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Introduction

Parkinson's disease (PD) is a frequent neurologic disorder among elderly individuals. Whereas the hallmark of the disease is the presence of abnormal movements, comorbid psychiatric and cognitive abnormalities are frequently found. The major aim for the present book was to include up-to-date information regarding the diagnosis, phenomenology, and treatment of the psychiatric and cognitive disorders of PD in one single volume.

Most patients with PD are usually cared for by internists and general practitioners, but the information about emotional and cognitive comorbid conditions is usually found in specialized neurologic and psychiatric journals. Our book is aimed at senior clinicians and trainees in internal medicine and general practice, at neurologists who may want a better understanding of their patients' "non-motor" problems, and at geriatric psychiatrists who may want to access the relevant information about emotion and cognition in PD, and update their knowledge about the motor complications and treatment of this disorder.

The second chapter provides a strong clinical background of the motor problems of PD before discussing the psychiatric and cognitive disorders related to the illness. We address the epidemiology and main clinical aspects of PD, and a clinical case is presented to illustrate the progression along the stages of the illness. There is also specific discussion of the different clinical complications that may emerge during the evolution of the disease and the subtypes of the illness. Treatment strategies for the motor disorder are specifically addressed, with discussion of emotional and cognitive benefits and complications of the different pharmacologic approaches such as the use of neuroprotective agents, levodopa (l-dopa) and dopaminergic agonists, anticholinergics, and other compounds. This chapter also includes a review of the most recent surgical treatments for PD, such as the stereotaxic

lesion or stimulation of the posteroventral-pallidum, the thalamus, and the subthalamic nucleus, with special emphasis on the potential cognitive and emotional implications of these techniques.

In the third chapter we revise the most important differential diagnoses of PD to help the clinician understand diagnostic dilemmas of the disease. We provide clinical vignettes and discuss clinical aspects and laboratory and neuropathologic findings of multisystem atrophy, progressive supranuclear palsy, and corticobasal degeneration. Special attention is given to the spectrum of Lewy body disease, and clues for the differential diagnosis between PD and other neurodegenerative conditions, drug-induced parkinsonism, and parkinsonism related to depression, stroke, and "cortical" dementias are also provided.

In the fourth chapter we discuss the most frequent cognitive deficits in PD such as deficits in executive functions, visuospatial abilities, speech, language, attention, and memory. We examine their prevalence, potential mechanisms, and neuroimaging correlates. There is also an in-depth discussion of dementia in PD. After presenting a clinical vignette, we discuss methodologic issues related to the diagnosis of dementia in PD, and review the prevalence and phenomenology of dementia in this disorder. We specifically review cognitive, emotional, motor, and neuroimaging differences between so-called "subcortical" dementias (e.g., PD) and "cortical" dementias (e.g., Alzheimer's disease (AD)), and revise the clinical correlates and mechanism of dementia in PD. Specific reference is made to neuropathologic aspects of dementia in PD, such as coexisting AD pathology, cortical Lewy bodies, and depletion of neurotransmitter systems.

In the fifth chapter we examine the prevalence and phenomenology of depression in PD. We discuss the main strategies used to diagnose an affective disorder among patients with a neurologic disorder that may "mimic" a depressive condition, and we revise the main psychiatric instruments and diagnostic criteria used to carry out the patient's evaluation. We then discuss the impact of depression upon cognitive functioning, activities of daily living, quality of life, and evolution of the motor disorder. Finally, we examine biological markers and neuroimaging correlates of depression in PD and discuss potential underlying mechanisms for this condition.

In the sixth chapter we address behavioral disorders frequently reported in PD such as anxiety, panic attacks, phobias, and apathy. We discuss clues

for the diagnosis of these problems and present illustrative cases. PD patients were reported as having "high moral standards," "moral exactitude," "great social conformism," and "inflexible social interactions." However, it was only recently that specific personality traits in PD have been investigated with standardized instruments. This chapter presents the main evidence for and against a specific personality "type" in PD.

In the seventh chapter we review the main cognitive and psychiatric side-effects of antiparkinsonian medication. We discuss the dilemma of improving the motor status of a patient while at the same time increasing the risk of behavioral problems, and examine alternatives for managing these difficult situations. The main psychiatric side-effects of antiparkinsonian medications are hallucinations, delusions, illusions, delirium, and sleep disorders. We examine their prevalence, main clinical correlates, and potential mechanisms. We then address the cognitive and emotional side-effects of specific antiparkinsonian drugs, such as l-dopa, dopaminergic agonists, amantadine, selegiline, and anticholinergic drugs.

