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Pathophysiology and Clinical Assessment of Parkinsonian Symptoms and Signs

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In his 1817 “An Essay on the Shaking Palsy,” James Parkinson recorded many features of the condition that now bears his name (1). Parkinson emphasized the tremor at rest, flexed posture, festinating gait (Fig. 1), dysarthria, dysphagia, and constipation. Charcot and others later pointed out that the term paralysis agitans used by Parkinson was inappropriate, because in Parkinson’s disease (PD) the strength was usually well preserved and many patients with Parkinson’s disease did not shake.

Although traditionally regarded as a motor system disorder, PD is now considered to be a much more complex syndrome involving the motor as well as the nonmotor systems. For example, oily skin, seborrhea, pedal edema, fatigability, and weight loss are recognized as nonspecific but nevertheless typical parkinsonian features. The autonomic involvement is responsible for orthostatic hypotension, paroxysmal flushing, diaphoresis, problems with thermal regulation, constipation, and bladder, sphincter, and sexual disturbances. The involvement of the thalamus and the spinal



FIGURE 1 A 74-year-old man with 9 years of bilateral parkinsonism demonstrated by hypomimia, hand tremor and posturing, stooped posture, and a shuffling gait.

dopaminergic pathway may explain some of the sensory complaints, such as pains, aches, and burning-tingling paresthesias (2). The special sensory organs may also be involved in PD and cause visual, olfactory, and vestibular dysfunction (3).

A large number of studies have drawn attention to the protean neurobehavioral abnormalities in PD, such as apathy, fearfulness, anxiety, emotional lability, social withdrawal, increasing dependency, depression, dementia, bradyphrenia, a type of anomia termed the “tip-of-the-tongue phenomenon,” visual-spatial impairment, sleep disturbance, psychosis, and other psychiatric problems (4,5).

The rich and variable expression of PD often causes diagnostic confusion and a delay in treatment. In the early stages, parkinsonian symptoms are often mistaken for simple arthritis or bursitis, depression, normal aging, Alzheimer’s disease, or stroke (Fig. 2). PD often begins on one side of the body, but usually becomes bilateral within a few months or years. However, parkinsonism may remain unilateral, particularly when it is a late sequela of posttraumatic hemiatrophy or when it is due to a structural lesion in the basal ganglia (6). In a survey of 181 treated PD patients, Bulpitt



A

FIGURE 2 (A) 74-year-old woman with facial asymmetry and right hemiatrophy for 5 years associated with right hemiparkinsonism. (B) Voluntary facial contraction reveals no evidence of right facial weakness.



B

FIGURE 2 Continued.

et al. (7) found at least 45 different symptoms attributable to PD. However, only 9 of these symptoms were reported by the patients, with more than fivefold excess compared with those of a control population of patients randomly selected from a general practice. These common symptoms included being frozen or rooted to a spot, grimacing, jerking of the arms and legs, shaking hands, clumsy hands, salivation, poor concentration, severe apprehension, and hallucinations. However, even these frequent symptoms are relatively nonspecific and do not clearly differentiate PD patients from diseased controls. In many cases, a follow-up for several years is needed before the diagnosis becomes apparent. Gonera et al. (8) found that 4–6 years prior to the onset of classic PD symptoms patients experience a prodromal phase characterized by more frequent visits to general practitioners and specialists as compared to normal controls. During this period PD patients, compared to normal controls, had a higher frequency of mood disorder, “fibromyalgia,” and shoulder pain.

Different diagnostic criteria for PD, based on clinical and pathological findings, have been proposed, but their reliability has not been vigorously tested. In one study of 800 patients diagnosed clinically as PD and prospectively followed by trained parkinsonologists from early, untreated stages, the final diagnosis after a mean of 7.6 years of follow-up was considered to be other than PD in 8.1% of cases (9). In a study of 143 cases of parkinsonism who came to autopsy and had a clinical diagnosis made by neurologists, the positive predictive value of the clinical diagnosis of PD was 98.6%, and for the other parkinsonian syndromes it was 71.4% (10).

While systemic, mental, sensory, and other nonmotor symptoms of PD are often quite disabling, PD patients are usually most concerned about the symptoms that relate to their disturbance of movement (11). Several studies have demonstrated that patients who predominantly manifest “axial” symptoms, such as dysarthria, dysphagia, loss of equilibrium, and freezing, are particularly disabled by their disease as compared to those who have predominantly limb manifestations (12). The poor prognosis of patients in whom these symptoms predominate is partly due to a lack of response of these symptoms to dopaminergic drugs.

The specific mechanisms underlying the various PD symptoms are poorly understood. An accurate assessment of the disorder’s motor signs should help to differentiate them from the motor changes associated with normal aging. Normal elderly subjects may have a mild extrapyramidal impairment, including slow movement and a shuffling gait. Other signs often attributed to PD also have been described with increased frequency among normal elderly subjects. These include disinhibition of the nuchocephalic reflex, glabellar blink reflex, snout reflex, head-retraction reflex, and the presence of paratonia, impaired vertical glaze, and cogwheel

visual pursuit (13). Although these signs occur more frequently in parkinsonian patients than other aged individuals, they are not specific for PD. However, they may indicate an age-dependent loss of striatal dopamine and dopamine receptors (14). The receptor loss may explain why these age-related motor signs do not improve with levodopa treatment (15).

This chapter will focus on these motor manifestations. The emphasis will be on the pathophysiology and clinical assessment of the cardinal signs of PD: bradykinesia, tremor, rigidity, and postural instability (Table 1).

