limb or one side for many years, and
in some patients it may be even confined to a single
finger for years before the appearance of other signs
(35). The jaw, tongue, head, or trunk may be affected
by tremor, although trunkal or head tremor is unusual.

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**Table 6-2**  Definition of Idiopathic Parkinsonism*

<table>
<thead>
<tr>
<th>A syndrome comprising a combination of the triad – tremor, rigidity, and akinesia, with inclusion and exclusion criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>(i) No detectable cause</td>
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<tr>
<td>(ii) Therapeutic response to dopaminomimetics</td>
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<td>(iii) No cerebellar deficits</td>
</tr>
<tr>
<td>(iv) Pyramidal features limited to possible hyperreflexia and an extensor plantar response</td>
</tr>
<tr>
<td>(v) No evidence of lower motorneuron dysfunction</td>
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<tr>
<td>(vi) Gaze deficits limited to limitation of upward gaze</td>
</tr>
<tr>
<td>(vii) Autonomic deficits limited to minor dysfunction and insufficient to cause repeated syncope: In this context drug-induced autonomic failure must be excluded.</td>
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</tbody>
</table>

*Takahashi and Calne (7)
in early IP unless it is a part of postural tremor. Tremor confined to the head or predominating there probably is not parkinsonism (36).

During early disease, tremor is often intermittent for many years (37) and is evident only under stress. Tremor is worsened by nervousness, fatigue, and stress, and it diminishes with voluntary activity or sleep and may have diurnal fluctuations. Tremor in the legs may be seen only when the patient is supine or keeps the legs in a certain posture and it usually disappears when walking. Tremor often increases in the arms while walking. Placing the patient under simultaneous physical and mental stress, such as requesting serial seven subtractions and contralateral tight hand gripping, can bring out tremor even in apparently noninvolved limbs.

It is common for the early tremor of IP to be seen when the hands are held in a posture against gravity or when the hands are being employed to execute voluntary movements (33,34,38).

Rigidity

Rigidity is an increased resistance to passive movement. The resistance is fairly regular and equal in both agonist and antagonist groups of muscles. It may be sustained (plastic or lead pipe) or intermittent and rachetty (cogwheel). Although the latter is usually thought to be parkinsonian rigidity complicated by parkinsonian tremor, it may occur in the absence of tremor and its frequency is often higher (6–12 Hz) (36). Rigidity is differentiated from (a) spasticity, which is classically velocity-dependent (clasp-knife phenomenon) and is associated with hypreflexia, Babinski’s sign, and a pyramidal distribution weakness; (b) geganhalten or paratonic rigidity, seen in dementia, and a variety of encephalopathic conditions, which are characterized by an opposition to passive movement that adjusts to the force applied (9,39); and (c) cogwheeling phenomenon, which may be seen in some cases of advanced essential tremor (40) as a result of coarse tremor interrupting passive movement, without an increase in tone.

Rigidity is often asymmetrical in the early stages of IP. It is commonly present at one or both wrists and in the neck. Like tremor, it may vary during the course of the day and with stress. As disease progresses the characteristic “flexed posture” evolves.

Assessment of rigidity is often difficult because the patient is unable to relax and cooperate; repeated examinations may be needed in both sitting and lying postures. Moreover, arthritic conditions, which are common in the elderly, can also cause local muscle spasm. Rigidity can be elicited by asking the patient to perform voluntary repetitive movements of the contralateral limb.

Bradykinesia

Akinesia (absence of movements) and hypokinesia (reduced amplitude of movement) are characteristics of IP (41). Bradykinesia, a general term used to describe the overall slowness of voluntary movements and poverty of normal associated movements, will be used in this chapter.

Bradykinesia is the most disabling component of IP and of all the clinical signs, its severity has the best correlation with dopaminergic dysfunction and cell loss as revealed by autopsy and PET scan studies. Moreover, it has the best symptomatic response to dopaminomimetic therapy. However, in early stages of IP, bradykinesia may manifest only as minimal slowness.