In the eighth, and last, chapter we discuss the main somatic and psychological treatments of the psychiatric disorders of PD. The efficacy and side-effects of different types of antidepressants (e.g., tricyclics, monoamine-oxidase inhibitors, selective serotonergic reuptake inhibitors) and antipsychotic agents (e.g., clozapine, risperidone, olanzapine, quetiapine) are specifically revised, and the usefulness of other treatment modalities, from relevant social and familial interventions to electroconvulsive therapy, is discussed.

Finally, the Appendix comprises seven scales that are frequently used to rate the physical and behavioral disorders of PD, as well as deficits in activities of daily living, and quality of life.

2

Epidemiologic, clinical, and therapeutic aspects of Parkinson's disease

Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported, with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured.

James Parkinson, 1817

Introduction

Since its initial description in 1817, PD remains an unsolved clinical problem, with a changing focus during the past four decades. Thus, the 1960s were the years of dopamine discovery; the 1970s witnessed a leap forward in the treatment of the disease by the introduction of replacement therapy with l-dopa; the 1980s witnessed motor complications emerging from chronic long-term l-dopa treatment; and the 1990s were primarily devoted to genetic and neuroimaging studies, the search for putative biological markers, and the rebirth of surgical treatment for the disease.

This chapter will examine relevant epidemiologic, clinical, and therapeutic aspects of PD and will provide the neurologic basis for the in-depth discussion of neuropsychiatric and cognitive aspects of the disease that follows.

Clinical vignette

A.B. is a 54-year-old accountant who noticed mild tremor in his right hand while reading the newspaper. A diagnosis of PD was made and the patient was started on l-dopa, which was followed by the disappearance of tremor. One year later, he noticed tremor during stressful situations, and his signature became smaller. He also noticed dragging of his right foot when walking. This overall picture illustrates the period of *stable response to l-dopa*.

Two years later, the patient developed clumsiness in both legs and abnormal gait. There was resting tremor in both hands, mostly in stressful situations. He had an abnormal

flexed posture and lacked bilateral arm swing. The patient became less communicative in social situations and had a marked reduction in voice volume. The motor response to l-dopa was stable during the day, but he would wake up in the morning with bilateral tremor, difficulty in walking, and slowness while washing and shaving, followed by marked improvement 10–20 minutes after taking the first dose of l-dopa. This illustrates the period of *stable response with early morning akinesia*.

Two years later, despite an increase in l-dopa dosage and combination therapy with bromocriptine, the patient showed difficulties with most daily activities, as well as recurrence of tremor and other parkinsonian signs about 3–4 hours after taking l-dopa. His balance was normal but he was unsteady when turning around, and the frequency of l-dopa intake had to be increased. This illustrates the period of *fluctuating response with wearing-off phenomena*.

One year later, the patient became severely disabled in his daily activities. Nights were very uncomfortable due to increased rigidity. During the day he experienced a rapid decrease in medication efficacy: more than 30 minutes were necessary to "switch On" (i.e., to experience motor improvement), and "Off" periods (i.e., lack of motor improvement) lasted for more than 2 hours (e.g., he was totally disabled after lunch). Bromocriptine doses were progressively increased, but without a consistent motor improvement. He developed involuntary movements during the period of best medication effect, which were noticed by his wife but not by the patient himself. This illustrates the period of *fluctuating response with wearing-off phenomena, delayed On, poor response with empty stomach, and peak dose chorea*.

Two years later the patient was on a schedule of 800 mg l-dopa and 3 mg pergolide every 3 hours, but continued to experience wearing-off about 2–3 hours after medication intake. He was well aware of severe right-side involuntary movements, both at the beginning and at the end of each l-dopa dose. He also reported that the effect of medication would suddenly disappear during stressful situations, to return about 5–10 minutes later. Occasionally, the medication failed to switch him On, which mostly ocurred after meals. The patient developed severe postural instability during Off periods. He was unable to work, and needed assistance with most regular chores. This illustrates the period of *fluctuating response with wearing-off phenomena, the On–Off phenomenon, delayed On, poor response with empty stomach, failure of dose, and biphasic dyskinesias*.