TABLE 1 Motor Features of Parkinsonism

Tremor at rest ^a
Rigidity ^a
Bradykinesia ^a
Loss of postural reflexes ^a
Hypomimia (masked facies)
Speech disturbance (hypokinetic dysarthria)
Hypophonia
Dysphagia
Sialorrhea
Respiratory difficulties
Loss of associated movements
Shuffling, short-step gait
Festination
Freezing
Micrographia
Difficulty turning in bed
Slowness in activities of daily living
Stooped posture, kyphosis, and scoliosis,
Dystonia, myoclonus, orofacial dyskinesia
Neuro-ophthalmological findings
Impaired visual contrast sensitivity
Visuospatial impairment
Impaired upward gaze, convergence, and smooth pursuit
Impaired vestibuloocular reflex
Hypometric saccades
Decreased blink rate
Spontaneous and reflex blepharospasm (glabellar or Myerson's sign)
Lid apraxia (opening or closure)
Motor findings related to dopaminergic therapy
Levodopa-induced dyskinesias (chorea, dystonia, myoclonus, tic)

^aCardinal signs.

BRADYKINESIA

Bradykinesia, or slowness of movement, is often used interchangeably with hypokinesia (poverty of movement) and akinesia (absence of movement). Bradykinesia is the most characteristic symptom of basal ganglia dysfunction in PD (16,17). It may be manifested by a delay in the initiation, and by slowness of execution, of a movement. Other aspects of bradykinesia include a delay in arresting movement, decrementing amplitude and speed of repetitive movement, and an inability to execute simultaneous or sequential actions. In addition to whole body slowness and impairment of fine motor movement, other manifestations of bradykinesia include drooling due to impaired swallowing of saliva (18), monotonous (hypokinetic) dysarthria, loss of facial expression (hypomimia), and reduced arm swing when walking (loss of automatic movement). Micrographia has been postulated to result from an abnormal response due to reduced motor output or weakness of agonist force coupled with distortions in visual feedback (19). The term bradyphrenia refers to slowness of thought, but bradyphrenia does not always correlate with bradykinesia, and therefore different biochemical mechanisms probably underlie these two parkinsonian disturbances (20).

After recording electromyographic (EMG) patterns in the antagonistic muscles of parkinsonian patients during a brief ballistic elbow flexion, Hallett and Khoshbin (21) concluded that the most characteristic feature of bradykinesia was the inability to “energize” the appropriate muscles to provide a sufficient rate of force required for the initiation and the maintenance of a large, fast (ballistic) movement. Therefore, PD patients need a series of multiple agonist bursts to accomplish a larger movement. Micrographia, a typical PD symptom, is an example of a muscle-energizing defect (21). The impaired generation and velocity of ballistic movement can be ameliorated with levodopa (22,23).

Bradykinesia, more than any other cardinal sign of PD, correlates well with striatal dopamine deficiency. Measuring brain dopamine metabolism of rats running on straight and circular treadmills, Freed and Yamamoto (24) found that dopamine metabolism in the caudate nucleus was more affected by posture and direction of movement. Dopamine metabolism in the nucleus accumbens was more linked to the speed and direction of the antagonists, appears to be normal in PD, and is probably more under cerebellar than basal ganglia control (21,25). In other words, in PD the simple motor program to execute a fast ballistic movement is intact, but it fails because the initial agonist burst is insufficient. The degree of bradykinesia correlates well with a reduction in the striatal fluorodopa uptake measured by positron emission tomography (PET) scans and in turn

with nigral damage (26). Studies performed initially in monkeys made parkinsonian with the toxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (27) and later in patients with PD provide evidence that bradykinesia results from excessive activity in the subthalamic nucleus (STN) and the internal segment of globus pallidus (GPi) (28). Thus, there is both functional and biochemical evidence of increased activity in the outflow nuclei, particularly STN and GPi, in patients with PD. As a result of the abnormal neuronal activity at the level of the GPi, the muscle discharge in patients with PD changes from the normal high (40 Hz) to pulsatile (10 Hz) contractions. These muscle discharges can be auscultated with a stethoscope (29). More recent studies suggest that the observed 15–30 Hz oscillations of the STN may reflect synchronization with cortical beta oscillation via the cortico-subthalamic pathway and may relate to mechanisms of bradykinesia since stimulation at the 15 Hz rate worsens bradykinesia and dopaminergic drugs promote faster oscillations (about 70 Hz) and improve bradykinesia, similar to the high-frequency stimulation associated with deep brain stimulation (DBS) (30,31).

Bradykinesia, like other parkinsonian symptoms, is dependent on the emotional state of the patient. With a sudden surge of emotional energy, the immobile patient may catch a ball or make other fast movements. This curious phenomenon, called “kinesia paradoxa,” demonstrates that the motor programs are intact in PD, but that patients have difficulty utilizing or accessing the programs without the help of an external trigger (32). Therefore, parkinsonian patients are able to make use of prior information to perform an automatic or a preprogrammed movement, but they cannot use this information to initiate or select a movement. Another fundamental defect in PD is the inability to execute learned sequential motor plans automatically (33). This impairment of normal sequencing of motor programs probably results from a disconnection between the basal ganglia and the supplementary motor cortex, an area that subserves planning function for movement. The supplementary motor cortex receives projections from the motor basal ganglia (via the globus pallidus and ventrolateral thalamus) and, in turn, projects to the motor cortex. In PD, the early component of the premovement potential (Bereitschaftspotential) is reduced, probably reflecting inadequate basal ganglia activation of the supplementary motor area (34,35). Recording from the motor cortex of MPTP monkeys, Tatton et al. (36) showed markedly increased gain of the long-latency (M2) segments of the mechanoreceptor-evoked responses. This and other findings indicate that PD patients have an abnormal processing of sensory input necessary for the generation and execution of movement.

Most of the neurophysiological and neurobehavioral studies in PD have concluded that the basal ganglia (and possibly the supplementary motor cortex) play a critical role in planning and in sequencing voluntary movements (37). For example, when a patient arises from a chair, he or she may “forget” any one of the sequential steps involved in such a seemingly simple task: to flex forward, place hands on the arm rests, place feet under the chair, and then push out of the chair into an erect posture. Similar difficulties may be encountered when sitting down, squatting, kneeling, turning in bed, and walking. Lakke (32) suggests that since the patient can readily perform these activities under certain circumstances, such as when emotionally stressed (“kinesia paradoxa”), the intrinsic program is not disturbed, and therefore these axial motor abnormalities are a result of apraxia. Thus, the PD patient has an ability to “call up” the axial motor program on command.