Bradykinesia and rigidity usually occur together and in most cases are comparable in severity (12). In the early stages, the signs may be confined to the distal muscles, but later in the disease the proximal muscles are involved. Before assessing bradykinesia, special care should be taken to exclude local painful lesions, corticospinal tract involvement, impaired cardiopulmonary reserve, dizziness, and visual impairment that may affect performance of the tests (12). Due consideration should also be given to the handedness of the patient during assessment of dexterity of the limbs. The following observations and tests are part of the Unified Parkinson’s Disease Rating Scale (UPDRS) and are often useful for assessing bradykinesia involving different parts of the body:

1. Reduction of Normal Associated Movements
   These include arm swing while walking, spontaneous facial expressions, gestures associated with conversation, and the frequency of blinking. Loss of arm swing is usually asymmetric in early IP, unlike that seen in normal aging.

2. Speech
   The patient is asked to speak loudly and clearly, for example, to repeat the names of the months. In early IP the voice may lack the normal fluctuations of volume and pitch and may fatigue quickly. In later stages there is slow initiation of speech, which is weak and monotonous.

3. Decreased Speed, Amplitude and Rhythm of Repetitive or Sequential Simple Movements on One Side of Body
   Movements often tested include repeated opposition of the forefinger and the thumb, alternating pronation–supination of the hand held vertically and then horizontally, opening and closing fists, quick repetitive hand, and heel
or toe tapping. Initially there is slowing and fatigue, then diminution in amplitude, and subsequently the movements becomes arrhythmic with frequent hesitations and arrests.

4. **Impaired Dexterity in Complex Motor Tasks that Need Frequent Changes in Direction**

   Tasks include asking the patient to button a coat, write a long sentence, write ‘m’ and ‘n’ alternately for a minute, and copy a horizontal or Archimedes spiral. A progressive decrease in the size of the letters or the spiral (micrographia) is useful, and serial documentation on follow-up helps to follow progression.

5. **Difficulty in Performing Simultaneous Repetitive Motor Tasks Involving Both Sides**

   Typically, the patient is asked to do alternate pronation and supination of both hands simultaneously. During this task the asymmetry often becomes more pronounced.

6. **Motor Tasks Involving Proximal and Trunkal Musculature**

   Bradykinesia related to these tasks are obvious in the later stages of IP. There may be difficulty in arising from a low chair without using the hands that are folded across the chest. In advanced stages, walking becomes slow and eventually impossible.

7. **Objective Methods of Assessing Bradykinesia**

   Different methods have been devised to quantify bradykinesia objectively and these are helpful in documenting the effects of therapy. These methods are less affected by inter-rater variabilities. One of the most accurate tests is performance on the Purdue Peg Board (42). The patient is asked to insert pegs in the holes on the Purdue Peg Board, first with each hand separately and then simultaneously, over a specified period of time (usually 30 seconds). The Purdue Peg Board score has been shown to correlate strongly with nigral dysfunction observed in PET scans (43). Rapid alternate tapping of forefinger and index finger on two separate keys of a computerized electronic drum with simultaneous contralateral hand activation has also been found to be a reliable test of bradykinesia with good correlation with fluorodopa PET scans (44). Of course, the severity of rigidity and tremor also influence the performance on all these tests.

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**Postural Instability and Gait Disorder**

Impairment of postural reflexes and abnormality of gait (P.I.G.D.) usually occur about 5 years after the onset of IP (45), although sometimes earlier (26,46,47). Very early impairment of balance warrants a search for other causes of parkinsonism such as progressive supranuclear palsy.

There may be subtle changes in the posture and gait in early stages of IP. The posture may show a slight flexion of the neck or trunk or a lean to one side. Abnormalities of gait may include: (a) loss of arm swing on one or both sides; (b) slowing, especially after walking for a long time; (c) shortened stride length and intermittent shuffle; (d) tripping over objects; (e) difficulty in negotiating narrow lanes; (f) difficulty in walking on toes, heels, tandem or backwards; and (g) inability to turn quickly. As the disease progresses, gait initiation becomes a problem, the steps become more uncertain, and there is festination. Short term arrests of ongoing movements, also known as freezing, usually occur in advanced disease (48) (see Chapter 7).

Postural reflexes are preserved in early IP and the “pull” test is usually negative. The patient is asked to stand with eyes open and feet comfortably apart. He is instructed to resist falling by taking one step using either foot when necessary. A sudden modest pull is applied on the shoulders, initially from the front and then from the back. Patients with impaired righting reflexes will take more than two steps to prevent themselves from falling (49,50).