Phenomenology of PD

Staging of illness

PD is a chronic and progressive disorder, which is usually divided into five different stages of severity (Table 2.1) (Hoehn & Yahr, 1967). As illustrated

Table 2.1. Modified Hoehn and Yahr staging of PD

Stage 0	No signs of disease
Stage 1	Unilateral disease
Stage 1.5	Unilateral disease plus axial involvement
Stage 2	Bilateral disease, without impaired balance
Stage 2.5	Bilateral disease, with recovery on pull test
Stage 3	Mild to moderate bilateral disease; some postural instability; physically independent
Stage 4	Severe disability; still able to walk or stand unassisted
Stage 5	Wheelchair-bound or bedridden unless aided

Adapted from Lang et al. (1995).

in the clinical vignette, stage I (i.e., stable response to l-dopa) is characterized by symptoms exclusively or more prominently on one side of the body (Hughes et al., 1993). Parkinsonian signs such as tremor, rigidity, and bradykinesia may be confined to one side of the body for months or years, with a mean duration for this stage of about 3 years. Activities of daily living (ADLs) are usually not affected in this stage. Stage 2 (i.e., stable response with early morning akinesia) is characterized by spreading of parkinsonian signs to the opposite side of the body and to axial structures. During this stage the side initially affected still remains relatively more affected, but there is flexed posture with adduction of limbs, facial masking with monotonous speech, mild disturbance of gait, generalized slowness, and a decreased amplitude of associated movements. These signs are mostly mild, and balance is usually not affected. Stage 3 (i.e., fluctuating response with wearing-off phenomena) is characterized by impairment of balance and abnormal postural reflexes. Patients walk unsteadily and have difficulties when turning around. When pushed, patients may take several steps backwards to maintain upright posture, and may fall. During this stage patients are functionally independent in household chores, but may show some limitations at work. Stage 4 (i.e., fluctuating response and On–Off phenomena) is characterized by increasing disabilities and partial dependence for most ADLs such as eating, dressing, and washing. All cardinal symptoms of the disease are markedly worse. During stage 5, the last of the illness, patients are completely dependent in their ADLs and restricted to a wheelchair or bed bound. They require constant nursing care, and the main cause of death is aspirative pneumonia (Morgante et al., 2000).

Before the introduction of l-dopa, the mean survival period after the onset of parkinsonian signs was 10 years, and the rate of observed mortality was three times that of the general population (Hoehn & Yahr, 1967). Following l-dopa introduction, life expectancy increased by a mean of 6 years (Yahr, 1976).

Clinical features

The cardinal signs of PD are resting tremor, rigidity, bradykinesia, and loss of postural reflexes. We will now address each of these signs separately.

Resting tremor

A 3–5 Hz hand tremor (''pill rolling'' tremor) is usually the initial symptom of the disease, and becomes most evident when hands are at rest. Parkinsonian tremor usually dampens during action or with support, but some PD patients may also show action tremor. Lower lip or chin tremor is not uncommon, but leg tremor is less frequent. Patients may show increased resting tremor when performing activities with the contralateral hand, during effortful thinking, and while walking.

Rigidity

Parkinsonian rigidity is characterized by a constant resistance to passive movement (''lead pipe'' rigidity). Patients usually describe a stiff feeling, and rigidity may be elicited during physical examination. A ratchety catching known as ''cogwheeling'' may be felt when wrists are passively rotated, or while moving the arms at the elbow and the legs at the knee. Cogwheeling results from a combination of rigidity and tremor, and is not specific to parkinsonism (Kurlan et al., 2000).

Bradykinesia

This term is used to refer to slowness of movement or impaired initiation of movement, whereas hypokinesia or akinesia refer to poor movement or lack of movement. This symptom is usually the most disabling to patients.

Postural instability

PD patients have problems in standing up from a sitting position, maintaining postural stability, and adopting an erect posture. Patients may lose

balance spontaneously or prove unable to maintain balance when pulled backwards. About one-third of PD patients have frequent falls.

PD patients may also show a diversity of additional motor symptoms, which are mostly variants of the cardinal signs described above. Hypomimia, or loss of facial expression, also termed "*masked face*," is most likely to be the result of combined bradykinesia and rigidity, and *dysarthria, hypophonia, and sialorrhea* may have a similar mechanism. Other manifestations of bradykinesia are *micrographia, decreased blink rate, loss of arm swing, and shuffling gait.* Respiratory problems are frequent and mostly result from respiratory muscle restriction due to rigidity. Other frequent findings are *blepharospasm* (i.e., involuntary bilateral eye closure produced by spasmodic contraction of the orbicularis oculi muscles), the "*striatal*" *hand* (i.e., a hand deformity often confused with rheumatoid arthritis), *foot deformity, and scoliosis* (Hartman & Abbs, 1988; Jankovic, 1987; Kurland et al., 1987; Logemann, 1988; Sudarsky & Ronthal, 1983; Weiner et al., 1984). A variety of oculomotor abnormalities have been described in PD patients, such as visual contrast deficits, upgaze limitation, abnormalities in smooth pursuit and vestibulo-ocular reflexes, decreased blink rate, positive glabellar reflex, eyelid aperture apraxia, and hypometric saccades (White et al., 1981).