The inability to combine motor programs into complex sequences seems to be a fundamental motor deficit in PD. The study of reaction time (RT) and velocity of movement provide some insight into the mechanisms of the motor deficits at an elementary level. Evarts et al. (38) showed that both RT and movement times (MT) are independently impaired in PD. In patients with asymmetrical findings, the RT is slower on the more affected side (39). The RT is influenced not only by the degree of motor impairment, but also by the interaction between the cognitive processing and the motor response. This is particularly evident when choice RT is used and compared to simple RT (20). Bradykinetic patients with PD have more specific impairment in choice RT, which involves a stimulus categorization and a response selection, and reflects disturbance at more complex levels of cognitive processing (40). *Bereitschaftspotential*, a premovement potential, has been found to be abnormal in PD patients and to normalize with levodopa (41). The MT, particularly when measured for proximal muscles, is less variable than the RT and more consistent with the clinical assessment of bradykinesia. Both MT and RT are better indicators of bradykinesia than the speed of rapid alternating movements. Ward et al. (42) attempted to correlate the median MT and RT with tremor, rigidity, or manual dexterity in 10 patients rated on a 0–4 modified Columbia scale. The only positive correlations were found between MT and rigidity and between RT and manual dexterity. Of the various objective assessments of bradykinesia, the MT correlates best with the total clinical score, but it is not as sensitive an indicator of the overall motor deficit as is the clinical rating. Ward et al. (42) concluded that although MT was a useful measurement, it alone did not justify the use of elaborate and expensive technology. The clinical rating scale probably more accurately reflects the patient’s disability because it includes more relevant observations.

TREMOR

Tremor, while less specific than bradykinesia, is one of the most recognizable symptoms of PD. However, only half of all patients present with tremor as the initial manifestation of PD, and 15% never have tremor during the course of the illness (43). Although tremor at rest (4–6 Hz) is the typical parkinsonian tremor, most patients also have tremor during activity, and this postural tremor (5–8 Hz) may be more disabling than the resting tremor. Postural tremor without parkinsonian features and without any other known etiology is often diagnosed as essential tremor (Table 2). Isolated postural tremor clinically identical to essential tremor, however, may be the initial presentation of PD, and it may be found with higher-than-

TABLE 2 Differential Diagnosis of Parkinson and Essential Tremor

	Essential tremor	Parkinsonian tremor
Age at onset (years)	10–80	55–75
Sex	M ≤ F	M ≥ F
Family history	+++	+
Site of involvement	Hands, head, voice	Hands, legs, jaw, chin, tongue
Characteristics	Flexion-extension	Supination-pronation
Influencing factors		
Rest	↓	↑
Action	↑	↓
Mental concentration walking	↓	↑
Frequency (Hz)	8–12	4–7
Electromyography contractions	Simultaneous	Alternating
Associated features		
Cogwheel rigidity	± (cogwheel without rigidity)	+
Dystonia	+	++
Hereditary neuropathy	+	0
Neuropathology	No discernible pathology	Nigrostriatal degeneration, Lewy bodies
Treatment	Alcohol, beta-blockers, primidone, botulinum toxin	Anticholinergics amantadine dopaminergic drugs surgery

expected frequency in relatives of patients with PD (44). The two forms of postural tremor can be differentiated by a delay in the onset of tremor when arms assume an outstretched position. While most patients with Parkinson's tremor have a latency of a few seconds (up to a minute) before the tremor reemerges during postural holding, hence "reemergent tremor," postural tremor of ET usually appears immediately after arms assume a horizontal posture (45). Since the reemergent tremor has similar frequency to that of rest tremor and both tremors generally respond to dopaminergic drugs, we postulate that the reemergent tremor represents a variant of the more typical rest tremor. It has been postulated that the typical tremor at rest results from nigrostriatal degeneration and consequent disinhibition of the pacemaker cells in the thalamus (46). These thalamic neurons discharge rhythmically at 5–6 Hz, a frequency similar to the typical parkinsonian tremor at rest (47,48). Some support for the thalamic pacemaker theory of PD tremor also comes from the studies of Lee and Stein (49), which show that the resting 5 Hz tremor is remarkably constant and relatively resistant to resetting by mechanical perturbations. Furthermore, during stereotactic thalamotomy, 5 Hz discharges are usually recorded in the nucleus ventralis intermedius of the thalamus in parkinsonian as well as in normal subjects, even in the absence of visible tremor (50). This rhythmic bursting is not abolished by deafferentation or paralysis (16). Because the frequency (6 Hz) of the postural (action) tremor is the same as the frequency of the cogwheel phenomenon elicited during passive movement, some authors have suggested that the postural tremor and cogwheel phenomenon have similar pathophysiologies (51) (Fig. 3).

The biochemical defect underlying either resting or postural parkinsonian tremor is unknown. Bernheimer and colleagues (52) showed that the severity of tremor paralleled the degree of homovanillic acid (HVA) reduction in the pallidum. In contrast, bradykinesia correlated with dopamine depletion in the caudate nucleus. In an experimental monkey model of parkinsonian tremor, a pure lesion in the ascending dopaminergic nigrostriatal pathway is not sufficient to produce the alternating rest tremor (53). Experimental parkinsonian tremor requires nigrostriatal disconnection combined with a lesion involving the rubrosegmentospinal and the dentatorubrothalamic pathways. A typical PD tremor is observed in humans and in experimental animals exposed to MPTP, a neurotoxin that presumably affects, rather selectively, the nigrostriatal dopaminergic system (54,55). However, the cerebellorubrothalamic system has not been examined in detail in this MPTP model. Furthermore, in MPTP subjects, a prominent action tremor was more typically seen than a tremor at rest.