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**Differential Diagnosis**

In the early stages of IP, the following conditions often need to be differentiated from it (See Chapters 53 and 54). Table 6-3 summarizes the most important features of some parkinsonian syndromes.

**Normal Aging**

Normal elderly persons can have some bradykinesia and slowed motor performance (11,51), loss of postural reflexes (50,52,53), slow and short-stepped gait (51,52), and an increased prevalence of essential tremor (54–56). These findings may lead to an erroneous diagnosis of IP. Although muscle tone is normal in the elderly, assessment of tone may be difficult in those with cognitive decline because of gegenhalten (52) or arthritis or there may be increased tone due to spondyloitic myelopathy or vascular disease. In normal aging (a) disabilities tend to be symmetric; (b) heel strike and arm swings are normal while walking and the gait is slightly wide-based unlike that seen in IP; (c) alternating
Table 6-3  Differential Diagnosis of Idiopathic Parkinsonism

<table>
<thead>
<tr>
<th></th>
<th>IP</th>
<th>SND</th>
<th>OPCA</th>
<th>SDS</th>
<th>CBGD</th>
<th>PSP</th>
<th>NPH</th>
<th>DLBD</th>
<th>ADP</th>
<th>PDCG</th>
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</thead>
<tbody>
<tr>
<td>Asymmetry at onset</td>
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<td>Rigidity</td>
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<td>Resting tremor</td>
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<tr>
<td>Bradykinesia</td>
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<td>+</td>
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<td>Dystonia</td>
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<td>Myoclonus</td>
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<td>Abnormal ocular motility</td>
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<td>Limb apraxia</td>
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<td>Speech apraxia</td>
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<td>Dysphagia</td>
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<td>Cerebellar signs</td>
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<td>Pyramidal signs</td>
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<td>Peripheral neuropathy</td>
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<td>Motor neuron disease</td>
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<td>Autonomic dysfunction</td>
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<td>Cognitive decline</td>
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<td>Sleep abnormalities</td>
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<td>Gait disturbance/</td>
<td>++ (L)</td>
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<td>L-Dopa responsiveness</td>
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- Absent; ± Inconsistent/Variable/Mild; +, Common/Moderate; ++, Frequent/Severe; (E)-Early, (L)-Late, FF-Frequent falls

Essential Tremor (ET)

Essential Tremor is the most common movement disorder and there is a dramatic increase in its prevalence with age (54,57,58). Essential Tremor is typically postural, may be accentuated with goal-directed movements of limbs, and is only occasionally present at rest (58–61). Moreover, with advancing age ET involves other body parts and there is increase in the amplitude and decrease in the frequency of the tremor (60,62–64). A diagnosis of ET is favored by (a) tremor of faster frequency (6–9 Hz); (b) tremor primarily on sustained posture or action; (c) bilateral involvement; (d) involvement of other parts of body such as head, voice, trunk; (e) absence of micrographia; (f) minimal or no signs of rigidity or bradykinesia; (g) family history of ET in some 50 percent of cases; (h) early age of onset; and (i) no response to levodopa.

Drug-Induced Parkinsonism (DIP)

Elderly subjects are especially prone to the development of drug-induced parkinsonism, perhaps because of underlying age-related striatal dopamine deficiency (65–67). The drugs responsible may be dopamine receptor antagonists, such as haloperidol or metoclopramide or dopamine depletors, such as reserpine or tetrabenazine. A history of such medications and improvement on discontinuation of the offending drug may help to distinguish DIP from IP. When parkinsonism continues or worsens slowly, even after discontinuation of the drug, there may be a preexisting preclinical nigrostriatal dopamine deficiency (preclinical parkinsonism) (68,69).