The following non-motor clinical signs may also be frequently present in PD.

Autonomic dysfunction

This disorder may result from the disease itself or from antiparkinsonian drugs, and includes constipation, excessive saliva production, excessive perspiration, bowel dysfunction, impotence, loss of libido, and hyposmia.

Orthostasis

Orthostatic hypotension is a reduction in systolic blood pressure of at least 20 mmHg or a reduction in diastolic blood pressure of at least 10 mmHg, within 3 minutes of standing. Symptomatic or asymptomatic orthostatic hypotension may be present in up to 15% of normal elderly subjects, but the presence of severe orthostatic hypotension and other autonomic signs suggests alternative diagnoses to PD, such as multiple system atrophy (Hughes et al., 1993).

Dementia

Cognitive impairment commonly develops in a large proportion of parkinsonian patients. This subject is further discussed in chapter 4.

Depression

Depressive mood is present in about 40% of cross-sectional samples of PD patients, and most PD patients may show depression at some point in their longitudinal evolution. This issue is further discussed in chapter 5.

Psychotic features

Hallucinations, delusions, and illusions occur in about 40% of parkinsonian patients on dopamine replacement therapy, but are uncommon as a manifestation of the disease itself. This subject is further discussed in chapter 7.

Clusters of parkinsonian signs and subgroups of the disease

A question now arising is whether PD constitutes one single and clinically homogeneous disorder, or whether it should be considered as a generic term that covers a variety of somewhat related clinical subgroups. Based on the clinical heterogeneity of PD, several authors proposed subgroups with specific clinical characteristics (Zetusky et al., 1985). The identification of subgroups may be useful provided that this classification predicts genetic risk, associated clinical complications, rate of progression, or response to treatment. Zetusky et al. (1985) used the term "classical-PD" to refer to those patients with tremor as the predominant parkinsonian sign. This type of PD has a relatively early onset, relatively mild bradykinesia and postural instability, a relatively low prevalence of dementia, and a relatively higher likelihood of a positive family history of either PD or postural tremor. The second type of PD was termed "akinetic–rigid", and is characterized by a relatively high prevalence of dementia, depression, postural instability, and gait disorders.

Several authors (Barbeau & Roy, 1982; Quinn et al., 1987; Yokochi & Narabayashi, 1981) separated an "early" from a "late" onset form of PD. The current consensus is to use the term "early-onset" PD whenever parkinsonian signs develop before 40 years of age. This group is further subdivided into a "juvenile" type, whenever parkinsonian signs develop

Table 2.2. Most prevalent motor fluctuations in PD

Short-lasting motor fluctuations
Paradoxic kinesis
Freezing gait
On–Off
Medium-lasting motor fluctuations
Beginning of dose motor deterioration
End of dose motor deterioration
Wearing-off
On–Off
Yo-yoing
Diurnal fluctuation
Sleep benefit
Long-lasting motor fluctuations
Menstrual fluctuations

Adapted from Quinn (1999).

before 21 years of age, and an "adult" type, whenever parkinsonian signs develop between 21 and 39 years of age. Juvenile-type PD was reported to have a strong genetic component (Pineda-Trujillo et al., 2001), whereas early-onset, adult-type PD usually shows dystonia as the initial symptom, and dyskinesias and motor fluctuations relatively early after the onset of illness. Finally, the term "late-onset" PD is used whenever parkinsonian signs develop after 40 years of age, and is the most frequent type of PD.

Motor fluctuations

Motor fluctuations are considered to be an inevitable result of long-term l-dopa therapy, and may produce severe disability. Motor fluctuations may disrupt daily activities, and may occur together with fluctuations in mood and in sensory and autonomic functions (Table 2.2). About half of the patients with PD develop motor fluctuations and dyskinesias at some point during the illness (Sweet & McDowell, 1975). Several factors, such as l-dopa dose and age at onset of motor signs, may influence the rate of motor complications in PD. After a 6-year treatment period, patients on a low-