In the early studies, mechanical and optic devices were used to record tremor (56). Electromyography (EMG) recordings and accelerometers,

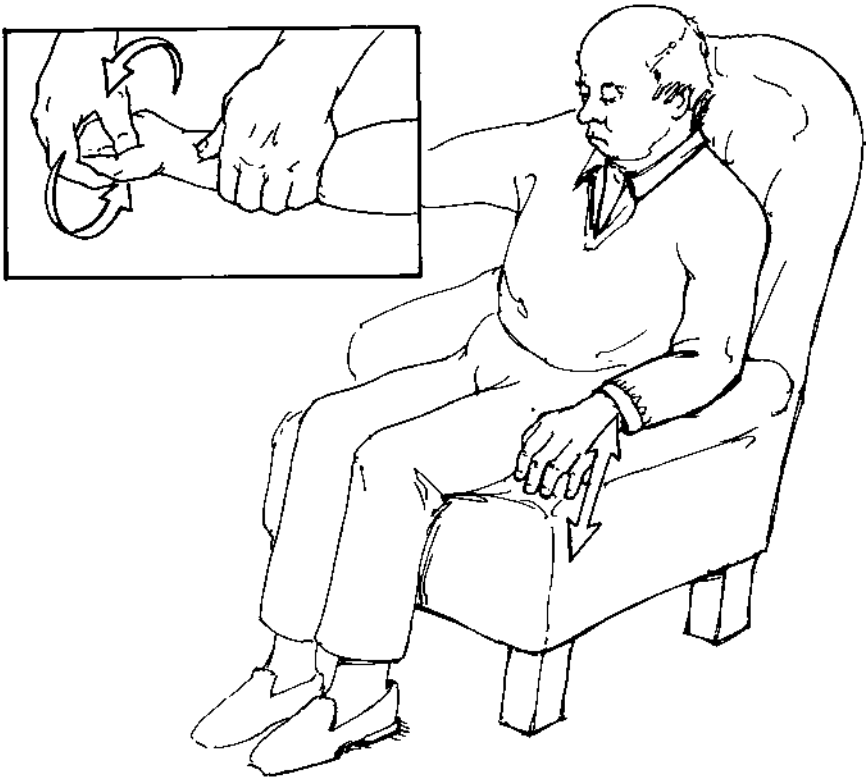


FIGURE 3 Parkinsonian cogwheel rigidity elicited by passive rotation of the wrist is enhanced by voluntary repetitive movement of the contralateral hand.

assisted by computer analysis, have been utilized to measure the characteristics of tremor. However, most accelerometers record tremor in a single plane. By using computed triaxial accelerometry, we recorded the distortion of the normal motion characteristics in patients with PD and ET during voluntary arm abduction-adduction movement (22). There was a good correlation between the reduction in the distortion and the clinical improvement in response to medications. However, the quantitative recordings of tremor, although accurate, are time consuming, costly, and influenced by the emotional state of the patient. Moreover, it is questionable whether such recordings provide a reliable index of a meaningful therapeutic response.

RIGIDITY AND POSTURAL ABNORMALITIES

Rigidity is less variable than tremor, and it probably better reflects the patient's functional disability. Rigidity may contribute to subjective stiffness and tightness, a common complaint in patients with PD. However, there is relatively poor correlation between the sensory complaints experienced by most patients and the degree of rigidity (57,58). In mild cases, cogwheel rigidity can be brought out by a passive rotation of the wrist or flexion-extension of the forearm while the patient performs a repetitive voluntary movement in the contralateral arm (59) (Fig. 3). Rigidity may occur proximally (e.g., neck, shoulders, and hips) and distally (e.g., wrists and ankles). At times it can cause discomfort and actual pain. Painful shoulder, probably due to rigidity but frequently misdiagnosed as arthritis, bursitis, or rotator cuff, is one of the most frequent initial manifestations of PD (60). Rigidity is often associated with postural deformity resulting in flexed neck and trunk posture and flexed elbows and knees. Some patients develop ulnar deviation of hands ("striatal hand"), which can be confused with arthritis (61). Other skeletal abnormalities include neck flexion ("dropped head" or "bent spine") (62) and trunkal flexion ("camptocormia") (63,64) (Figs. 4, 5). Duvoisin and Marsden (65) studied 20 PD patients with scoliosis and found that 16 of the patients tilted away from the side with predominant parkinsonian symptoms. However, subsequent studies could not confirm this observation (66).

The neurophysiological mechanisms of rigidity are still poorly understood. Spinal monosynaptic reflexes are usually normal in PD. Recordings from muscle spindle afferents revealed an activity in rigid parkinsonian patients not seen in normal controls. This suggested an increased fusimotor drive due to hyperactivity of both alpha and gamma motor neurons. However, this fusimotor overactivity probably is an epiphenomenon, reflecting the inability of PD patients to relax fully. Passive shortening of a rigid muscle, due to PD or seen in tense subjects, produces an involuntary contraction called the Westphal phenomenon. While the mechanism of this sign is unknown, it probably is the result of excessive supraspinal drive on normal spinal mechanism. This shortening reaction may be abolished by procaine infiltration of the muscle. Thus, there is no convincing evidence of a primary defect of fusimotor function in parkinsonian rigidity (67).

The measurement of torque or of resistance during passive flexion-extension movement has been used most extensively as an index of rigidity. Utilizing these techniques, it has been demonstrated that rigidity correlated with increased amplitude of the long-latency (transcerebral) responses to sudden stretch. These long-latency stretch reflexes represent a positive



A

FIGURE 4 A 63-year-old woman with progressive scoliosis to the right side for 20 years and left hemiparkinsonism manifested by hand and leg tremor, rigidity, and bradykinesia: (A) front view; (B) back view.



B

FIGURE 4 Continued.