Vascular Parkinsonism (VP)

Multiple basal ganglionic infarcts can lead to parkinsonism that mainly affects the legs (lower body parkinsonism) (70,71). Characteristic features that help to differentiate VP from IP include (a) more symmetric signs; (b) short-stepped, wide-based, shuffling gait (marche à petits pas) with or without freezing, and without festination; (c) gegenhalten but no cogwheeling and no tremor; (d) pyramidal, cerebellar, and pseudobulbar signs, mild hemiparesis, dysarthria (prominent), dementia, urinary incontinence; (e) documented vascular risk factors (such as hypertension, diabetes mellitus,
previous strokes and heart disease); (f) acute or subacute onset and stepwise progression; (g) improvement of clinical signs without the use of levodopa; (h) imaging studies showing basal-ganglionic infarcts or frontal and periventricular white matter lesions (72,73).

**Progressive Supranuclear Palsy (PSP)**
A diagnosis of PSP needs to be considered in patients with progressive parkinsonism and disturbances of gaze. Clinical features favoring a diagnosis of PSP include (a) symmetric onset; (b) lack of tremor; (c) early falls, especially backwards, because of postural imbalance; (d) prominent axial (especially neck) rigidity; (e) extended knee and trunk with stiff and broad-based gait; (f) pseudobulbar features such as early dysarthria, dysphagia, and emotional lability; (g) “astonished” facial expression caused by overaction of the frontalis muscles; (h) supranuclear ophthalmoparesis typically manifested by paralysis of vertical gaze (especially downgaze); (i) defective ocular fixation; (j) blepharospasm and apraxia of eyelid opening, eyelid closure, or both; (k) early cognitive dysfunction; and (l) lack of significant response to levodopa (74–81).

**Cortical-Basal Ganglionic Degeneration (CBGD)**
Cortical-Basal Ganglionic Degeneration is a rare disorder characterized by asymmetric motor impairment and both cerebrocortical and basal ganglionic dysfunction. Features that distinguish it from IP include (a) presence of ideational and ideomotor apraxias; (b) rapid (6–8 Hz), irregular, jerky, action/and postural tremor, usually starting in one upper limb; (c) limb dystonia; (d) cortical sensory loss with accompanying complaints of numbness and paraesthesia in the fingers; (e) alien limb phenomenon; (f) cortical myoclonus; (g) pyramidal signs; (h) oculomotor and eyelid abnormalities; (i) dysarthria and dysphagia; and (j) lack of response to levodopa (82–84).

**Parkinsonism with Cerebellar and Autonomic Dysfunction: The Multiple System Atrophies (MSA)**
MSA is a group of disorders clinically characterized by any permutations of the designated clinical syndromes of extrapyramidal, pyramidal, cerebellar, or autonomic dysfunctions (85). Nearly 89% of the patients have parkinsonism at some point in the course of their illness (86), yet they seldom respond well to levodopa. Striatonigral degeneration (SND), Shy–Drager syndrome (SDS), and olivopontocerebellar atrophy (OPCA) are the three best characterized subtypes of MSA.

**Striatonigral Degeneration (SND)**
Striatonigral Degeneration is difficult to differentiate from IP. Autopsy-proven cases of SND have been misdiagnosed to have IP largely because of occasional good response to levodopa (87). Differentiating features from IP include (a) symmetric onset; (b) minimal or no resting tremor, but may have a fast jerky postural tremor; (c) early-onset falling; (d) severe dysarthria, and dysphonia; (e) excessive snoring, respiratory stridor, and sleep apnoea; (f) cerebellar or pyramidal signs; (g) rapid progress; and (h) poor or transient response to levodopa (87–89).

**Shy-Drager Syndrome (SDS)**
Shy-Drager Syndrome (90–92) is characterized by an akinetic-rigid parkinsonism with early onset of severe postural hypotension not related to drugs. Other typical findings include (a) bowel and bladder dysfunction, impotence, upper airway obstruction, cardiac arrhythmia, disturbances of sweating and temperature regulation, and pupillary changes (a progressive parasympatheticomia); and (b) symmetrical manifestations. Sometimes patients have cerebellar signs, corticospinal signs, cortical bulbular signs, peripheral neuropathy, and muscle wasting. Patients seldom respond to levodopa, which may worsen postural hypotension.