FIGURE 5 A 44-year-old woman with PD showing typical dystonic (“striatal”) hand with flexion at the metacarpophalangeal joints, extension at the proximal interphalangeal joints, and flexion of the distal interphalangeal joints. The dystonia completely resolved with levodopa (61).

(release) phenomenon, mediated by motor pathways that do not traverse the basal ganglia. The earlier techniques of passively flexing and extending the limbs were later refined by Mortimer and Webster (68), who designed a servocontrolled electronic device to move the limb at a constant angular velocity. They and others (69–71) demonstrated a close relationship between the enhanced long-latency stretch reflexes and the degree of activated rigidity. The opposite is true in Huntington's disease, in which these long-latency stretch reflexes are diminished or absent. Using measurements of the tonic stretch reflex as an index of rigidity, Meyer and Adorjani (72) found an inverse correlation between the "dynamic sensitivity" (ratio between the increase in reflex EMG at a high versus low angular velocity) and the severity of parkinsonian rigidity. On the other hand, the "static" component of the tonic stretch reflex (the maximum reflex activity at greatest stretch or at sustained stretch) positively correlated with the severity of rigidity. Both the dynamic and the static components of the tonic stretch reflex may be reduced by antiparkinson drugs (72). Although Lee and Tatton (70) showed diminution of the amplitude of the reflex after treatment, correlating it with improvement in rigidity, the measurement of long-latency responses is quite cumbersome, time consuming, and possibly unreliable (73). Moreover, a marked overlap in the long-latency response between PD and normal subjects has been noted (74).

POSTURAL INSTABILITY

The loss of balance associated with propulsion and retropulsion is probably the least specific, but most disabling, of all parkinsonian symptoms. Purdon-Martin (75), after studying nine brains of patients with postencephalitic parkinsonism, concluded that the globus pallidum degeneration was most responsible for the loss of righting reflexes and of postural instability in parkinsonian patients. Reichert et al. (3) correlated postural instability in PD patients with reduced or absent vestibular responses. Traub et al. (76) studied postural reflexes in 29 PD patients by recording anticipatory postural responses in the legs (triceps surae) in response to perturbations of one of the arms. In normal subjects, a burst of activity can be recorded from the calf muscles at a latency of 80 msec after the perturbation. This postural adjustment occurs even before any movement can be recorded in the legs (latency, 150 msec). Therefore, this reflex adjustment is anticipatory and centrally generated. In PD, the anticipatory postural reflexes are absent or markedly diminished. Such abnormalities were present in 10 of the 18 patients with moderately severe PD and in 2 of 11 Parkinson's disease patients without obvious postural instability. Since some patients with normal anticipatory reflexes can still fall, it is likely that other mechanisms

contribute to the falls of parkinsonian patients (77,78). Furthermore, patients with progressive supranuclear palsy, who are much more prone to falling than PD patients, have normal anticipatory postural responses (76). Weiner et al. (79) found moderate or severe loss of balance in response to a standing postural perturbation in 68% of 34 patients in a geriatric care facility. They suggested that a postural reflex dysfunction was largely responsible for the unexplained falls in the elderly.

Loss of postural reflexes usually occurs in more advanced stages of the disease and, along with freezing (see below), is the most common cause of falls, often resulting in hip fractures. The loss of protective reactions further contributes to fall-related injuries. Many patients with postural instability, particularly when associated with flexed trunkal posture, have festination, manifested by faster and faster walking as if chasing its center of gravity in order to prevent falling. When combined with axial rigidity and bradykinesia, loss of postural reflexes causes the patient to collapse into the chair when attempting to sit down. The “pull test” (pulling the patient by the shoulders) is commonly used to determine the degree of a patient’s retropulsion or propulsion.

FREEZING AND OTHER GAIT ABNORMALITIES

The slow, shuffling, narrow-based gait is one of the most characteristic features of PD (80). The parkinsonian gait reveals certain features that overlap with the gait disturbance associated with normal pressure hydrocephalus (81,82). In a study of 50 subjects older than 70 years, Sudarsky and Ronthal (83) established a principal cause of the gait disorder in all but seven subjects (“essential gait disorder”). They, but not others (84), suggested that this senile gait is related to normal pressure hydrocephalus. The gait and postural problems associated with PD probably result from a combination of bradykinesia, rigidity, loss of anticipatory proprioceptive reflexes, loss of protective reaction to a fall, gait and axial apraxia, ataxia, vestibular dysfunction, and orthostatic hypotension. When gait disorder, with or without freezing and postural instability, is the dominant motor dysfunction, than “lower body” parkinsonism should be considered in the differential diagnosis (85). This syndrome is thought to represent a form of “vascular” parkinsonism associated with a multi-infarct state. Furthermore, gait disorder and postural instability are typically associated with progressive supranuclear palsy (86,87).

One of the most disabling symptoms of PD “freezing,” also referred to as “motor blocks”, is a form of akinesia (loss of movement) (88,89). The observation that some patients even with severe bradykinesia have no freezing and other patients have a great deal of freezing but minimal or no

bradykinesia suggests that the two signs have different pathophysiologies. Furthermore, that bradykinesia usually responds well to levodopa whereas freezing does not indicates that freezing may be a manifestation of a nondopaminergic disturbance. Freezing consists of a sudden, transient (a few seconds) inability to move. It typically causes “start hesitation” when initiating walking, as well as a sudden inability to move the feet (as if “glued to the ground”) when turning or walking through narrow passages (such as the door or the elevator), crossing streets with heavy traffic, or approaching a destination (target hesitation). Patients often learn a variety of tricks to overcome the freezing attacks, including marching to command (“left, right, left, right”), visual cues such as stepping over objects (end of a walking stick, pavement stone, cracks in the floor, etc.), walking to music or a metronome, shifting body weight, and rocking movements (85,90,91). When freezing occurs early in the course of the disease or is the predominant symptom, a diagnosis other than PD should be considered. Disorders associated with prominent freezing include progressive supranuclear palsy, multiple system atrophy, and vascular (“lower body”) parkinsonism (85,92).