**Olivopontocerebellar Atrophy (OPCA)**
Progressive cerebellar ataxia (appendicular and gait) with or without parkinsonism characterize this disorder (93,94) and some of these patients may have parkinsonism as the initial manifestation. Parkinsonian features are usually asymmetric and do not respond to levodopa. Other manifestations of OPCA include (a) oculomotor abnormalities such as horizontal nystagmus, gaze paresis, impaired convergence, jerky pursuit, and slow saccades; (b) dysarthria and dysphagia; (c) upper and lower motor neuron signs; (d) peripheral neuropathy; (e) retinal degeneration; (f) cognitive dysfunction; and (g) autonomic dysfunction.

**Disorders with Dementia as an Important and Often Early Manifestation**

**Diffuse Lewy Body Disease (DLBD)**
DLBD is a chronic progressive disorder of parkinsonian symptoms accompanied by dementia (95–98). DLBD patients usually have an earlier age of onset and multiple psychiatric features (depression, auditory and visual hallucinations, and paranoid ideations), cognitive dysfunction (especially fluctuating features), and
are prone to levodopa-induced psychosis. Parkinsonian features are initially mild and patients more frequently have bradykinesia rather than tremor. However, these differences may not be reliable to distinguish DLBD presenting with parkinsonism as the initial manifestation from IP, especially because some patients with DLBD may have partial benefit from levodopa (see Chapters 15 & 16).

**Alzheimer’s Disease with Parkinsonism (ADP)**

Parkinsonism is significantly more common in Alzheimer’s disease (AD) than expected in a matched general population (99). Some causes can be identified such as: neuroleptic usage (100), concomitant IP (101), and DLBD (102,103). In addition, advanced AD may lead to degeneration extending to the pyramidal pathways. When parkinsonian features are early in evolution of deficits, ADP may be clinically indistinguishable from IP (101).

**Parkinsonism-Dementia Complex of Guam (PDCG)**

PDCG, also known as Lytico-Bodig, was first observed in Guam and is characterized by parkinsonian features and dementia (104,105). Other features that may be seen are those of motor neuron disease (106) and supranuclear ocular motility disorder (107).

**Normal Pressure Hydrocephalus (NPH)**

NPH is characterized by a triad of symptoms: gait abnormality, urinary incontinence, and dementia (108–110). The gait is slow and short-stepped but is reputed to differ from the gait of IP in that it is wide-based, apractic, and irregular, and patients find it difficult to lift the feet from the floor. The leg function improves in a recumbent position. Other differentiating features from IP include: (a) symmetric signs; (b) brisk tendon reflexes in the legs; (c) minimal or absent tremor; (d) history of head trauma, meningitis, or subarachnoid haemorrhage; (e) lack of response to levodopa; (f) computerized tomography scanning or magnetic resonance imaging of brain showing dilatation of all ventricles.

**Creutzfeldt–Jakob Disease (CJD)**

Although the majority of patients with CJD may have extrapyramidal symptomatology during the course of their illness, only few (9 percent) have them on their first examination (111). The main features that distinguish CJD from IP are rapidly progressive dementia, personality changes, cerebellar ataxia, and myoclonus.

**Pallidopontonigral Degeneration (PPND) and Disinhibition-Dementia-Parkinsonism-Amyotrophy Complex (DDPAC)**

These are different phenotypic expressions of the same genotype. Distinguishing features from IP include an autosomal dominant disorder characterized by a typical onset in the fourth decade and rapid progression (112). There may be early personality changes, psychiatric symptoms, profound memory loss, and a frontal lobe type of dementia. In addition, gaze paresis, levodopa unresponsive parkinsonism progressing to akinetic mutism, and clinical features resembling motor neuron disease may also be seen (113). A gene for this disorder has been identified on chromosome 17 (113).

**Early-Onset Parkinsonism (EOP)**

Although IP is a disorder of the elderly, symptoms may begin at a younger age. According to the age of onset, EOP has been classified as (a) “young-onset” (IP beginning between 21 and 40 years of age), or (b) “juvenile-onset” (symptom onset ≤21 years of age) (114). A positive family history is common in both (115), and clinical features are similar to late onset IP, except for more prominent dystonia in the younger patients, and an initial brisk improvement with a low dose of levodopa, followed by an earlier onset of motor fluctuations. EOP needs to be distinguished from other parkinsonian syndromes in adolescence and young adults.

**Dopa-Responsive Dystonia (DRD)**

Dopa-Responsive Dystonia is an autosomal dominant disorder usually presenting at 4 to 8 years of age with dystonic gait that worsens as the day progresses and improves with sleep. Tremor is uncommon. There may be hyperreflexia in the legs and extensor plantars. Diurnal variation of symptoms, a dramatic response to low doses of levodopa (50–200 mg per day with a decarboxylase inhibitor), and maintenance of the excellent response without development of motor fluctuations all distinguish DRD from juvenile IP (116,117). DRD can present at an older age and then it resembles IP more closely.

**Hemiparkinsonism-Hematrophy-Syndrome (HPHA)**

HPHA is a rare condition in which parkinsonian features, often with dystonia, are confined to one side
of the body with hemiatrophy, probably as a result of brain injury at an early stage of brain development (118,119). Younger age of onset, persistent unilateral localization, slow progression, hemiatrophy, lack of a good response to levodopa, and neuroradiologic abnormalities (120) all help to differentiate this condition from IP.

**Toxin-Induced Parkinsonism**

*Methylphenyltetrahydropyridine (MPTP)* can cause levodopa-responsive extrapyramidal features indistinguishable from IP (121,122). A history of intravenous drug use, sudden onset of symptoms (not always) and early complications of levodopa therapy (such as dyskinesias, motor fluctuations, psychiatric symptoms) may help to distinguish MPTP-induced parkinsonism from IP.

**Chronic manganese intoxication** can result in a progressive parkinsonian syndrome. However, these patients must be differentiated from early IP by a confirmed history of exposure to manganese, disturbances of gait (“cock-walk”) and balance (tendency to fall backwards), prominent dystonia, infrequent tremor, lack of response to levodopa (123), and a normal fluorodopa PET scan (124).

**Hereditary/Metabolic Parkinsonism**

**Wilson’s Disease (WD)**

Wilson’s Disease, a treatable condition, needs to be ruled out in all patients with early onset parkinsonism. WD can be of pseudoparkinsonian type (125) with asymmetric tremor (resting, postural, or kinetic), akinesia, dystonia, dystarthis, and gait abnormalities as the presenting symptoms. Distinguishing features from IP include a coarse proximal component of the tremor (wing-beating), early psychiatric symptoms, cerebellar signs, diagnostic Kayser–Fleischer rings as determined by slit-lamp examination in the eyes, nonneurologic manifestations (such as hepatic and renal disturbances) and diagnostic laboratory tests for copper and ceruloplasmin.

**Juvenile Huntington’s Disease**

Juvenile Huntington’s disease can present with rigidity, dystonia, and bradykinesia as the predominant manifestations (126,127). Chorea, subcortical dementia, and abnormal ocular motility are the important manifestations that differentiate it from IP. Dopaminomimetics may alleviate bradykinesia and rigidity (128) but can cause exacerbation of chorea and dementia. Genetic testing is the most accurate diagnostic tool.

**Machado-Joseph Disease**

Type I Machado-Joseph disease can lead to prominent extrapyramidal manifestations such as dystonia and rigidity (129). Additional features of progressive cerebellar ataxia and external ophthalmoplegia help to distinguish Machado-Joseph disease from early onset IP.

**Hallervorden-Spatz Disease**

Hallervorden-Spatz disease is an autosomal recessive disorder with onset of neurologic dysfunction mainly in childhood. The cardinal symptoms are an extrapyramidal movement disorder (mainly rigidity and dystonia), intellectual impairment, and pyramidal tract signs. Nonneurologic symptoms may include foot deformities, skin pigmentation, and tapetoretinal degeneration. Magnetic resonance imaging and bone-marrow studies are helpful for diagnosis (130).

**DIAGNOSIS OF EARLY IDIOPATHIC PARKINSONISM**

**Screening Questionnaire – Validity, Sensitivity, and Specificity**

Epidemiologic studies for early detection of IP (131–135) have addressed the validity, specificity, and sensitivity of different screening questionnaires. A set of nine questions (Table 6.4) was originally devised by Tanner and coworkers (135). Duarte and coworkers (131) applied specific weights to each of these questions. A cutoff point of 42 on this weighted questionnaire achieved both 100 percent sensitivity and 100 percent specificity when tested on 50 IP patients and 100 ophthalmological patients, respectively. However, this questionnaire needs further validation on a larger population.