OTHER MOTOR MANIFESTATIONS

There are many other motor findings in PD (Table 1), most of which are directly related to one of the cardinal signs. For example, the loss of facial expression (hypomimia, masked facies) and the bulbar symptoms (dysarthria, hypophonia, dysphagia, and sialorrhea) result from orofacial-laryngeal bradykinesia and rigidity (93,94). Respiratory difficulties result from a variety of mechanisms, including a restrictive component due to rigid respiratory muscles and levodopa-induced respiratory dyskinesias (95,96).

Of the various oculomotor problems characteristically seen in PD, the following are most common: impaired saccadic and smooth pursuit, limitation of upward gaze and convergence, oculogyric crises, spontaneous and reflex blepharospasm, apraxia of lid opening (involuntary levator inhibition), and apraxia of eyelid closure (97,98). Although supranuclear ophthalmoplegia is often used to differentiate progressive supranuclear palsy from Parkinson’s disease, this oculomotor abnormality has also been described in otherwise typical parkinsonism (99).

ASSESSMENT OF DISABILITY

The assessment of PD is difficult because the movement disorder is expressed variably in an individual patient (inpatient variability) at

different times, and it is influenced by emotional state, response to medication, and other variables. Moreover, there is a marked interpatient variability of symptoms and signs. To study this heterogeneity and to determine possible patterns of clinical associations, we analyzed the clinical findings in 334 patients with idiopathic PD. We identified at least two distinct clinical populations of parkinsonian patients (100). One subtype was characterized by a prominent tremor, an early age at onset, and a greater familiar tendency. Another subtype was dominated by postural instability and gait difficulty (PIGD) and was associated with greater degree of dementia, bradykinesia, functional disability, and a less favorable long-term prognosis.

These findings are supported by the results of an analysis of 800 patients with untreated PD included in the multicenter trial of Deprenyl and Tocopherol Antioxidative Therapy of Parkinson's Disease (DATA-TOP). The PIGD group had greater occupational disability and more intellectual impairment, depression, lack of motivation, and impairment in activities of daily living than a corresponding group of patients with tremor-dominant PD (12). Based on the analysis of clinical correlates in this cohort of patients, the investigators concluded that patients with older age of onset and a presentation with PIGD and with bradykinesia are more likely to have a more aggressive course than those whose symptoms being early and are dominated by tremor (101). In order to determine the overall rate of functional decline and to assess the progression of different signs of PD, we prospectively followed 297 patients (181 males) with clinically diagnosed PD for at least 3 years (101). Data from 1731 visits over an average period of 6.36 years (range: 3–17) were analyzed. The annual rate of decline in the total Unified Parkinson's Disease Rating Scale (UPDRS) scores was 1.34 units (when assessed during "on") and 1.58 (when assessed during "off"). Patients with older age at onset had a more rapid progression of disease than those with younger age at onset. Furthermore, the older onset group had significantly more progression in mentation, freezing, and parts I and II UPDRS subscores. Handwriting was the only component of the UPDRS that did not significantly deteriorate during the observation period. Regression analysis of 108 patients, whose symptoms were rated during their "off" state, showed faster rate of cognitive decline as age at onset increased. The slopes of progression in UPDRS scores, when adjusted for age at initial visit, were steeper for the PIGD group of patients as compared to the tremor-dominant group. These findings, based on longitudinal follow-up data, provide evidence for a variable course of progression of the different PD symptoms, thus implying different biochemical or degenerative mechanisms for the various clinical features associated with PD.

Thus, PD should not be considered a unitary disorder, but a syndrome with characteristic patterns of symptoms, course, response to therapy, and different etiologies. The different subsets of PD may have different pathogenesis and even different genetic predisposition. Tremor-dominant PD may be related to an autosomal dominant essential tremor (44).

The accurate and reliable evaluation of motor dysfunction is essential for an objective assessment of the efficacy of potentially useful drugs. Various mechanical, electrophysiological, and clinical methods have been utilized to measure the motor findings in PD objectively. Some of the techniques are designed to measure the frequency, amplitude, force, velocity, acceleration of contraction, and other quantitative parameters of the abnormal movement. However, such measurements may have little relevance to the actual functional disability of the patient.

In assessing the motor symptoms and signs of PD, two approaches have been used, both of which strive to quantitate the motor findings (73). One method utilizes neurological history and an examination with subjective rating of symptoms, signs and functional disability, and the other method utilizes timing of specific tasks or neurophysiological tests of particular motor disturbances. While the latter method is considered to be more “objective” and “scientific,” it is not necessarily more accurate, reliable, or relevant than the clinical rating. However, both approaches have certain advantages and disadvantages, and, when combined, they may provide a useful method of assessing the severity of the disability and the response to therapy.

Most of the subjective methods of assessment of parkinsonian disability utilize rating scales of various symptoms and disabilities. Probably the most widely used method of staging PD is the Hoehn-Yahr scale (102). While this staging scale is useful in comparing populations of PD patients, it is relatively insensitive to changes in a patient’s clinical state. Therefore, the Hoehn-Yahr scale is not useful in monitoring the response of individual patients to therapy.

Thus, it is important that the severity of the disease is objectively assessed in the context of the individual’s goals and needs. Although a variety of neurophysiological and computer-based methods have been proposed to quantitate the severity of the various parkinsonian symptoms and signs, most studies rely on clinical rating scales, particularly the UPDRS (103–107) (see Appendix). In some studies the UPDRS is supplemented by more objective timed tests, such as the Purdue Pegboard test and movement and reaction times (17). There are also many scales, such as the Parkinson’s Disease Questionnaire-39 (PDQ-39) and the Parkinson’s Disease Quality of Life Questionnaire (PDQL), that attempt to assess the overall health related quality of life (108).