**Criteria for Diagnosis of Idiopathic Parkinsonism**

Clinicopathologic studies have shown a false-positive rate of about 20 to 25 percent (89,136) and a false-negative rate of 5 to 10 percent, depending on patient selection (136,137). The use of strict exclusion and inclusion criteria may increase the specificity at the cost of reducing the sensitivity. For epidemiologic and screening purposes it is important to have criteria with higher sensitivity as achieved by a screening questionnaire. Subsequently, the positive cases may be categorized as (a) clinically possible, (b) clinically probable, and (c) clinically definite, according to the criteria proposed by Calne and coworkers (138) (Table 6.5). To each of these levels may be added a designation “with” or “without” laboratory support.
### Table 6-4  Screening Questionnaire for Detection of Parkinson’s Disease*

<table>
<thead>
<tr>
<th>No.</th>
<th>Question</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Do you have trouble arising from a chair?</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>Is your handwriting smaller than it once was?</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>Do people tell you that your voice is softer than it once was?</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>Is your balance, when walking, poor?</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>Do your feet suddenly seem to freeze in door-ways?</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>Does your face seem less expressive than it used to?</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>Do your arms and legs shake?</td>
<td>9</td>
</tr>
<tr>
<td>8</td>
<td>Do you have trouble buttoning buttons?</td>
<td>8</td>
</tr>
<tr>
<td>9</td>
<td>Do you shuffle your feet and take tiny steps when you walk?</td>
<td>8</td>
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</table>

*Duarate et al. (131)

### Table 6-5  Categories of Idiopathic Parkinsonism*

1. **Clinically possible IP:**
   - The presence of any one of the salient features: tremor, rigidity, or bradykinesia. Impairment of postural reflexes is not included because it is too nonspecific. The tremor must be of recent onset, but may be postural or resting.

2. **Clinically probable IP:**
   - A combination of any two of the cardinal features: resting tremor, rigidity, bradykinesia, or impaired postural reflexes. Alternatively, asymmetrical resting tremor, asymmetrical rigidity, or asymmetrical bradykinesia are sufficient.

3. **Clinically definite IP:**
   - Any combination of three of the features: resting tremor, rigidity, bradykinesia, or impaired postural reflexes. Alternatively, two of these features are sufficient, with one of the first three displaying asymmetry.

*Calne et al. (138)

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**Laboratory Features**

There are no absolute diagnostic laboratory tests for the premortem diagnosis of IP and even the pathologic criteria are unclear. High-resolution magnetic resonance imaging and computerized tomography scanning of the brain may be helpful to exclude secondary causes of parkinsonism such as normal pressure hydrocephalus, cerebrovascular disease, progressive supranuclear palsy, Huntington’s disease, and olivopontocerebellar atrophy. PET scanning and [123I]βCIT single photon emission tomography (SPECT) are useful to detect nigrostriatal changes. (See Chapters 25 and 26) [123I]βCIT SPECT (139) and [123I]FP-CIT SPECT (140) are useful in demonstrating loss of striatal dopamine transporter content in early IP. Functional imaging with PET scanning has provided many insights into the pathophysiology of neurodegenerative disorders including IP. [18F]6-fluoro-L-dopa ([18F]FD) has been used to quantitate presynaptic nigrostriatal function and its reproducibility in normal human subjects has been well established (141). It has been shown that [18F]FD uptake rate constant (Ki) has significant correlations with the dopamine levels in the striatum and with the dopaminergic cell densities in the substantia nigra (142). Similar conclusions have been reached from experimental studies of the nigrostriatal pathways in animals (143). Age-related neuronal loss or impaired function in the nigrostriatal pathways result in a linear decrease in the striatal Ki (144). Nigrostriatal dopaminergic neurons have a high degree of plasticity (145) and a prolonged clinically silent stage of nigral neuronal loss exists before the early symptoms of IP appear. The clinical signs do not appear until 50% of nigral neurons and 80 percent of striatal dopamine is lost (21,145).