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APPENDIX: UNITED RATING SCALE FOR PARKINSONISM (103), DEFINITIONS OF 0–4 SCALE

Mentation, Behavior, and Mood

1. Mentation

0 = None.

1 = Mild. Consistent forgetfulness with partial recollection of events and no other difficulties.

2 = Moderate memory loss, with disorientation and moderate difficulty handling complex problems. Mild but definite impairment of function at home with need of occasional prompting.

3 = Severe memory loss with disorientation as to time and often place. Severe impairment in handling problems.

4 = Severe memory loss with orientation preserved to person only. Unable to make judgments or solve problems. Requires much help with personal care. Cannot be left alone at all.

2. Thought Disorder (due to dementia or drug intoxication)

0 = None.

1 = Vivid dreaming.

2 = “Benign” hallucinations with insight retained.

3 = Occasional to frequent hallucinations or delusions, without insight, could interfere with daily activities.

4 = Persistent hallucinations, delusions, or florid psychosis. Not able to care for self.

3. Depression

0 = Not present.

1 = Periods of sadness or guilt greater than normal, never sustained for days or weeks.

- 2 = Sustained depression (one week or more).
- 3 = Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest).
- 4 = Sustained depression with vegetative symptoms and suicidal thoughts or intent.

4. Motivation/Initiative

- 0 = Normal.
- 1 = Less assertive than usual; more passive.
- 2 = Loss of initiative or disinterest in elective (nonroutine) activities.
- 3 = Loss of initiative or disinterest in day-to-day (routine) activities.
- 4 = Withdrawn, complete loss of motivation.

Activities of Daily Living

5. Speech

- 0 = Normal.
- 1 = Mildly affected. No difficulty being understood.
- 2 = Moderately affected. Sometimes asked to repeat statements.
- 3 = Severely affected. Frequently asked to repeat statements.
- 4 = Unintelligible most of the time.

6. Salivation

- 0 = Normal.
- 1 = Slight but definite excess of saliva in mouth; may have nighttime drooling.
- 2 = Moderately excessive saliva with some drooling.
- 3 = Marked excess of saliva with some drooling.
- 4 = Marked drooling, requires constant tissue or handkerchief.

7. Swallowing

- 0 = Normal.
- 1 = Rare choking.
- 2 = Occasional choking.
- 3 = Requires soft food.
- 4 = Requires NG tube or gastrostomy feeding.

8. Handwriting

- 0 = Normal.
- 1 = Slightly slow or small.

2 = Moderately slow or small; all words are legible.

3 = Severely affected; not all words are legible.

4 = The majority of words are not legible.

9. Cutting Food

0 = Normal.

1 = Somewhat slow and clumsy, but no help needed.

2 = Can cut most food, although clumsy and slow, some help needed.

3 = Food must be cut by someone, but can still feed slowly.

4 = Needs to be fed.

10. Dressing

0 = Normal.

1 = Somewhat slow, but no help needed.

2 = Occasional assistance with buttoning, getting arms in sleeves.

3 = Considerable help required but can do some things alone.

4 = Helpless.

11. Hygiene

0 = Normal.

1 = Somewhat slow, but no help needed.

2 = Needs help to shower or bathe; or very slow in hygienic care.

3 = Requires assistance for washing, brushing teeth, combing hair, going to bathroom.

4 = Foley catheter or other mechanical aids.

12. Turning in Bed

0 = Normal.

1 = Somewhat slow and clumsy, but no help needed.

2 = Can turn alone or adjust sheets, but with great difficulty.

3 = Can initiate, but not turn or adjust sheets alone.

4 = Helpless.

13. Falling

0 = Normal.

1 = Rare falling.

2 = Occasionally falls, less than once per day.

3 = Falls an average of once daily.

4 = Falls more than once daily.

14. Freezing

0 = None.

1 = Rare freezing when walking, may have start-hesitation.

2 = Occasional freezing when walking.

3 = Frequent freezing. Occasionally falls from freezing.

4 = Frequent falls from freezing.

15. Walking

0 = Normal.

1 = Mild difficulty. May not swing arms or may tend to drag leg.

2 = Moderate difficulty, but requires little or no assistance.

3 = Severe disturbance of walking, requiring assistance.

4 = Cannot walk at all, even with assistance.

16. Tremor

0 = Absent.

1 = Slight and infrequently present.

2 = Moderate; bothersome to patient.

3 = Severe; interferes with many activities.

4 = Marked, interferes with most activities.

17. Sensory Symptoms

0 = None.

1 = Occasionally has numbness, tingling, or mild aching.

2 = Frequently, has numbness, tingling or aching, not distressing.

3 = Frequent painful sensations.

4 = Excruciating pain.

Motor Examination (single point in time)

18. Speech

0 = Normal.

1 = Slight loss of expression, diction, and/or volume.

2 = Monotone, slurred but understandable; moderately impaired.

3 = Marked impairment, difficult to understand.

4 = Unintelligible.

19. Facial Expression

0 = Normal.

1 = Minimal hypomimia, could be normal “poker face.”

2 = Slight but definitely abnormal diminution of facial expression.

3 = Moderate hypomimia, lips parted some of the time.

4 = Masked or fixed facies with severe or complete loss of facial expression, lips parted 1/4 inch or more.

20. Tremor at Rest

0 = Absent.

1 = Slight and infrequently present.

2 = Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.

3 = Moderate in amplitude and present most of the time.

4 = Marked in amplitude and present most of the time.

21. Action Tremor

0 = Absent.

1 = Slight; present with action.

2 = Moderate in amplitude; present with action.

3 = Moderate in amplitude, with posture holdings as well as action.

4 = Marked in amplitude, interferes with feeding.

22. Rigidity (judged on passive movement of major points with patient relaxed in sitting position; cogwheeling to be ignored)

0 = Absent.

1 = Slight or detectable only when activated by mirror or other movements.

2 = Mild to moderate.

3 = Marked, but full range of motion easily achieved.

4 = Severe, range of motion achieved with difficulty.

23. Finger Taps (patient taps thumb with index finger in rapid succession with widest amplitude possible, each hand separately)

0 = Normal.

1 = Mild slowing and/or reduction in amplitude.

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.

3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.

4 = Can barely perform the task.

24. Hand Movements (patient opens and closes hands in rapid succession with widest amplitude possible, each hand separately)
- 0 = Normal.
 - 1 = Mild slowing and/or reduction in amplitude.
 - 2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
 - 3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
 - 4 = Can barely perform the task.
25. Hand Pronation-Supination (pronation-supination movements of hands, vertically or horizontally, with as large as amplitude as possible, both hands simultaneously)
- 0 = Normal.
 - 1 = Mild slowing and/or reduction in amplitude.
 - 2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
 - 3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
 - 4 = Can barely perform the task.
26. Leg Agility (patient taps heel on ground in rapid succession, picking up entire leg. Amplitude should be about three inches)
- 0 = Normal.
 - 1 = Mild slowing and/or reduction in amplitude.
 - 2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
 - 3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
 - 4 = Can barely perform the task.
27. Arising from Chair (patient attempts to arise from a straight-back wood or metal chair with arms folded across chest)
- 0 = Normal.
 - 1 = Slow, or may need more than one attempt.
 - 2 = Pushes self up from arms of seat.
 - 3 = Tends to fall back and may have to try more than one time, but can get up without help.
 - 4 = Unable to arise without help.

28. Posture

0 = Normal.

1 = Not quite erect, slightly stooped posture; could be normal for older person.

2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.

3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.

4 = Marked flexion with extreme abnormality of posture.

29. Gait

0 = Normal.

1 = Walks slowly, may shuffle with short steps, but no festination or propulsion.

2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.

3 = Severe disturbance of gait, requiring assistance.

4 = Cannot walk at all, even with assistance.

30. Postural Stability (response to sudden posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared)

0 = Normal.

1 = Retropulsion, but recovers unaided.

2 = Absence of postural response, would fall if not caught by examiner.

3 = Very unstable, tends to lose balance spontaneously.

4 = Unable to stand without assistance.

31. Body Bradykinesia (combining slowness, hesitancy, decreased armswing, small amplitude, and poverty of movement in general)

0 = None.

1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.

2 = Mild degree of slowness, giving and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.

3 = Moderate slowness, poverty or small amplitude of movement.

4 = Marked slowness, poverty or small amplitude movement.

Complications of Therapy

Score these items to represent the status of the patient in the week prior to the examination.

Dyskinesias

32. Duration: What proportion of the walking day are dyskinesias present? (Historical information)

0 = None

1 = 1–25% of day

2 = 26–50% of day

3 = 51–75% of day

4 = 76–100% of day

33. Disability: How disabling are the dyskinesias? (historical information; may be modified by office examination)

0 = Not disabling

1 = Mildly disabling

2 = Moderately disabling

3 = Severely disabling

4 = Completely disabling

34. Pain: How painful are the dyskinesias?

0 = No painful dyskinesia

1 = Slight

2 = Moderate

3 = Severe

4 = Marked

35. Presence of Early Morning Dystonia (historical information)

0 = No

1 = Yes

Clinical Fluctuations

36. “Off” Duration: What proportion of the waking day is the patient “off” on average?

0 = None

1 = 1–25% of day

2 = 26–50% of day

3 = 51–75% of day

4 = 76–100% of day

37. “Off” Predictable: Are any “off” periods predictable as to timing after a dose of medication?
0 = No
1 = Yes
38. “Off” Unpredictable: Are any “off” periods unpredictable as to timing after a dose of medication?
0 = No
1 = Yes
39. “Off” Sudden: Do any of the “off” periods come on suddenly, e.g., over a few seconds?
0 = No
1 = Yes

Other Complications

40. Anorexia, Nausea, Vomiting: Does the patient have anorexia, nausea, or vomiting?
0 = No
1 = Yes
41. Sleep Disturbances: Does the patient have any sleep disturbances, e.g., insomnia or hypersomnolence?
0 = No
1 = Yes
42. Symptomatic Orthostasis: Does the patient have symptomatic orthostasis?
0 = No
1 = Yes

Modified Hoehn and Yahr Staging

- Stage 0 = No signs of disease
Stage I = Unilateral disease
Stage I.5 = Unilateral disease plus axial involvement
Stage II = Bilateral disease, without impairment of balance
Stage II.5 = Mild bilateral disease, with recovery on pull test
Stage III = Mild to moderate bilateral disease; some postural instability; physically independent

Stage IV = Severe disability; still able to walk or stand unassisted
Stage V = Wheel chair bound or bedridden unless aided

Modified Schwab and England Activities of Daily Living Scales

- 100%—Completely independent. Able to do all chores without slowness, difficulty or impairment. Essentially normal. Unaware of any difficulty.
- 90%—Completely independent. Able to do all chores with some degree of slowness, difficulty and impairment. Might take twice as long. Beginning to be aware of difficulty.
- 80%—Completely independent in most chores. Takes twice as long. Conscious of difficulty and slowness.
- 70%—Not Completely independent. More difficulty some chores. Three to four times as long in some. Must spend a large part of the day with chores.
- 60%—Some dependency. Can do most chores, but exceeding slowly and with much effort. Errors; some impossible.
- 50%—More dependent. Help with half, slower, etc. Difficulty with everything.
- 40%—Very dependent. Can assist with all chores, but few alone.
- 30%—With effort, now and then does a few chores alone or begins alone. Much help needed.
- 20%—Nothing alone. Can be a slight help with some chores. Severe invalid.
- 10%—Totally dependent, helpless. Complete invalid.
- 0%—Vegetative functions such as swallowing, bladder and bowel functions are not