Preclinical detection of parkinsonism has been reported (146,147) where asymptomatic subjects had reduced striatal FD uptake and had developed parkinsonism within months. Striatal dopamine deficiency has also been observed in subjects at risk of developing...
parkinsonism, for example, after exposure to MPTP (148), in Guamanians from regions with Lytico-Bodig (149,150), in co-twins of patients with IP (151–153), in first-degree relatives in a family with dominantly inherited parkinsonism (154), and in individuals who have recovered from drug-induced parkinsonism (68). In early IP symptom onset has been estimated at a putamen Ki of between 57 percent and 80 percent of normal (155). These findings are consistent with the observation by Fearnley and Lees [21] of a curvilinear decline in the nigral cell count with increasing symptom duration in IP and a short presymptomatic period of 4.7 years at the age of 60. Moreover, in a mathematical model, the presymptomatic period was calculated to be 5 to 14 years for patients aged 65 years, depending on the severity of impact of the initial result (23). The rate of progression of the nigrostriatal lesion in IP has been estimated to be 2.5 times that of normal aging (156), but since progression is faster initially, this figure only gives a crude estimate.

Of the four cardinal signs of IP (rigidity, tremor, bradykinesia, and postural imbalance) only bradykinesia, as measured by the UPDRS/Modified Columbia Scale (MCS) or Purdue pegboard, has been found to have the best correlation with the striatal Ki of FD scans (22,43,157). A less robust correlation has been observed with the axial (posture, stability, and gait) and rigidity subscales of MCS, but not with the tremor subscale (43). The methods of assessment of bradykinesia by the MCS and by pegboard are complementary and a combination of these methods improved the correlation with PET (43). Bradykinesia measurements showed the highest correlation with the contralateral but not ipsilateral Ki, implying lateralization of the dopaminergic deficit (43). Bradykinesia has also been shown to have significant correlation with the degree of postmortem striatal dopamine deficiency (158), with nigral cell count (159), and with the decreased concentration of homovanillic acid in cerebrospinal fluid (160). Thus bradykinesia has the best correlation with the nigrostriatal dopaminergic deficit in IP, and therefore the pegboard value and bradykinesia score should be the primary outcome variables for studies addressing the natural evolution of the disorder (22,23).

Response to Dopaminomimetics

Virtually all patients with IP benefit from dopaminomimetic therapy provided they are able to tolerate a reasonable intake of these drugs (up to 1,500 mg of levodopa per day with a peripheral decarboxylase inhibitor (138,161). When in doubt about the response of IP, a sudden cessation of the dopaminomimetic treatment should help answer the question, particularly if the dose is high (138). Injection of a dopaminomimetic agonist such as lisuride or apomorphine (after prior treatment with domperidone) is an alternative and quicker method of detecting a response, although not always practical. Though unresponsiveness to dopaminomimetics strongly argues against a diagnosis of IP, responsiveness is not a diagnostic criterion because some other forms of Parkinsonism such as progressive supranuclear palsy (78,162) and multiple system atrophies (86,163) may show a transient or partial response to dopaminomimetics and some pathologically proven cases of IP have been found to be unresponsive (164).

CONCLUSION

Tremor at rest, rigidity, and bradykinesia are the early manifestations of Idiopathic Parkinsonism. The average age of onset of symptoms is the middle of the sixth decade. These symptoms are usually asymmetric and in the initial stages may be intermittent and only worsened by stress. In the early stages of the disease, patients may have nonspecific symptoms such as fatigability, arthralgia, cramps, internal tremulousness, and vague sensory disturbances that may be mistaken for aging, neuromuscular diseases, or other systemic disorders. Initially symptoms are often related to specific tasks. A therapeutic response to an adequate dose of levodopa is seen in virtually all patients. Early impairment of postural reflexes, significant abnormalities of gait, disturbances in ocular motility, autonomic dysfunction unrelated to drugs, progressive dementia, cerebellar signs, focal neurologic deficits, and unresponsiveness to levodopa warrant a search for other causes of parkinsonism. There are no absolute diagnostic tests for the premortem diagnosis of idiopathic parkinsonism. Functional imaging with [18F]6-fluorodopa positron emission tomography is useful to quantitate the presynaptic nigrostriatal dysfunction and it correlates well with the clinical manifestation of bradykinesia.

Acknowledgments

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